

BATCH J093

THE PATHOLOGY OF NEGLIGENCE

REPORT OF THE JUDICIAL INQUIRY TRIBUNAL

To determine the causes of deaths of patients
of the Punjab Institute of Cardiology,
Lahore in 2011-2012



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

In the Name of Allah, The Beneficent, The Merciful

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ABBREVIATIONS

API	<i>Active Pharmaceutical Ingredient</i>
BHT	<i>Butylated Hydroxytoluene</i>
CDTL	<i>Central Drug Testing Laboratory</i>
cGMP	<i>Current Good Manufacturing Practices</i>
DTL	<i>Drug Testing Laboratory</i>
Excipients	<i>Inactive Ingredients</i>
FTIR	<i>Fourier Transform Infrared Spectrometer</i>
GC/MS	<i>Gas Chromatography/Mass Spectrometer</i>
GMP	<i>Good Manufacturing Practices</i>
HPLC	<i>High Performance Liquid Chromatography</i>
IHP	<i>International Health Partners</i>
LC/MS	<i>Liquid Chromatography/Mass Spectrometer</i>
LSP	<i>London School of Pharmacy</i>
MHRA	<i>Medicines and Healthcare products Regulatory Agency</i>
OPD	<i>Out Patient Department</i>
PIC	<i>Punjab Institute of Cardiology</i>
SOP	<i>Standard Operating Procedures</i>

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER -1-



INTRODUCTION

The Government of Punjab issued Notification No.SO(JUDL-III)9-84/2012, under the West Pakistan Tribunals of Inquiry Ordinance, 1969 (the Ordinance). The Notification was issued pursuant to a request made by the Government of Punjab to the Chief Justice, Lahore, High Court Lahore, to appoint a Judge of the Court to conduct an inquiry pursuant to section 3 of the Ordinance. Mr. Justice Sheikh Azmat Saeed, the Honourable Chief Justice, Lahore High Court (as he then was), named me to assume the role of the Tribunal of Inquiry.



Efroze Chemical Industry

1.2. The Tribunal of Inquiry was necessitated on account of numerous deaths being reported prima facie due to bone marrow suppression and other related complications amongst patients registered with the Punjab Institute of Cardiology ("PIC"), Lahore. The terms of reference of the Tribunal were as follows:-



Punjab Institute of Cardiology (PIC)

- i) *To ascertain the cause(s) of death(s) and ailment(s);*
- ii) *To determine if any such cause is related to the drug(s) administered and procured from the PIC, Lahore;*
- iii) *If the drug reaction is established as the cause of death and/or ailment, to*

determine the source, manufacturing, processing, storage, dispensing and dosage of such drug(s);

- iv) To fix responsibility of lapses at each stage;*
- v) To make recommendation for averting such like incidents in future.*

1.3. The Notification empowered the Tribunal to co-opt any expert and/or person for the purpose of this inquiry. Syed Shahid Nasir, Ex-Member, Central Licensing Board, Cabinet Division, 207-Sector “S”, Phase-II, DHA, Lahore, was co-opted as an expert. It was directed that he shall attend all hearings of the Tribunal.

1.4. In the course of its working, the Tribunal summoned and examined seventy two witnesses who placed thousands of documents on record. An effort was made to examine a wide range of witnesses who could possibly have any information regarding the facts, circumstances, causes and effects of the aforementioned catastrophe. The witnesses who appeared before the Tribunal included doctors, representatives of the Punjab bureaucracy, pharmacists, representatives of WHO, employees of the Punjab Institute of Cardiology, representatives of the distributor of pharmaceutical products, Government Analysts, Federal and Provincial Drug Inspectors, employees of Efroze Chemicals Industries (Private) Limited, Pharmacologists, Pathologists, epidemiologists, Histopathologists, Advocates, representatives of the Investigating Agencies, Professors of reputable medical institutions, Director of the Punjab Forensic Science



Agency, Chief Chemical Examiner Government of Punjab, Chemical Examiners Office, independent experts including professionals from Agha Khan University Hospital, Karachi, Shaukat Khanum Memorial Cancer Hospital, Lahore, representatives of Pakistan Medical Association and members of the public who wanted to appear before the Tribunal.

SETTING UP THE INQUIRY

1.5 Design and operation of the inquiry process poses several unique challenges. The terms of reference which defined issues to be investigated and reported on, cannot be expected to advise as how to begin. I was fortunate in that I could consult my colleagues at the Lahore High Court who had spear headed other public inquiries for guidance. I thank them for their help and support.

PUBLIC INQUIRIES

1.6 A public inquiry in Pakistan is an official review by an inquiry tribunal of specific events or actions. Its purpose is to establish the facts and the causes of the subject matter of the inquiry, to fix responsibility and to make recommendations that may prevent the recurrence of undesirable events. An inquiry tribunal is not a civil or a criminal court of law, and the role of the tribunal is not to reach conclusions regarding the civil or criminal liability of any person involved in the subject matter of the tribunal.

1.7 By its very nature, the inquiry is investigative in its approach. It encourages an open, fair, efficient and transparent process. Every inquiry is unique, shaped by its mandate. While prior inquiries do provide guidance, each tribunal must design its own rules and procedures. That is a daunting

task. However, all inquiry tribunals in the past and, I am sure, in the future will look into three fundamental principles to guide the inquiry process ***“fairness, impartiality and transparency”*** and apply them at each stage of the inquiry with an open and unbiased mind.

BACKGROUND OF THE INQUIRY:

1.8 The inquiry was conducted with reference to three broad areas, namely, the Punjab Institute of Cardiology (PIC) whose patients suffered the drug reaction and many of whom, unfortunately died, the distributor who supplied the drugs



PIC



Efroze Chemical Industry

in question

and Efroze Chemicals (Private) Limited, the manufacturer of Isotab 20 mg, the drug that was ultimately found to be tainted/contaminated. Our report follows the same structure. Our analysis and findings

on each phase of the inquiry are reflected within the body of the report.

INQUIRY PROCESS

i) APPOINTMENT OF REGISTRAR:

One of the most important decisions we undertook at the outset of the inquiry was to appoint a capable and qualified Registrar to work closely with us through every stage of the process. Mr. Irfan Ahmad Saeed, District and Sessions Judge, was appointed as the Registrar of the Tribunal. His considerable experience as a Judicial Officer as well as having acted as Registrar of at least two previous Tribunals of inquiry, made him the best choice for the job. We are grateful for

his advice, professionalism and administrative skills in facilitating the work of the Tribunal.

We were also fortunate to have talented and dedicated Research Officers to assist the Tribunal in its work. Mr. Muhammad Amir Munir and Mr. Nadir Shah Gillani, Civil Judges and presently working as Research Officers at the Research Center of the Lahore High Court, rendered valuable assistance to the Tribunal by conducting research and organizing material produced by witnesses for the assistance of the Tribunal. We are thankful to both of them.

ii) COMMUNICATIONS AND MEDIA RELATIONS:

Mr. Irfan Ahmad Saeed, Registrar of the Tribunal also acted as the Communications and Media Relations Officer of the Tribunal. His experience with public inquiries was useful in interacting with the media on a subject as delicate and sensitive as the alleged contamination of cardiac drugs and occurrence of numerous deaths in the Province of Punjab.¹ His duties included



Media News regarding incident

¹ Even upto the submission of this Report, if words “drug reaction” are googled, the Lahore incident of drug reaction finds mention at the first page of fetched weblinks by google.

issuing daily press releases regarding proceedings before the Tribunal which were designed to keep the public informed without causing undue panic and/or a media frenzy.

iii) **INFRASTRUCTURE:**

The proceedings were conducted in the Judges Library (New Wing) of the Lahore High Court.

An audio recording system was put in place. The statements of witnesses and replies given by them in response to questions of the Tribunal were duly recorded through audio equipment. Transcripts

were prepared daily by Mr. Muhammad Tariq, Staff Officer/Private Secretary, Mr. Aamer Khalique Chishti, Private Secretary and Mr.



LAHORE HIGH COURT

Hearing Room LHC new Judges Library



Abad ur Rehman, Additional Private Secretary of the Tribunal. The transcripts were signed by the witnesses and were exhibited on record. Some of the witnesses also produced statements in writing which were duly exhibited on record in their statements under oath. In case the Tribunal raised any questions, the said witnesses responded to the same under oath. Such responses were

signed by the witnesses and exhibited on record as part of their statements. Some of the witnesses also produced documents which are duly marked and placed on record. Mr. Zia-ur- Rehman,

Reader/Custodian of Record of the Tribunal ensured proper maintenance of the record.

iv) **TERMS OF REFERENCE AND RULES OF PROCEDURE:**

The Terms of Reference of the Tribunal were incorporated in the aforesaid notification No.SO(JUDL-III)9-84/2012 issued by the Home Department, Government of Punjab. In terms of section 4 of the West Pakistan Tribunals of Inquiry Ordinance, 1969 (Ordinance II of 1969), the Tribunal had the powers of a civil court, while trying a suit under the Code of Civil Procedure, 1908. In terms of section 8 of the Ordinance, the Tribunal had the power to regulate its own procedure (including the fixing of places and times of its sittings and to decide whether to sit in public or in private). A copy of the Terms of Reference is attached to this report as **Schedule-1**.

v) **PUBLIC PARTICIPATION:**

On 7th February, 2012, the Tribunal passed an order directing the Registrar to issue notices to the General Public regarding commencement of the inquiry proceedings of the Tribunal. The general public and especially those who may have any information relating to the drug reactions manufacturing process, storage, dispensing and procurement of drugs and treatment provided at PIC or any other material or information, which may be helpful to the Tribunal in uncovering the truth were called upon to approach the Tribunal. In compliance with the order, notices were prominently published in various Urdu and English Daily Newspapers of wide circulation. (Copies of notices that appeared on behalf of the Tribunal in the newspapers are attached with this report). Pursuant to publication of the aforesaid notices representatives of Pakistan Medical Association and some private individuals filed applications which were duly entertained. All such persons were invited to appear before the Tribunal on specified dates. Some applicants did not turn up. Those who appeared before the Tribunal were heard and their statements were duly recorded. Some of the applicants prayed for grant of compensation

for loss of a blood relation on account of the alleged drug reaction. They were directed to file appropriate applications with the Government of Punjab or before the Special Tribunal appointed by the Government of Punjab headed by Mr. Justice (Rtd.) Muhammad Saeed Akhtar to process claims for compensation.

vi) **INVESTIGATION:**

During the course of inquiry, a large number of witnesses were summoned and examined. Each witness who was summoned, was informed beforehand the purpose of his appearance before the Tribunal and asked to bring his statement in writing in the form of an affidavit. He/she was asked to read the said statement/affidavit under a fresh oath before the Tribunal. The statement in writing was exhibited on record. Any questions of the Tribunal which were responded to by the witnesses under oath were transcribed and the witnesses signed the transcript. The documents produced by the witnesses were marked appropriately and placed on record.

The aforesaid procedure was adopted to make the proceedings of the inquiry transparent, more efficient and to remove any room for ambiguity about what was said. All witnesses consented to the aforesaid procedure. At no stage was there any disagreement.

Members of the public were given a right to appear before the Tribunal. Any person who expressed a wish to appear before the Tribunal was asked to approach the Registrar who gave such person an intended time and date on which the Tribunal would hear him/her. Owing to the sensitive nature of the inquiry and to avoid causing panic amongst public at large arising out of various facts which were likely to be probed by the Tribunal relating to the quality, safety and efficacy of pharmaceutical products manufactured within the Country, procedures followed by doctors, clinicians and the fact that hundreds of lives had been lost on account of alleged use of contaminated/spurious drug, it was considered appropriate and prudent to grant only limited access to

media persons who were provided the requisite information on a daily basis by way of a press release by the Registrar of the Tribunal. Television cameras and crews were not allowed to cover the proceedings. Hearings were conducted on day-to-day basis from Mondays to Fridays. I would like to thank all participants for their commitment to our schedule.

vii) **EXPERT WITNESSES:**

The Tribunal was fortunate to have the assistance of a number of experts in cardiology, pharmacology, medicine, chemistry, pharmacy, pathology, histopathology, epidemiology etc. Further, representatives of the World Health Organization



headed by Mr. Michael Deats, WHO Headquarter, Geneva, Muhammad Bin Shahana, WHO, EMRO Cairo, Syed Khalid Saeed Bukhari, WHO Country Office, Islamabad, and Miss Trudy Hilton of International Health Partners (IHP) UK, provided valuable assistance on the issues that needed to be addressed by the Tribunal. All four



witnesses are experts with extensive international experience in the field of drug regulation, pharmacy and pharmaceutical products. The Tribunal, in addition to placing on record the statements in writing produced by the witnesses, also questioned them on specific issues for in-depth analysis of the issues.



The exercise proved to be fruitful, useful and informative.

viii) **APPOINTMENT OF LOCAL COMMISSION TO VISIT KARACHI:**

During the course of proceedings before the Tribunal, it was considered necessary that experts be sent to physically visit the factory premises of Efroze Chemicals (Private) Limited at Karachi. The said factory manufactured and supplied a cardiac medicine namely Isotab 20 mg to the Punjab Institute of Cardiology which

was subsequently found contaminated with an anti-malarial drug named Pyrimethamine. It was considered necessary to obtain first hand factual information about the state of affairs at the



Hand Written Manufacturing Records

factory, manufacturing procedures and practices followed by it and the records and documentation maintained by the factory. It was also necessary to find out whether or not the factory was following the Good Manufacturing Practices ("GMP") and the Current Good Manufacturing Practices ("cGMP") which are of extreme importance for safe manufacturing of drugs. It may be pointed out that strict adherence to GMPs and cGMPs is internationally recognized and acknowledged as fundamentally important in manufacture of pharmaceuticals.

These represent the only and most effective safety nets to prevent



Efroze

contaminated and or defective drugs from getting out of the

manufacturer's factory and reaching hospitals' pharmacies, chemists, drug stores etc. and ultimately the patient. It may be kept in mind that once a contaminated drug gets out of the factory, it is almost impossible to trace and identify the contaminant. In any event, if at all it can be done, the process is long, cumbersome and expensive. In the meantime many human lives are exposed to grave and sometimes fatal danger.

Vide order dated February 16, 2012, Mr. Irfan Ahmad Saeed,



Efroze

District and Sessions Judge/Registrar of the Tribunal, was appointed as a Commission. With their consent and in view of their vast experience in the field of safe manufacture of pharmaceutical

products in compliance with GMPs and cGMPs the WHO Mission as well as Miss Trudy Hilton were asked to accompany the Commission as experts.

1.9 ***The mandate of the aforementioned Commission was as follows:-***

“(i) To visit Karachi on 17th February, 2012, and meet the following officials for the purpose of collecting information/data:-

(a) *The Area Federal Drug Inspector;*

(b) *The Investigating/ Inquiry Officer, who conducted investigation/partial investigation of the case on the part of the Federal Investigation Agency.*

(ii) To visit Central Drug Testing Laboratory, Karachi:

- (iii) To meet such other officials in the hierarchy of investigation and Health Department, Government of Sindh as they may consider necessary;
- (iv) To visit Efroze Chemicals Industries, Karachi. They shall be given access to the factory premises including production areas, storage areas and all other facilities of the factory. They shall also be provided full access to any or all records relating to production of medicines that may be available with the factory administration or with the investigating agency. It was further directed that all concerned staff of the factory shall be made available to the Commission to be interviewed for the purposes of obtaining information.” (Order of the Tribunal dated 16.02.2012)



Efroze Raw Material Store

1.10 The report prepared by the team headed by the aforesaid Commission was submitted before the Tribunal and is annexed with this report as Schedule 3.

1.11 Towards conclusion of recording of evidence and on the basis of material placed before the Tribunal, we were of the opinion that it will be in the interest of justice and



Korungi Creek Warehouse

will significantly clarify various issues which were still unclear if a visit to the factory premises as well as Kaurangi Creek warehouse (presence of which was discovered during the course of recording evidence) of Efroze Chemicals Industries is conducted from the point of view of assessing cGMP compliance by the said company. It was accordingly directed that the Co-opted Expert (to act as a Commission) accompanied by the Registrar of the Tribunal as well as Mr. Abad ur Rehman, Private Secretary of the



Tribunal shall go for the aforesaid inspection. It was also directed that the Federal Inspector of Drugs, the concerned Director, FIA, and Dr. Obaid Ali Chief Analyst of Central Drug Laboratory, Karachi shall also be present during the inspection. The second inspection report which focuses on GMP and cGMP compliance by Efroze Chemicals Industries (Private) Limited is also a part of this report as

Schedule-4.

EXPENDITURE:

1.12. With a view to ensure the independence of the Tribunal and transparency of its proceedings, every possible effort was made to ensure that the expenditure for conducting proceedings was kept to the minimum. Neither the Tribunal nor its Registrar or any of the other staff received or claimed any compensation, allowance or other monetary benefit from the Government of Punjab, any of its agencies or departments or any private party. Being employees of the Lahore High Court, the entire staff received their regular salaries and allowance from the Lahore High Court without claiming any additional benefit for the immense amount of additional labour

and strife much beyond the regular working hours, that went into conducting this inquiry.

1.13. The Coopted Expert also did not receive any remuneration or compensation for his services and agreed to perform the same gratis in national interest. He was provided pick up and drop transport facility by the Health Department Government of Punjab, from his residence in DHA Lahore, to the Lahore High Court, to attend proceedings of the Tribunal.

1.14. The first team that visited Karachi consisted of the Local Commission, i.e., the Registrar of the Tribunal, three Members of the WHO Mission and one representative of International Health Partners. The Members of the WHO Mission paid for their own air travel, boarding, lodging and transportation. The representative of the International Health Partners was an official guest of the Government of Punjab having come to Pakistan on the invitation of the Government of Punjab to help deal with the situation arising out of drug reaction related deaths. Her air travel, boarding and lodging were arranged by the Government of the Punjab. The Commission/Registrar of the Tribunal made his own arrangement for boarding and lodging at Karachi. His air travel was arranged by the Government of the Punjab in view of his official assignment.



ISOTAB Tablet

1.15. The second team consisted of the Co-opted Expert, the Registrar and the Private Secretary of the Tribunal. The air travel, boarding and lodging arrangements of the Co-opted Expert and the Private Secretary of the Tribunal were made by the Government of Punjab. The Registrar of the Tribunal made his own boarding and lodging arrangements. His travel from Lahore to Karachi was arranged by the Government of Punjab in view of his official assignment. Details of all expenses incurred during the proceedings is given as **Schedule-8**.

1.16. At the conclusion of the hearing, I sought further assistance from some experts relating to additional factual and technical aspects which needed clarification. This was done through re-summoning such experts as witnesses and their examination by the Tribunal. Their additional statements also constitute a part of the record.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER -2-



FIRST SIGNS OF DRUGS CONTAMINATION

2.1 In the middle of December 2011, patients started appearing in various hospitals of Lahore with symptoms of bleeding, nausea and unexplained darkening of skin. Shortly thereafter reports started appearing in the electronic and print media that patients were dying of drug reactions. There was considerable difference of opinion and controversy amongst doctors and health care professionals within the hospitals as well as on panel discussions which were transmitted by various television channels about the causes of such deaths. One set of experts suggested that the deaths were being caused by Dengue Virus or by reason of toxicity caused by the said virus. The other opinion was that the symptoms and resulting deaths were possibly caused by some drug reaction.

The news of these mysterious deaths has been doing the rounds since early January, and the current death toll (at the time of reporting) stands at 75, with over 200 patients (from all over Punjab) admitted in Lahore's Mayo, Jinnah, Services, General and Ganga Ram hospitals. Medicines issued by the Pakistan Institute of Cardiology (PIC) remain the common link among these patients.

<http://dawn.com/2012/01/27/bad-medicine-2/>

2.2. During the last quarter or so of 2011 the City of Lahore was inundated by a serious outbreak of dengue fever. This led to the deaths of over 300 patients and placed health services under severe strain. This situation forced the Government of Punjab to implement increased surveillance and monitoring for patients approaching hospitals with symptoms of dengue fever. It also led to the establishment of an expert panel of doctors headed by Professor Dr. Faisal Masud, Principal Services Institute of Medical Sciences ("SIMS") to monitor the situation.

2.3. Some of the symptoms exhibited by patients reporting to hospitals in December, 2011, were quite similar to those exhibited by

patients suffering from dengue fever, namely, bleeding, low platelet count and low white blood cell (“WBC”) Count. On the other hand, doctors and surveillance teams set up by the Government of Punjab were reporting zero *AEDSAEGYPTI* Larva (Larva of the mosquito that carries the Dengue Virus) Detection².

2.4. By the end of December, 2011, there was a surge in deaths involving over fifty patients. Experts were baffled that the normal vectors for dengue

59 fresh cases of fever reported in different hospitals across metropolis

http://www.dailytimes.com.pk/default.asp?page=2012\02\27\story_27-2-2012_pg1_4

were diminishing while the suspected cases of dengue were increasing. This presented a dilemma. Some of the clinicians, however, noticed that the usual symptoms associated with dengue, particularly high fever, were absent. Professor Dr. Faisal Masud privately kept track of the cases being reported to different hospitals and discovered that in sixteen cases monitored by him, patients were suffering from reduced white blood cell count, reduction in platelets and bone marrow suppression but no fever. These findings suggested a toxic reaction either by drug over-dose or contamination.

2.5. It appears that a large number of patients who reported at



PLC Free Dispensary

the Punjab Institute of Cardiology were suffering from nausea, bleeding and darkening of skin. They were referred to Services Hospital, Mayo Hospital, Jinnah Hospital and other hospitals for

² Report of the Chief Minister's Inspection Team Dated 28.01.2012.

treatment of dengue in view of the fact that PIC is a specialized cardiology hospital. A team of doctors which was monitoring the situation soon established a key common denominator in all patients. It was discovered that all patients who had reported to different hospitals were cardiac patients and had received a range of five medicines from the free pharmacy of Punjab Institute of Cardiology, Lahore. The drugs in question had been dispensed around the first week of December 2011.

2.6. The fact that the concerned teams of doctors were able to draw some basic and vital conclusions within a matter of few weeks and eliminate dengue virus or any of its strains or complications as the cause of the symptoms, became possible on account of the following factors:

- i) patients exhibited some dengue like symptoms;
- ii) the outbreak of dengue fever in 2011 had increased systematic vigilance at the government level;
- iii) the contaminated medicine was only distributed by one hospital;
- iv) patients approached hospitals in Lahore; and
- v) the geographic concentration enabled the identification of common denominators and coordination between hospitals/doctors within a reasonable time.

CLINICAL RESPONSE

2.7 On the basis of his findings that patients reporting to different hospitals with symptoms of bleeding, pigmentation of skin, low platelets count and bone marrow suppression were not suffering from Dengue and all of them were cardiac patients, who had received free medicines from the free dispensary of PIC, Dr. Faisal Masood contacted Professor Dr. Muhammad Azhar, Chief Executive of PIC on 11.01.2012. He informed Professor Dr. Muhammad Azhar that the patients were probably reacting to one or more drugs dispensed to cardiac patients.



Prof. Dr. Muhammad Azhar of PIC called an urgent meeting of the Hospital Committee of PIC on 12.01.2012, which was attended by 22 doctors working at PIC. He informed the meeting that the patients were reporting with bone marrow suppression and Pancytopenia in different hospitals and these patients had been mainly taking cardiac medication issued by the Free Pharmacy of PIC. There was a high possibility of drug reaction being caused by one or more of these drugs. It was therefore, decided that the department of health may be requested to constitute a technical committee for an epidemiological study to investigate the cases admitted in different hospitals with complaints of bone marrow suppression and Pancytopenia. It was further decided to send samples of all drugs available in PIC Out Patient Department ("OPD") to the Drug Testing Laboratory/Forensic Laboratory for report and fresh analysis. In addition, the committee recommended that all cardiac medicines in tablet form being issued to OPD patients should be stopped except Tablet Atenolol and Tablet Isotab, for the

safety of cardiac patients till further orders. By way of a stop gap arrangement, the committee approved a list of medicines and recommended that the Health Department may be requested to allow purchase of the medicines/alternate medicines as an emergency.

2.8. It is significant to note that the said committee also recommended that the Government of Punjab Health Department be approached for purchase of cardiac medicines from multi-national companies for safety of patients and to avoid such drug reaction in future. Further, it was decided that the Government may be requested to devise new procurement rules in this regard. It was also decided that the firms who had supplied the medicines to PIC may be asked to submit drug testing reports with PIC. The committee also decided to inform the public through press and television about use of cardiac medicines taken from the free pharmacy of PIC.

2.9. Six dedicated phone numbers were to be provided and it was directed that a doctor and a pharmacist will be available on the helpline round the clock to provide advice and guidance.

2.10. Professor Dr. Muhammad Azhar also informed the meeting that he had talked to Secretary Health about the issue. The health department had advised to constitute a special committee including Cardiologists and 3 pharmacists from other hospitals to advise about the use of cardiac medicines. A committee headed by Dr. Nadeem Hayat Malik, Professor of Cardiology PIC, Lahore was accordingly constituted. The 9 members committee included a pharmacist from Jinnah Hospital Lahore as well as Services Hospital Lahore in addition to hospital pharmacist of PIC

and senior doctors of cardiology working at PIC. A 24 hour monitoring room was set up for creating public awareness on the telephone. The said committee met the same day. (Minutes of the meeting of the hospital committee held on 12.01.2012 are Mark IW-1/7).

2.11. On the same day i.e. 12.01.2012, the special committee met under the chairmanship of Dr. Nadeem Hayat Malik, Professor of Cardiology, PIC Lahore at noon. The said committee reiterated the recommendations of earlier committee. However, this committee recommended that all cardiac medicines in tablet form (including Atenolol and Isotab) being issued to OPD patients be stopped for safety of cardiac patients till further orders. This committee also recommended that by way of a stop gap arrangement an approved list of medicines recommended by the hospital consultants committee be procured as an emergency case after seeking permission from the health department. This committee also reiterated the earlier recommendations that Punjab Health Department may be approached for purchase of cardiac medicines from multi-national companies.

**COMMITTEE SET UP BY THE
SECRETARY HEALTH**

2.12. On 13.01.2012, the Secretary Health, Government of Punjab issued notification No.SO(H&D)1-36/2012(EC). Through this notification, a committee was constituted to probe into the incidents of mortalities of cardiac patients due to alleged drug reactions as reported in certain segments of the media. Professor Dr. Muhammad Azhar, Chief Executive PIC/Head of the Institute was the convener of the said committee. Professor Dr. Faisal Masood, Principal Services Institute of Medical Sciences, Professor Arif Mehmood Siddiqui, Professor of Medicine, Allama Iqbal Medical College, Lahore, Professor Dr. Saeed Anwar, Professor of Pharmacology, Allama Iqbal Medical College and Professor Dr. Naveed Iqbal Ansari, Professor of Pharmacology, Gujranwala Medical College were its members. The mandate of the committee was to ascertain the veracity of the facts mentioned in the press reports and furnish its report within 48 hours to Health Department.



2.13 The committee met and submitted its report dated 14.01.2012 to the Secretary Health, Government of Punjab. It observed that the cause of mortalities in cardiac patients was likely to be Idiosyncratic reaction to some ingredients in one of the cardiac medicines dispensed to patients causing bone marrow suppression at the level of stem cells. The committee observed that it was difficult at that point in time to define the exact nature of the problem. However, it identified top five common denominator drugs in the order of frequency to be tested by Professor Dr. Naveed Iqbal Ansari, Professor of Pharmacology, Gujranwala Medical

College at the Drug Testing Laboratory Lahore. The following drugs were identified:-

- i) Cardiovestin 20 mg manufactured by Mega Pharmaceuticals.
(Simvastatin)
- ii) Soloprin 300 mg manufactured by Pharma Wise.
(Soluble Aspirin)
- iii) Corcont 5 mg manufactured by Swiss Pharmaceuticals.
(Amlodipine Besylate)
- iv) Zafnol 50 mg manufactured by Zafa Pharmaceuticals.
(Atenolol)
- v) Isotab 20 mg manufactured by Efroze Chemical Industries.
(Isosorbide Mono Nitrate)

2.14 The committee directed that batches of suspected drugs be taken into custody in accordance with legal procedures. Professor Dr. Naveed Iqbal Ansari was to help the committee, personally supervise putting together batches of the said 5 medicines, prepared according to the procedure and protocol of the concerned manufacturer uptill the level of packing. It was directed that the standard manufacturing batch will be tested by HPLC procedure against the batches of all five medicines

confiscated from the hospital. Results were to be presented before the Committee.

2.15. The aforesaid committee also approved the recommendation of the special committee of PIC regarding stop gap arrangement for purchase of medicines. It also recommended that dispensation of all five medicines mentioned above may be stopped immediately in all government hospitals and alternatives may be used as it was unlikely that active ingredients were causing reactions. This committee also endorsed the earlier recommendation that the government may be advised to formulate new procurement rules for purchase of quality medicines.

2.16. The samples of 05 medicines identified by the committee were tested at the Drug Testing Laboratory, Lahore (DTL) on 14.01.2012. DTL took about a week to test the samples and prepare its reports. As per DTL reports, the following results were communicated:-

- i) DTL Report No.40 dated 21.01.2012
03 Batches of Cardiovestin were declared of standard quality;
- ii) Report No.41 dated 21.01.2012,
02 Batches of Cardiovestin were declared substandard;
- iii) All other medicines were declared to be of standard quality except for certain procedural errors like failure to mention Maximum Retail Price (MRP) etc.

2.17. As per report of the Drug Testing Laboratory (DTL), the sample tablets of Cardiovestin had brown spotting on the surface as well as

the inner core and there was an abnormal peak in the finger print. However, the DTL stated that they were unable to find the reason for abnormal peak in the finger print as the Laboratory did not have the capacity to measure or identify unknown ingredients.

2.18. It appears that the Drug Testing Laboratories in Pakistan as well as other parts of the World test drugs only to confirm presence of Active Pharmaceutical Ingredients (API) mentioned on the label and as specified in the Standard Formulation of said drug in the pharmacopeia. The methodology for testing of the active ingredients is provided by the manufacturer. The names and quantities of other materials or excipients (inactive ingredients) in the medicine are neither mentioned on the label nor are the same tested. It may be noted that a particular pharmaceutical product may consist of one or more Active Pharmaceutical Ingredients, which is the actual medicine in the drug in addition to many other ingredients/excipients which are inert. These are used as anti-adherents, binders or coating and have no medicinal value or function. These include pre-gelatinized starch, talcum powder, stearate etc. The

“Active Pharmaceutical Ingredient”

means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient)

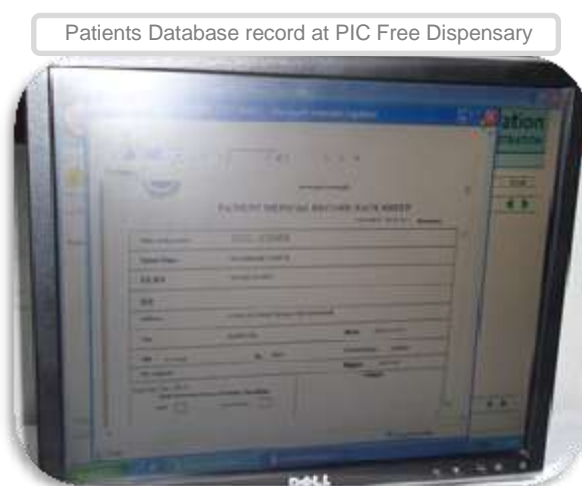
Rule 2(aa) of the Drugs (Licensing, Registering & Advertising) Rules. 1976

Drug Testing Laboratories do not test such excipients. Further, in view of the fact that there are thousands of chemical compounds in the world, it is not possible by ordinary methods to check for and establish the identity of an unknown/unidentified chemical compound in a medicine. As a corollary, if any harmful ingredient finds its way in a medicine, routine laboratory testing as conducted by the Drug Testing Laboratory to measure and verify

the existence of the Active Pharmaceutical Ingredient (API) in accordance with the label claim, cannot identify the presence of the harmful ingredient. Therefore, as would be discussed in the later part of this report, it is fundamentally important that extreme care and caution be exercised and strict and fool proof standardized steps and procedures be put in place backed by immaculately maintained records and documentation for the manufacturing process to ensure that no mixing or contamination takes place in a medicine at the time of its manufacture.

2.19. In view of the fact that barring technical issues with some of the samples sent for testing and there being no clear cut finding regarding contamination of any of the medicines and confirmation of the fact that the Active Pharmaceutical Ingredients were present in all samples, the aforesaid committee correctly formed the opinion that there was likelihood of contamination in one or more of the excipients used as anti-adherents binders, coatings or in some other material used at the time of manufacture of the tablets which were causing an adverse reaction. They were of the opinion that the cause of the suspected re-action which affected bone-marrow could be finally determined only if the culprit excipient was identified.

2.20. It appears that between 14th of December, 2011 and 21st of December, 2011, efforts were made to approach cardiac patients, who had received one or



more of the aforesaid five medicines from the free pharmacy of PIC to advise them to stop using the said medicine and use alternate medication. In this regard, some data available in the Computerized Database of PIC which contained names, addresses and in some cases mobile telephone numbers of patients, was utilized to establish contact with such patients. It was a daunting task in view of the fact that during a period of about 06 weeks, approximately 46000 patients had received medication from the free pharmacy of PIC. According to the information provided to the Tribunal only about 8000 patients could be directly contacted by telephone.

2.21 In the meantime, the Health Department issued directions to the manufacturers of the five drugs mentioned above, immediately to withdraw the medicines from the market. Directions were also issued to all Medical Superintendents of Teaching and DHQ Hospitals to stop using the suspected medicines. Similar instructions were also sent to all the Executive District Officers (Health) in Punjab. The Tribunal has reason to believe that such instructions were followed.

2.22 On 21.01.2012, vide notification No.SO (DC) 06.06.2011, the Secretary Health, Government of Punjab constituted a 19 Members Technical Committee of experts headed by Dr. Javed Akram, Principal, Allama Iqbal Medical College, Lahore. The committee was inter alia mandated to initiate a scientific investigation into the incidents of deaths to ascertain the facts regarding adverse drug reaction and formulate guidelines for treatment. It was also required to suggest a drug retrieval mechanism for retrieval of the culprit drugs from patients of PIC. The committee held its meetings on 22.01.2012 and 23.01.2012 in the Committee Room of Allama Iqbal Medical College, Lahore. After due

deliberations, the committee constituted 08 specialized sub-committees.

The specialized sub-committees were as follows:-

- i) **Analysis Committee** headed by Professor Hamid Latif, Professor of Chemistry Department, University of the Punjab, Lahore. (Later on Dr. Muhammad Ashraf Tahir, Director General Forensic Science Agency, Punjab replaced him for technical reasons);
- ii) **Postmortem Board** headed by Dr. Muhammad Ashraf Tahir, Director General Forensic Science Agency, Punjab, Lahore;
- iii) **Drug Retrieval Committee** headed by Dr. Zahid Pervaiz, Director General, Health Service, Punjab;
- iv) **Epidemiology Committee** headed by Dr. Farkhanda Kokab, Institute of Public Health, Lahore;
- v) **Clinical Guidelines Committee** headed by Professor Faisal Masud, Principal, Services Institute of Medical Sciences, Lahore;
- vi) **Legal Committee** headed by Mr. Kashif Javed, Prosecutor for Drug Courts, Prosecution Department, Government of Punjab, Lahore;
- vii) **Production Surveillance Committee** headed by Dr. Farzana Chaudhry, Chairperson, Pharmacy Department, University of Veterinary Sciences, Lahore; and
- viii) **Information Dissemination Committee** headed by Khawaja Salman Rafique, MPA.

2.23. On the same day i.e. 23.01.2011, the Health Department issued letters to manufacturers of the aforesaid five medicines directing them to furnish the following details:-

RAW MATERIAL
(Active and inactive ingredients)

- i) *Source*
- ii) *Purchase Record*
- iii) *Test Analysis Certificate by the manufacturer of raw material*
- iv) *Storage conditions of medicines and the raw material*
- v) *Raw material consumption record;*
- vi) *Internal test/analysis record.*

MANUFACTURING/PRODUCTION RECORD

- i) *Total number of batches produced;*
- ii) *Batch size;*
- iii) *Complete batch record;*
- iv) *Internal Quality Control arrangements;*
- v) *Storage instructions for finished goods;*
- vi) *Source of packaging material*

SALE/ADMINISTRATION

- i) Batch sale record;*
- ii) Name and addresses of distributors/whole sellers and government institutions;*
- iii) Date of supply of the batch;*
- iv) If supplied to PIC only, certificate to be furnished.*

2.24. The manufacturers were also directed to get their manufacturing units inspected for current Good Manufacturing Practices (cGMP Compliance) and also furnish a certificate that cGMP Standards had been followed during the manufacturing processes of the said drugs. Simultaneously, the Chief Drug Inspector addressed letter dated 23.01.2012 to the Drug Controller (Licensing) Cabinet Division, Block-C, Pak Secretariat, Islamabad requesting him to nominate inspection teams to check the GMP Compliance by Efroze Chemical Industries, Karachi (Tab. Isotab 20mg), Swiss Pharmaceuticals, Karachi (Tab. Corcont), Zafa Pharmaceuticals, Karachi (Tab Atenolol 100 mg), Mega Pharmaceutical Pvt. Ltd., Lahore (Tab. Cardiovestin 20mg) and Pharma Wise Laboratories, Lahore (Tab. Soloprin). On the same day, the Chief Drug Inspector, Punjab also addressed letters to all Drug Inspectors in Punjab directing them to check the availability of the afore-noted drugs in the market and to ensure that the said drugs were not sold in the market.

2.25. The Health Department also issued a letter to PIC directing it to establish separate counters for patients who had received the suspected medicines and to make available alternate combinations of drugs at these counters to patients free of cost. Further, a direction was issued to retrieve

the aforesaid medicines from patients by constituting special teams at district level. Such teams were directed to start work immediately. Patients from whom these medicines were retrieved were asked to contact PIC, Lahore for supply of substitute medication.

2.26. The Health Department also initiated a public awareness campaign through print and electronic media. Patients were informed that helplines had been set up at PIC and patients, who had received medicines from PIC between 21st of December, 2011 and 10th of January, 2012 may return the said medicines and receive alternate medicines.

2.27. Another Committee headed by the Chairman of the Chief Minister's Inspection Team consisting of a Professor of Medicine, Professor of Cardiology, Professor of Pharmacology, Director General, Punjab Forensic Science Agency, Principal, Services Institute of Medical Sciences, Lahore etc. was also constituted to investigate and inquire into the matter and submit a report within 48 hours. The committee submitted an interim report on 22.01.2012. However, owing to complexity of the issue, it sought more time to finalize its report. The final report was submitted on 28.01.2012 in which useful recommendations were made, however, conclusive findings were not given on account of non-availability of sufficient data and the non-conclusive nature of investigation undertaken by the investigating agencies.

2.28. It may also be pointed out that on 24.01.2012, an FIR was lodged with Police Station Shadman within whose jurisdiction PIC is located alleging that deaths had occurred on account of drug reaction to Soloprin, Cardiovestin, Isotab, Alphagril and Corcont; out of the said medicines one

2.29. In a hasty and knee jerk reaction, immediately after lodging the aforesaid FIR, the Punjab Police arrested members of the senior management of the aforesaid companies for the purpose of interrogation. The Federal Investigating Agency (FIA) was also alerted, who also took some members of the management of the manufacturing companies into custody for interrogation.

2.30. The first priority of the Government of the Punjab in these circumstances should have been to protect public health. Despite the fact that the Chief Minister, Punjab was out of the country, the health department made efforts by involving experts of various disciplines who could provide assistance in this regard to establish the cause, putting in place a treatment regime and recalling/retrieving suspected medicines from patients. The next priority was to carry out an investigation to determine cause, fix responsibility and take action in accordance with law. These efforts required team work and coordination with a focal person being aware of all developments to take decisions at a senior level. The Secretary Health (who was suddenly changed for reasons not entirely clear) and the Special Secretary Health Mr. Daud Bareach performed the aforesaid function.

2.31. It is also pertinent to point out that after submission of the report by the Chief Minister's Inspection Team, the Chief Executive, Superintendent, Members of the Medicine Inspection Committee as well as the Store Keeper of Punjab Institute of Cardiology were placed under suspension.

2.32. The Chief Minister, Punjab, who amongst others, also holds the portfolio of Health Minister, chaired a meeting in the evening of 23.01.2012 on his return from abroad. The said meeting was attended by

most of the experts who were members of 08 sub-committees constituted earlier. They briefed him regarding technical aspects of the matter. In view of the fact that efforts to identify the contaminant that was causing the reaction had not succeeded, it was decided to take immediate steps to



send samples taken from the store of PIC as well as those recovered from patients, who had suffered from drug re-action, separately packed, to different laboratories in UK, USA and France for testing and possible

identification of the contaminant. Two officers of the Government of Punjab, who happened to have valid visas for UK and France etc. were dispatched to UK with the samples. With the assistance of International Health Partners (IHP),³ a British Charity active in Pakistan, they submitted the samples of all five suspected drugs to the London



School of Pharmacy (LSP). The testing undertaken at LSP revealed that one of the medicines namely Isotab manufactured by Efroze Chemical Industries, Karachi, containing 20mg of Isosorbide-5 Mononitrate, also contained a significant quantity of an unknown ingredient. However, on account of non-availability of the requisite equipment and facilities required to identify the unknown ingredient, the samples were sent to the laboratory of Medicines and Healthcare Regulatory Agency (MHRA) UK⁴ for more advanced analysis. They had state of the art equipment and trained analysts to undertake an assignment of this nature. They also had access

³ <http://www.ihpuk.org/>.

⁴ <http://www.mhra.gov.uk/#page=DynamicListMedicines>.

to a Poison Control Center/Database of UK in addition to other data information and technical facilities. They were also provided material information including blood test reports and slides including bone-marrow analysis of patients who had died, to assist them in identifying the contaminant. The MHRA Laboratory succeeded in identifying the contaminant as Pyrimethamine with each tablet of Isotab 20mg manufactured by Efroze Chemical Industries, Karachi containing approximately 50mg of the said contaminant. Pyrimethamine is used, amongst others, as an anti-malarial drug. One of its properties is that it causes bone marrow suppression. It subsequently transpired that Efroze Chemical Industries, Karachi is licensed to manufacture Maladar tablets and syrup in which pyrimethamine is used as the Active Pharmaceutical Ingredient. The normal dose of pyrimethamine for a person is 25mg per week for 03 weeks. Ingested in controlled doses and under medical supervision it is a cure for malaria. However, patients of PIC, who were prescribed Isotab 20mg were taking 02 to 03 tablets per day. They were, therefore, unknowingly ingesting 100-150mg pyrimethamine on daily basis instead of 25mg per week. This equates to about 14 times the normal dose for a patient and can cause very serious medical complications. It is also significant to note that pyrimethamine is an anti-malarial drug and was not one of the ingredients of Isotab 20mg, which is an anti-angina cardiac medicine. The symptoms displayed by patients i.e. bleeding, low blood platelets, bone marrow suppression, skin pigmentation are classical symptoms of pyrimethamine over dosage.

2.33. It may also be noted that contamination was found only in one batch of Isotab 20mg namely Batch No.J093 manufactured by Efroze

Chemical Industries, Karachi. The tests did not show any contamination in other batches of Isotab 20mg nor did the reports identify any significant or life threatening defects in samples of other medicines sent for testing.

2.34. According to the information provided to the Tribunal, the methodology used by MHRA to identify the contamination was as follows:-

- i) *Gas Chromatography/Mass Spectroscopy (GC/MS). This separates the ingredients of a medicine and allows identification by comparing the Mass Spectrum of any peaks dedicated to a special ingredient;*
- ii) *Liquid Chromatography/Mass Spectroscopy (LC/MS). This separates the ingredients and allows identification by comparing the mass spectrum of any peaks dedicated to the mass spectrum of corresponding peaks from a reference standard. Based on the GC/MS Laboratory match, the standard of pyrimethamine was injected to confirm its presence in the sample of Isotab 20mg Batch J093 by LC/LS;*
- iii) *The samples were also tested by Infrared Spectroscopy FTIR. This gave a match to the reference standard of pyrimethamine.*

2.35. The Tribunal has been informed that the techniques used by MHRA are more commonly used in Forensic Chemistry Laboratories. It constituted an investigative approach rather than normal testing of pharmaceutical products to confirm the label claims of active pharmaceutical ingredients. We have also been informed that the detection of the contamination within a span of 4 or 5 days was sheer good luck on the part of the investigators/analysts as it can possibly take months of intensive testing to find and identify a contaminant. Various examples of drug contamination in industrial and scientifically advanced countries

including US have been cited where despite availability of the latest and state of the art equipment and highly qualified experts, it took months to detect and identify a contaminant.

2.36. Different batches of the aforesaid drugs were also sent to laboratories in France and USA, which also confirmed the findings of MHRA relating to presence of pyrimethamine in Isotab 20mg, Batch J093 manufactured by Efroze Chemical Industries.

2.37 The Tribunal has also been informed that samples of different batches of the suspected drugs were earlier sent to DTL, Lahore. The Central Drug Laboratory, Karachi and Hussain Ebrahim Jamal (HEJ) Institute, University of Karachi for analysis. The aforesaid laboratories/institutes were not able to identify the contaminant on account of lack of equipment/technical skills, data base and an investigative approach. Likewise, efforts to identify the contaminant by involving PCSIR, Pharmacy Department, University of the Punjab and Office of Chemical Analyst, Punjab etc. did not bear fruit for the same reasons.

2.38. The findings of MHRA were immediately communicated to the Government of Punjab on 31.01.2012.

2.39. From the literature produced before the Tribunal and statements of various experts including doctors, pharmacists, pathologists etc. Pyrimethamine is known to cause symptoms of bone-marrow suppression, blackening of skin and lowering of white platelets. On this basis, it was concluded that pyrimethamine contamination in Isotab 20mg, Batch J093 manufactured by Efroze Chemical Industries, Karachi was the real cause of the adverse drug reaction in patients. Experts at MHRA were

able to quickly make the connection on the basis of their analysis of the drug, data base of poisons available to them and information regarding bone marrow reports provided to them to identify the contaminant as Pyrimethamine. The MHRA also shared this information with the team of World Health Organization (WHO) that was supporting investigation of this matter.

2.40. MHRA further informed the Government of the Punjab that pyrimethamine related bone marrow suppression could be treated with Calcium Folate. Information in the tox-base dated 21.01.2012 and other related information in the relevant literature shows that pyrimethamine toxicity is treatable with Calcium Folate, which is an antidote for the said condition.

2.41. The Royal Free Trust Hospital,⁵ Hampstead UK played a generous role in this regard. It arranged to send Calcium Folate Injections from England for patients in Pakistan. The Government of Punjab also made immediate arrangements to procure calcium folinate injections locally and made the same available in sufficient quantities in all concerned hospital. The following guidelines were framed by the committee of doctors constituted by the Government of the Punjab and issued through the Secretary Health to all hospitals for treatment of patients suffering from bone-marrow suppression due to adverse drug re-action:-

- i) *provide 30mg of Folinic Acid 06 hourly for 02 days and then 12 hourly till the patient is fully cured;*

⁵ <http://www.royalfree.nhs.uk/>.

ii) Stop all steroid treatment and continue supportive treatment

2.42. We have been informed that on account of the anti-dote having being found and administered, majority of patients, who were under treatment, started recovering quickly barring those patients whose bone-marrow structure had been so irretrievably damaged or who had developed other complications directly related to pyrimethamine over dose that the anti-dote failed to improve their condition or help in their recovery. Such patients did not survive.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER -3-



PUNJAB INSTITUTE OF CARDIOLOGY (PIC)

3.1. PIC has been operating since 1988. The hospital specializes in cardiology. It treats thousands of outpatients and inpatients around the year. On the initiative of the Government of Punjab, PIC has set up a Free

PIC new Campus



Pharmacy. Outpatients are issued cards and are provided free cardiac medicines for up to one month at a time. When the dispensed quantity of medicines is consumed, on presentation of the card which is endorsed by a doctor, another

month's supply of medicines is issued. Most of the times the patient does not undergo any detailed examination or tests. Medicines are issued as a matter of routine, unless the patient complains of any complication in which event he is examined by a doctor. It appears that after three months the patient is expected to have a blood test done, produce its report before a doctor who may renew the prescription and make adjustments that he may consider necessary. We found that the process of testing and examination is not meticulously followed.

3.2. PIC was dispensing five medicines in different combinations to patients. Some of the patients subsequently started reporting adverse reactions.

PIC old Campus



The said medicines were:-

S.No.	Active Pharmaceutical Ingredient	Brand Name	Indication	Manufacturer
1.	Aspirin 300mg	Soloprin	NSAIDS	Pharmawise Lab. Lahore
2.	Atenolol 100 mg	Atenolol	Beta Blocker	Zafa Pharmaceuticals, Lahore.
3.	Amlodipine Besylate 5 mg	Corcont	Ca Channel Blocker	Swiss Pharmaceuticals, Karachi.
4.	Isosorbide-5-mononitrate 20 mg	Isotab	Anti-Anginal	Efroze Chemical Industries, Karachi.
5.	Simvastatin 20 mg	Cardiovestin 20mg	Anti-Lipidemic	Mega Pharmaceuticals, Lahore

3.3. PIC maintains computerized patient records which showed that between 1st of December, 2011 to the second week of January, 2012, 46000 patients had been dispensed a combination of the aforementioned medicines (**See the record produced by IW-20 Mr. Dawood Bareach, Special Secretary Health**). This record included some telephone numbers and addresses on the basis of which such patients could be contacted. As soon as Isotab-20 mg was identified as the contaminated medicine, the hospital confirmed that it had dispensed this medicine to a large number of patients with instructions to take them two or three times a day.

PROCUREMENT OF ISOTAB 20-MG TABLETS

3.4. PIC had been procuring Isotab 20 mg for the past two years through Umar Traders, a distributor of various pharmaceutical companies

including Efroze Chemical Industries, the manufacturer of Isotab. The procurement is allegedly done in accordance with the provisions of Punjab Procurement Rules, 2009 (PPR). The record examined by the Tribunal indicates that a tender notice in the daily newspapers was published on 12.5.2011 for purchase of various items including medicines on the basis of Annual Rate Contract. (Copy of the advertisement is Mark IW-12/8, 8/38). Sixty-four firms purchased tender documents (Mark IW-12/10 and 12/12). Tenders were received and technical bids were opened on 20.5.2011. Fifty-one firms participated in the tender (Mark IW-12/9). A single stage two envelop bidding procedure as laid down under the Punjab Procurement Rules was adopted. (See Rule No.36(b) of PPR, 2009). These bids were scrutinized by a committee (No.AO-Com/PIC19475 dated 15.06.2011) and a report prepared. Copy of the report is mark IW-8/40. Subsequently, financial bids were opened on 10.9.2011 (Mark IW-12/9). A comparative statement was prepared. A copy of the comparative statement is mark IW-8/42. A negotiations meeting was held on 27.9.2011 (Mark IW-8/41) and purchase orders were issued to the lowest bidders (Mark IW-8/43). In view of the fact that after negotiations, the bid of Umar Traders for supply of Isotab 20 mg manufactured by Efroze Chemical Industries was the lowest, the contract was awarded to Umar Traders for that year for supply of 8.8 million tablets of Isotab 20 mg. The Hospital had the option to place orders throughout the year at the said rate for such quantities of medicines as it anticipated to be its requirement during that year. In the first place PIC issued a supply order to Umar Traders on 17th September, 2011 for 100 thousands packs of Isotab 20 mg containing 20 tablets per pack (2 million tablets) at a cost of Rs.760,000/- (Rs.7.60 per pack – Rs.0.38 per tablet) for delivery within thirty days. (Mark IW-8/37).

3.5. Under the Punjab Procurement Rules 2009 neither annual rate contract was permissible nor could negotiations have been undertaken. The PIC administration for some reason assumed that under the said rules rate contract and negotiations were permissible. However, the inquiry conducted by the Chairman, Chief Minister's Inspection Team did not find any *mala fide* on the part of PIC administration in this regard. He opined that PIC administration had tried to follow the rules as per their own understanding. According to him, lack of understanding the rules at the implementation stage was not restricted to PIC. The clarification issued by Health Department vide letter No.SO(PIII)2-3/2010 (P) dated 22.12.2011 shows that there was some confusion in this regard which needed clarification (see statement of Medical Superintendent PIC (IW-12)). Our inquiry also confirmed absence of mala fides or deliberate violation of PPR, on the part of administration of PIC.

3.6 The consignment of Isotab 20 mg was delivered to PIC on 8th October, 2011. The delivery challan indicates that two batches of Isotab 20 mg, namely, J092 and J095 containing 52,550 packets (1,051,000 tablets) and 47450 packets (949,000 tables), respectively, were delivered. (copy of the delivery challan is mark IW-10/39). However, from the documents available on record including the computerized invoice sent by the manufacturer, i.e., Efroze Chemical Industries (Pvt.) Limited to Umar Traders (Mark-IW-14/6) it has been established that the consignment consisted of six batches, namely J091, 092, 093, J094, J095 and J096. Further, it has been admitted by various witnesses who appeared before the Tribunal including representatives of the manufacturer and the distributor that six batches aggregating two million tablets were delivered to

PIC (reference may be made to the statement of IW 54 Mr. Shakeel Ahmed Khan, GM Plant Efroze Chemical Industries and IW-55 Mr. Khurram Munaf, Director Technical:-

“6. I cannot tell when Isotab Batch No.J098, J100 and J101 were manufactured. For the first time we came to know about drug reaction to medicines dispensed by PIC in the last week of December, 2011/First week of January, 2012. When this information was disseminated through the media, I am not aware of any steps taken by the management to test the samples of Isotab Batch No.J093 retention samples supplied by the company to PIC. I am aware that the company had manufactured Batch No.J091 to J096 (six batches) and supplied the same to PIC through its distributor namely Umar Traders. The invoice not only mentioned each batch number but also gave details of quantity comprising each batch. However, the distributor only mentioned two batch numbers namely J092 and J095 in the delivery challan. I am not aware of any steps that may have been taken by the management of the company to recall the contaminated medicine. The company has procedures in place for recall of any medicine that may have been found defective. According to my information, there is no ADR system in place in our company. (Statement of IW-54)

8. When Batch No.J091 to J096 of Isotab were manufactured, the same were dispatched to the distributor alongwith the invoice, which

gave the details of batch numbers and quantities. The said exercise is managed and controlled by G.M. Plant/Supply Chain namely Shakeel Ahmad Khan. I have no direct knowledge as to why the distributor mentioned only two batch numbers i.e. J092 and J095. However, during discussion with the owners of Umar Traders namely Tariq Rehman and Musharaf Rehman, they informed me that they do not personally go to the Truck Stop to get the consignments released. Their employees go to get the consignments released and they randomly note down the batch numbers and mention the same on invoice. Thereafter the consignment is sent directly to the institution, which receives the same on the basis of delivery challan. (Statement of IW-55)”

3.7. Even otherwise, admittedly the manufacturing capacity of the mixing machine on which the ingredients for Isotab 20 mg were allegedly mixed has a maximum capacity of 70 kg which translates into a maximum of 400,000 tablets per batch (see statement of IW-60 Tabish Nomani Production Executive). Consequently, the delivery challan, which only mentions batch No.J092 and J095, is obviously incorrect (Mark IW-11/7). The consignment was entered in the stock registers of PIC on 10.10.2011 (Mark IW-11/8) which also incorrectly mentions receipt of two batches, namely, J092 and J095 containing 52,550 and 47,450 packets respectively. Therefore, the entries in the stock registers of PIC are also patently incorrect. These were based on the incorrect entries in the delivery challan.

3.8. It may be noted that the manufacturer/distributor is liable to pay the fee for the Drug Testing Laboratory:-

“Firm will pay prescribed fee of Drug for testing in Drug Testing Laboratory (DTL) and provide the receipt and samples of every batch for (DTL) to the Hospital. Strips/Bottles should be marked “PIC Property”. Partial supply will not be accepted.” (Note on Mark IW-8/10)”

3.9. This could be one of the reasons to reduce the number of batches shown in the delivery notes, thus reducing the amount payable by the distributor/manufacturer to DTL. Whatever the motive, we are in no manner of doubt that the consignment consisted of six batches. Only two were mentioned in the delivery challan and the same two were mentioned in the records of PIC. This “error” had very serious implications because batch No.J093, which subsequently turned out to be contaminated was not shown to have been supplied or received in any official record.

3.10. The explanation offered by the distributor in this regard is highly unsatisfactory and does not ring true. It was stated before the Tribunal that the consignments were sent from Karachi through trucks which were unloaded at the warehouse of the trucking company at Lahore. An employee of the



distributor went to the warehouse of the trucking company, checked the cartons which are stacked over one another and at random noted down a few batch numbers on the delivery challan. He then got the cartons loaded on another vehicle and delivered them directly to the store of PIC. Besides many other contradictions between the statements of the two partners and an employee of the distribution company, there was no explanation forthcoming as to why batch numbers on the delivery challan were not accurately copied from the invoice which admittedly reached the distributor before the consignment arrived. In the facts and circumstances of the case, the possibility of intentional concealment/misreporting of batch numbers cannot be ruled out.

3.11. Likewise, the explanation given by Zulfiqar Ali, Dispenser/storekeeper (IW-21) in his statement before the Tribunal does not ring true. He stated that when the consignment was brought by the representative of the distributor, loaders who came with the vehicle brought the consignment inside the store and stacked it in a congested area in the



store. He stated that he only checked the batch numbers mentioned in the delivery challan submitted on behalf of the distributor and entered the same in the registers. He did not

counter check the batch numbers mentioned in the delivery challan with the batch numbers mentioned on the cartons. It is an admitted fact that the

consignment consisted of at least 40 cartons (Mark IW8/18A). It would be too much of a co-incidence that cartons with only batch Nos.J092 and J095 were in front rows when the cartons were allegedly stacked in the PIC store and that no carton with any other batch number was visible. In addition, once the consignment had been received, it was required to be examined by the Hospital Committee consisting of three doctors who were supposed to take samples from each batch to be sent for testing to the Drug Testing Laboratory (Mark IW-8/4). If the said process was followed it is hard to understand why cartons with batch numbers other than J092 and J095 did not catch anybody's attention. We are not convinced that the inspection committee performed its job diligently and carefully. They have to answer for the obvious lapses on their part before the competent authorities.

3.12. The statements made and documents submitted before the Tribunal show that samples were taken out of Batch Nos.J092 and J095 which were sent to the Punjab Drug Testing Laboratory for testing on 19.12.2011. It is significant to note that samples from Batch No.J093 was neither taken nor sent to the Drug Testing Laboratory. (See statement of IW-13 Mohammad Yousaf Pharmacist, PIC and IW-21 Zulfiqar Ali, Storekeeper in addition to mark IW-11/7 i.e. Inspection Report). These circumstances clearly point towards the fact that an actual inspection by the Inspection Committee did not take place and the concerned doctors signed off on the document relying on what they were told by the storekeeper who may have taken out the samples from Batch No.J092 and J095 which were sent for testing. The Drug Testing Laboratory tested samples received by it from Batch No.J092 and J095 between 26 to 29 October, 2011 and confirmed that the samples contained the correct amount of Active

Pharmaceutical Ingredients i.e. Isosorbide-5-mononitrate. The Drug Testing Laboratory had conducted the tests in accordance with their Standard Operating Procedures ("SOP") which require testing for the label claim. They were not asked to test for any other substance. They used the internationally recognized testing methods to confirm presence of 20 mg Isosorbide-5-Mononitrate. However, the most important aspect of the matter is that there was no possibility of any contamination being detected for the reason that the sample from Batch J093 was never sent for testing. As stated above, the said batch did not exist in any official record.

3.13. The Stock (inward and outward) Register for Isosorbide-5-Mononitrate 20 mg indicates that as of 10.10.2011 (Mark IW-11/8), a quantity of 1,072,307 tablets out of earlier batches was available in the stores of PIC. On the said date a fresh consignment of two million tablets (comprising various batches including Batch J093) was received which was

Delivery Challan Showing Delivery of Two batches

entered in the inward outward register showing batch Nos. J092 and J095 and omitting others including Batch J093. (see Mark IW.12/17). Consequently, samples from all batches actually received were not sent for testing to the Drug Testing Laboratory.

3.14. This state of affairs and lack of Standard Operating Procedures ("SOP") at the store of PIC is evident from yet another incident. On 29.7.2011 three batches of Cardiovestin tablets aggregating two million tablets was received by PIC. The Stock Register indicates that on the said date 105,236 tablets from previous stock were still available. Till 29.9.2011, 20,07,613 tablets were dispensed/issued, whereafter tablets from the batch received in July 2011 would have been used in October/November 2011. During this time spotting was detected on the pills, which was reported to various officials of the hospital. The stance taken by the Medical Superintendent was that the batch received in July had entirely been consumed in September and only a small portion consisting of about fifty packets of 200 Tablets each was available in the stock from Batch No.11E451. Mr. Zulfiqar Ali, Dispenser/Storekeeper in his statement before the Committee headed by the Chairman, Chief Minister's Inspection Team however, admitted that medicines of Batch No.11E451 had spots on them and this batch was returned to Mega Pharma, the supplier company which provided its replacement. According to him, this return was made on the Direction of Deputy Medical Superintendent (Stores). In case any defective medicine was purchased it was the responsibility of the Supervising Officer to look into the matter and coordinate with the manufacturer as well as the Drug Testing Laboratory to ascertain what had gone wrong. The entire process should have been properly documented. Surprisingly, there is no documentation or record of any nature whatsoever regarding the above fact. Matters were handled in a sloppy and slipshod manner which cannot be allowed in any organization, least of all a hospital, treating cardiac patients.

3.15. A very important document in this regard is PIC Bidding Document (Mark IW-14/9) wherein at Page 12, the procedure to deal with the issue of defective drugs has been provided in Paragraph No.10/11. It provides that in case a medicine is found against the required standards the procuring agency may reject the goods and the supplier shall arrange replacement or arrange for alteration necessary for rectification. Para No.13 of the Contract Form (Page 19 of IW-14/9) provides for destruction of substandard medicines at the cost of supplier. No exercise of this nature was undertaken in case of Cardiovestin, which had admittedly developed spots, nor were the causes and effects of such spotting ever investigated.

3.16. Mr. Muhammad Waris Gaba, Deputy Medical Superintendent (Purchase), in his statement denied that he had heard that spotting had been found on some tablets of Cardiovestin. Mr. Muhammad Yousaf, Pharmacist, PIC, in his statement before the Chairman, Chief Minister's Inspection Team, stated that medicine from Batch No.11E451 of Cardiovestin recovered from a patient had spots and he had directed the storekeeper to get the batch replaced and the said batch was accordingly replaced. Dr. Jafar Saleem, Medical Superintendent, PIC, stated that he never directed replacement of any defective medicine. According to him, it was in August/September, 2011, that a strip of Cardiovestin with blackish spots on the tablets was recovered from a patient. He took a report from the Drug Testing Laboratory, which was satisfactory. However, as a matter of abundant caution, he directed stoppage of use of the said medicine but was informed by Dr. Ali Hassan, Deputy Medical Superintendent (Stores) that the entire batch had already been issued and only fifty packets were left.

3.17. Although an effort has been made to change and resile from the earlier statements by various officers of PIC, there is sufficient material on record to establish that spotted tablets from Batch No.11E451 Cardiovestin were got replaced without following any legal procedure or maintaining any record. This incident has been highlighted to show loopholes and weaknesses in the procedural structure of the store of PIC. (See the statements of Ameer Mohammad IW-9, Dr. Syed Ali Hasan, Ex-DMS, PIC, IW-11 and Zulfiqar Ali, Ex-Store Keeper PIC, IW-21).

3.18. The question of appearance of spotting on Cardiovestin was subsequently raised by the Tribunal with various witnesses including the Chief Executive of Mega Pharma. He stated that on the advice of his in-house pharmacist it was decided to add a few ingredients because despite putting 100% active ingredients (Simvastatin), Essay Test indicated 80% to 90% presence of Active Pharmaceutical Ingredient ("API"). In order to stabilize the medicine, ascorbic acid BHT was added and the medicine stabilized. However, it was revealed that in high temperature and humid conditions the tablets had a tendency to develop minor brownish spotting on them, which was probably on account of oxidization of ascorbic acid. It was stated that addition of ascorbic acid did not affect the suitability of the medicine and was fit for human consumption. It was, however, admitted by the Chief Executive of Mega Pharma that the ascorbic acid and Butylated Hydroxytoluene ("BHT") did not constitute a part of the registered formulation and the addition constituted a technical violation of the relevant law and the rules. However, as confirmed by test reports received from foreign as well as local laboratories, Cardiovestin did not contain any contaminant which may have caused the aforementioned drug reaction. The

instance of replacement of spotted medicines and unauthorized addition of ingredients are serious matters which need to be examined and dealt with by the competent authorities in accordance with law. The information about the spotted Cardiovestin diverted attention of all concerned experts towards Cardiovestin. Most experts suspected that the said drug may be the cause of the adverse drug reaction. This turned out to be a false alarm and led to wastage of precious time (see the statement of Dr. Muhammad Tahir Azam, IW.51).

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WEAKNESS OF ADMINISTRATIVE STRUCTURE AND FAILURE OF SYSTEMS AT PIC

4.1 There is sufficient evidence available on record which indicates that the manufacturer, namely, Efroze Chemical Industries sent 200,000 tablets of Isotab 20 mg which consisted of six different batches. However, Umar Traders did not mention all six batches including Batch No.J093 in the delivery challan. When the consignment consisting of 40 cartons including Batch No.J093 was delivered at the PIC Store, the entries made in the records of the Hospital indicated receipt of the said consignment in two batches namely Batch No.J092 and J095. The distributor also provided paid challans for the testing fee of the Drug Testing Laboratory for two batches only. There was either collusion, gross negligence or carelessness on the part of the concerned officials at PIC who failed to detect that the consignment consisted of six different batches instead of two mentioned in the delivery challan. The said information was mechanically and without any counterchecking entered in the registers. Even the Inspection Committee of the hospital failed to notice, detect and point out this glaring discrepancy. Subsequently, only samples from the said two batches i.e. J092 and J095 were sent to the Drug Testing Laboratory along with testing samples. It is significant to highlight that no sample from Batch No.J093 was sent to the Laboratory for testing. Even if Drug Testing Laboratory had the capacity to detect contamination, it would have failed to detect the same on account of the reason that the contaminated drug was never sent for testing.

4.2 Samples of Batch Nos.J093 and J095 were sent to Drug Testing Laboratory. These were tested for the Active Pharmaceutical

Ingredients as per the label claim. After running the requisite standard tests, the samples were found to be of standard quality. The requisite certificates were accordingly issued.

4.3 The Tribunal has also examined witnesses and gone through the company's records. It is clearly and categorically established and admitted by representatives of the company as well as Umar Traders that six batches including Batch No.J093 consisting of 380,000 tablets were dispatched from Karachi and were received at the warehouse of the trucking company at Lahore. The entire consignment consisting of forty cartons was delivered from the warehouse of the trucking company directly to the hospital store by Amjad Iqbal IW.16. (Also see the statements of Tariq Rehman, IW.14 and Muhammad Musharraf Rehman, IW.15, partners of Umar Traders). There is, therefore, no ambiguity as to how Batch No.J093 reached PIC. There was complete absence of SOPs at PIC to deal with such an eventuality. Staff and officials were not aware of the importance of maintaining proper and accurate records. Further, there was complete absence of administrative control and supervision and counterchecks which is an alarmingly dangerous way to run a hospital.

DISCOVERY OF ISOTAB 20MG BATCH J093 THROUGH RECOVERY OF TABLETS FROM PATIENTS

4.4 It is important to point out that since the five suspected medicines were identified, samples were taken from hospital's stores and sent for testing. An effort was also made to collect retention samples from the manufacturer and sent for testing to Drug Testing Laboratory. In view of the fact that certain batches which had actually been supplied, had already been dispensed in their entirety, it was not possible to collect samples of such batches which could be sent for testing. In order to ensure that the testing exercise was comprehensive and complete, an effort was made to retrieve medicines from patients who were complaining of adverse reactions, had died, subsequently died or reported to hospitals and subsequently recovered. It was as

PUNJAB INSTITUTE OF CARDIOLOGY			
PATIENT MEDICAL RECORD FACE SHEET			
Medical Record No.	2012-029220		
Patient Name	GURJIT SINGH		
Age	32 years	Sex	Male
Address	MOAZAM ABAD TOWN, BHU.		
City	BANGSHEH		
Phone			
Religion	MUSLIM		
Signature			
Doctor's Name	Dr. G. S. Singh		
Signature			

PIC Patients Medical record Sheet

a result of this exercise that it was discovered (by chance) that other batches including Batch No.J093 had also been supplied by Efroze Chemical Industries which did not find mention in any record of PIC. Had this exercise not been undertaken and reliance had only been placed on samples taken from the hospital's stores and hospital records, the culprit drug would never have been found. These circumstances show the importance of maintaining accurate and meticulous records of all medicines

received by hospitals and dispensed to patients. There is an urgent need to revise and revamp the record keeping requirements at hospitals. These should be computerized and based upon accurate invoices issued by the manufacturer. On receipt, invoices should be checked and physically compared with the consignments received to ensure accuracy. This systematic procedure was found completely absent at PIC.

PIC VISIT

4.5. On 11.4.2012 the Tribunal visited Punjab Institute of Cardiology (PIC). The purpose of the visit was to gain firsthand information about the process followed by the Hospital in acquiring medicines, receiving the same in the storage areas and dispensing them



Outward view of PIC Patients free dispensary

through the free pharmacy run by PIC. In the first place, the Tribunal inspected the store where consignments of cardiac medicines including Isotab were received. The store in question had earlier been visited by the Investigating Officer who had sealed consignments of drugs suspected of causing drug reactions.

4.6. The storeroom of the hospital which looks like a make shift/temporary arrangement from its location and condition, is situated in the basement of the hospital. It is a small store considering the size



PIC Store

and workload of the hospital. The store is not well organized nor does it have adequate and suitable air conditioning facilities. On the day of inspection, the store was staffed by a pharmacist as well as a storekeeper. At the relevant time only a storekeeper was deputed at the store. The Tribunal was informed that incoming consignments are carried into the store by workmen provided by the supplier/distributor. The storekeeper conducts a random check to see if the quantities ordered have actually

been supplied and batch numbers mentioned in the delivery challan tally with the batch numbers on cartons of medicines. A few cartons are opened and strips of medicines, in case of tablets are taken out at random which are sent for testing to the Drug Testing Laboratory under cover of a letter issued by the hospital. The consignment is thereafter ready to be



Medicines Box at Free Dispensary

inspected by the inspection team of the hospital. The inspection team also conducts a random check to verify that the total quantity of medicines ordered has been received and is available in the store. At the relevant

time, drugs were dispensed to patients even before reports from DTL were received (See statement of Dr. Muhammad Azhar IW-1). According to the pharmacist present in the store, the process now being followed is that the drug is retained in the quarantine area till such time that the results from the Drug Testing Laboratory (DTL) are received after this episode, medicines are no longer being dispensed before such results are received.

4.7. It appears that different quantities of drugs are sent to the wards as well as pharmacy on receipt of requisitions which are signed and countersigned by the ward doctor, the ward Incharge and the concerned nursing staff who receive the drugs released by the store. Manual records of drugs received, drugs already in stock and drugs issued are maintained.

It was noticed that no computerized records of receipt and issuance of drugs are maintained. The air-conditioning of the store was not up to the mark. There was only one refrigerator in the store for storage of heat sensitive drugs. The



PIC store



PIC store

Tribunal was not satisfied with the condition of the store, its equipment or the manner in which the drugs had been stored or their records maintained. The store did not have adequate space or proper shelving which is necessary to run an organized and efficient store. Controls and procedures are either non-

existent or lax, haphazard and disorganized. Although there is security staff in the periphery, it appears only to be an informal arrangement because

incoming and outgoing material is rarely checked. There is no system of in and out passes. At best the storekeeper issues a slip if any consignment is to be returned to the supplier/distributor. The security official deputed at the out gate collects the slip and lets the vehicle carrying goods pass through. No record of such slips is maintained.

4.8. The Tribunal also visited the outdoor facility of the hospital. It is a newly built facility. The building has not formally been handed over to the hospital. However, some of the rooms have been made functional in which outdoor patients were being examined by consultants/doctors. New patients arrive on the ground floor. A counter has been set up where relevant data of fresh patients is entered into a computer. Such data includes name, address, telephone number and



PIC staff counseling the patients

Computerized patients record



medical history of the patient. The Tribunal was, however, informed that this data entry is a recent development. This procedure was not in place when the drug reaction episode occurred. This explains why data relating to most of the patients who had received drugs from the free pharmacy was not available. Only about eight thousand patients could be contacted out of

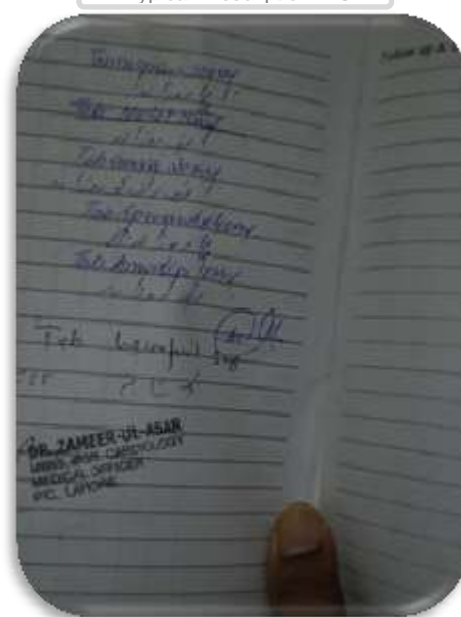
approximately 46000 patients who had received drugs from the free pharmacy.

4.9. On the first floor, there were counters for dispensing of free medicines. A person who wishes to obtain free medicines presents his prescription at the counter. The prescription contains the Medical Record Number of the Patient alongwith the names and quantities of prescribed medicines. The Computer Operator punches in the medical record number of the patient and displays his prescription. The patient is accordingly given a token which shows a number. The person sitting in the next window is a dispenser who fills the prescription and calls the patient by his token number. On his number being called, the patient can approach the window where he is given the drugs ordinarily covering one month's supply for the same.

4.10. There was another make shift counter in the hall where two interns who were pharmacists by training, were providing counseling to patients regarding mode and manner in which the drugs were to be used. The Tribunal was informed that between 1200 to 1400 patients come to the Hospital every day to receive free drugs. It was obvious to the Tribunal that the number of pharmacists and other related staff in this department was totally inadequate. The interns were unpaid volunteers with no incentive in terms of pay or stipend. There is no structured process for induction of pharmacists. Only one fulltime pharmacist was available who was required to perform multiple functions. The Tribunal was informed that only the outdoor department needed at least five fulltime pharmacists to handle the number of patients who come every day to receive free medicines.

4.11. The Tribunal was interested in knowing the procedure required to be followed by the Hospital Staff in case an adverse drug reaction is reported. To our utter surprise there was none. We were informed that a patient who complains of a drug reaction or who has been taking free medicines for three months is referred to the concerned doctor for re-evaluation which may include undergoing certain tests, if considered necessary by the

Typical Prescription PIC



consulting doctor. Even this is a new procedure introduced recently after the episode involving drug reaction. The general impression which was duly substantiated by our inspection was that although individual efforts are being made by the Chief Executive, members of the management team, consultants, pharmacists and other relevant staff on daily basis to run the hospital efficiently and to adopt certain procedures on individual initiative, there is total and utter lack of Standard Operating Procedures (SOPs) and systems on an institutional level. There is neither long term planning nor any effort to put in place any systems. Despite existence of a separate I.T. Department, use of information technology is virtually non-existent. The available resources are not being put to optimum use because of lack of training and expertise. The hospital is clearly under staffed lacks the requisite funds and over whelmed with the increasing number of patients who visit the hospital on a daily basis to receive free cardiac medication. The Introduction of free pharmacy and free dispensing of cardiac drugs has

added an unbearable burden on the already over stretched resources and overworked workforce of the hospital. The number of patients generally and those seeking free medicines is increasing consistently. No steps or planning has been put in place to deal with the situation at hand. No future planning appears to have been undertaken. Unless urgent steps are taken to address these issues the system will not only produce more catastrophes but will ultimately collapse.

4.12. The process of acquisition of cardiac medicines is not only defective and inefficient but also fraught with pitfalls. These weaknesses led to the present incident and unless removed will lead to more. The process of acquisition of medicines and their dispensing needs to be separated from the hospital. The consultants whose sole job should be limited to providing clinical advice and writing prescriptions should be freed from the burden of dealing with the administration and logistic problems posed by running a hospital/free dispensary. The problems are bound to multiply with the passage of time and the ever increasing volume of patients. Unless serious steps are taken to put a workable system in place and adequate resources are provided keeping in view the ground realities, limitations of management capacity, resources and funds, on top priority and urgent basis, this is yet another disaster waiting to happen.

4.13. It was also evident that although there are some programmes for training of doctors, there is no system in place for continuing education and training of administrative staff, nurses, pharmacists and other paramedical staff.

4.14. A good healthcare system caters for continued training of doctors and gives equal importance to training of administrative staff, nurses, paramedical staff and pharmacists, who form part and parcel of an efficient healthcare system. Further, internationally recognized practices and procedures for healthcare institutions need to be implemented and followed as these would develop a culture of professionalism in PIC which was conceived to be one of the premier cardiac hospitals in the country.

4.15. There is also an urgent need to supervise and train the staff who deliver and receive pharmaceutical consignments. It should be impressed upon them that the correct consignment numbers and their sequence be noted down accurately, as this has a bearing upon the larger scheme of things. In addition to being responsible people, on adequate level of education and training for this goal must be made mandatory.

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RETRIEVAL OF SUSPECTED MEDICINES

5.1. As soon as the common denominators amongst patients reporting drug reaction had been identified namely they were all cardiac patients and had received drugs from the free pharmacy of PIC, Lahore, further, dispensing of the said drugs was immediately stopped w.e.f. 12.01.2012. Simultaneously, PIC initiated an exercise of contacting patients whose telephone contacts were available informing them that use of the said drugs may be discontinued, they should return the medicines and receive alternate medication free of cost. Out of estimated 46,000 patients, who had received medication during the period in question, only about 8,000 could be contacted through telephone. A media campaign was also initiated with the object of informing patients to discontinue use of the 05 suspected medicines, surrender them to the hospital and receive substitute medication. Special counters were set up and dedicated help lines manned by qualified staff were made available to help patients. The Government of Punjab also launched an effort to contact and retrieve the suspected medicines. Government Personnel were mobilized from different departments at the district and tehsil level, who visited patients at the addresses available with PIC to recover the medicines and fill a questionnaire specifically designed for this purpose. This was a daunting task and had to be organized and carried out in a short period of time owing to the sensitivity of the matter and the urgency involved. No evidence has been brought before the Tribunal to show the quantity of the medicines recovered and the exact number of patients contacted. Therefore, no finding can be recorded on the effectiveness of the effort to physically

retrieve the suspected drugs from the patients. This exercise however resulted in discovery of the fact that PIC had dispensed drugs (from batch J093 and others) which found no mention in any of its records. Samples from batch J093 recovered from patients led to discovery of the fact that one of the batches dispensed by PIC to thousands of patients was contaminated. Had this link not been found it may have been impossible to trace the contaminant. Many more lives would have been lost.

5.2. It appears that PIC maintains an IT Database in a rudimentary form. It includes details of patients with telephone numbers and their medication. Further, the data is incomplete, at times inaccurate and not entirely useful for situations where a patient may need to be contacted in an emergency. It has also been suggested that 20 to 30% of the patients, who receive medication from the free pharmacy are ghost patients, who receive free medicine and sell it in the market. This loop hole needs to be plugged.



5.3. The availability of accurate data/information about patients can be vital in emergency situations where the need to contact a patient may suddenly arise. With the availability of information technology, such database can be built relatively easily and at an affordable cost. Further, the genuineness of the patient can also be ensured by verifying and crosschecking his identity. This objective can be achieved by making production of national identity cards compulsory and crosschecking the

same with the database of NADRA. In situations where a patient does not possess a national identity card, some alternate methodology needs to be devised to verify the genuineness and identity of the patient. Further, with the increase of tele-density in the country, there is increased accessibility to mobile telephones. People in towns and even villages possess mobile phones and even if a patient does not own a mobile telephone, somebody in his family, neighbourhood or village has a mobile telephone, whose number can be entered in the database relating to the patient as the contact person in emergencies. Such contact can be used as a conduit to communicate the requisite information to the patient and can make the difference between life and death. There is an urgent need to develop database on the above lines in consultation with the Information Technology Board of the Government of the Punjab.

5.4. Although serious efforts were made to contact patients, recover the suspected medicines or at least communicate the requisite information to them, these efforts were not based upon any Standard Operating Procedures (SOP) or guidelines put in place to deal with eventualities of this nature. The health sector in Punjab needs to set up an effective system for recall and retrieval of defective drugs, should a situation like this arise in the future. It may be mentioned that in every well regulated health sector internationally efficient recall procedures are established and implemented to prevent and deal with quality failure of pharmaceutical products, which can lead to disastrous situations as witnessed in the present case.

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FINDING THE CULPRIT INGREDIENT

6.1. ROLE OF LOCAL DRUG TESTING LABORATORIES

The local drug testing facilities consist of the Drug Testing Laboratory (DTL), Lahore. This Laboratory is primarily concerned with testing of drugs under the Drug Act. The Tribunal visited the Drug Testing Laboratory on 12.4.2012. During the presentation provided to the Tribunal it was clearly and categorically stated by the Director of the Laboratory that the capacity of DTL is limited to verifying the label claim of the manufacturer regarding presence of active pharmaceutical ingredient in the drug, using the methodology provided by the manufacturer. DTL neither has the capacity nor is it possible for it to undertake investigative work of the nature that was required to find drug contamination of the type that occurred in the drug reaction cases of PIC. Such investigative work requires state of the art equipment, highly trained professionals and close coordination with clinicians in order to find presence of contaminants in drugs. As pointed out above, notwithstanding lack of capacity and equipment, samples of Isotab 20 mg manufactured by Efroze Chemical Industries which were sent for testing to DTL did not belong to Batch No.J093 (which was subsequently found to contain contamination of Pyrimethamine). Samples of the said drug sent to DTL were from Batch Nos.J092 and J095, which were not contaminated and were, therefore, found by DTL to be of standard quality. Once the international laboratories had identified presence

of Pyrimethamine in Batch No.J093, samples from the said batch were sent to DTL for testing. In view of the fact that it was known that the drug contained Pyrimethamine, the requisite tests specified for Pyrimethamine as per International Pharmacopeia were run by DTL to verify presence of Pyrimethamine in the samples. After conducting the requisite tests on its HPLC Equipment, DTL verified that samples of Batch No.J093 which had been recovered from patients and were sent to it for testing contained approximately 50 mg of Pyrimethamine per tablet. The equipment at DTL is outdated and totally inadequate to meet the requirements of a modern, effective and efficient laboratory. Immediate steps are required to be taken to revamp DTL and procure the requisite equipment.

6.2. **ROLE OF OTHER LOCAL INSTITUTIONS, LABORATORIES AND UNIVERSITIES.**

It has been noticed that in a desperate effort to find the contaminant in one of the five drugs that had been identified, the Health Department, Government of Punjab, involved a wide cross section of experts, laboratories and testing facilities available in Universities and other institutions. In this regard Professors of Pharmacology, the Pharmacy Department, University of Punjab, Professors of Epidemiology, Forensic Science Agency, Chief Chemical Examiner, The Pakistan Atomic Energy Commission and PCSIR were involved. Further, Hussain Ebrahim Jamal Institute ("HEJ") at the University of Karachi which reportedly possesses better equipment was also approached to find and identify the culprit drug and the contaminant in such drug. However, none of the local institutions,

laboratories and universities was able to identify the contaminant presumably on account of lack of the requisite equipment, know-how, training and availability of the relevant electronic database which would have been helpful in investigation of this nature. (See the statements of IW.26, IW.27, IW.30, IW.32, IW.33, IW.34, IW.35, IW.36, IW.38, IW.39 and IW.40).

6.3. **THE CENTRAL DRUG TESTING LABORATORY (CDL)**

The CDL in Karachi is a Federal Laboratory. The main function of CDL is qualitative analysis of drugs and medicines and to convey results of the analytical reports to the concerned authorities. It was found that it is neither properly funded nor adequately equipped. During the visit of the Commission most HPLC apparatus which constitutes the backbone of a drug testing laboratory, was either found out of order or outdated. It may be pointed out that samples of the suspected medicines were also sent to CDL for testing. However, in view of the fact that CDL like DTL is equipped and trained only to test for presence of active ingredient as per the label claim, it was not able to detect the contamination. However, after MHRA had discovered presence of Pyrimethamine in Isotab Batch No.J093, samples of the said drug were again sent to CDL at Karachi. This time it was able to confirm on the basis of running standard tests as prescribed in International, United States and British Pharmacopeia for Pyrimethamine to identify presence of the said substance in substantial quantities in the samples from Batch No.J093. While recording evidence, it transpired that when the Federal Drug Inspector accompanied by FIA reached the factory

premises of Efroze Chemicals in Karachi, they found a solution made from tablets of Isotab 20 mg taken from the retention samples of Batch No.J093 at the factory premises of Efroze Chemicals. CDL was able to confirm that the said solution contained substantial quantity of Pyrimethamine in addition to the Isosorbide-5-Mononitrate as claimed in the label. The said samples were prepared by the Chemical Analysts of the Company during the night of 31st January, 2012 and 1st February, 2012, when information was flashed on the television networks that samples of Isotab 20 mg from Batch No.J093 manufactured by Efroze Chemicals had been found contaminated with Pyrimethamine by the Laboratory of MHRA. (See the statement of Dr. Obaid Ali, Federal Government Analyst, IW.17, Mr. Khurram Munaf, Director Technical, Efroze Chemical Industries, IW-55, Tabish Nomani, Production Executive, Efroze Chemical Industries IW-60 etc.

6.4. **ROLE OF INTERNATIONAL LABORATORIES**

After having failed to identify the contaminant in the five suspected drugs at the local level, the Government of Punjab took steps to send the samples to laboratories in other countries on urgent basis. Two officials of the provincial government were dispatched to United Kingdom with separate packets containing samples of drugs taken from stores of PIC as well as those recovered from the patients. In this regard valuable and timely assistance was provided by International Health Partners (IHP) in arranging analysis of drug samples in U.K. and France. The samples were analyzed by the London School of Pharmacy, London ("LSP"), as well as the

Laboratory of the Medicines and Healthcare Regulatory Agency, MHRA, England. The report of the London School of Pharmacy reported presence of a contaminant peak in the chromatogram of Isotab 20 mg samples. It was, however, not possible for the said Laboratory to identify the exact nature of the contaminant. The samples were, therefore, handed over to MHRA Central Testing Laboratory which carried out analysis of Liquid Chromatography/Mass Spectroscopy (LC/MS) and Gas Chromatography/Mass Spectroscopy (GC/MS) equipment and observed that the mass and mobility of the unusual peak of the contaminant co-migrated with a compound called Pyrimethamine. After confirmation of these findings MHRA reported to the Pakistani Authorities that two samples of Isotab 20 mg tablets were positive for a significant amount of Pyrimethamine. Both samples of Isotab 20 mg had the same batch number "J093". It was further reported that two other samples of Isotab 20 mg (lot number not known) did not show the presence of

Pyrimethamine. Since the contaminated product contained approximately 50 mg Pyrimethamine, it was the opinion of the MHRA that since the tablet



was taken twice thrice a day, this made a fourteen-fold over dose of Pyrimethamine which clearly caused the adverse reaction. Secondly authentic and widely available information about Pyrimethamine shows that it causes bone marrow toxicity which is the main feature of a chronic over dose, as tested by the National Poison Information

Service ⁶ UK (NPIS) Toxic Base Data Base. Further, the drug/chemical is known to cause symptoms of bone marrow suppression, blackening of skin and lowering of white blood cells. On these basis it was concluded that Pyrimethamine contamination in Isotab 20 mg Lot No.J093 was the real cause of the adverse reaction in patients. Copies of the test reports as well as communications sent by MHRA are available on the record. Subsequently, the findings of MHRA were confirmed by other International Laboratories, DTL Lahore and CDL Karachi. Most importantly, even the internal analysis conducted in their own laboratories by Efroze Chemicals on the basis of retention samples of Batch J093 which were lying in custody of the company, confirmed contamination/mixing of Pyrimethamine in Batch No.J093. (See statements of IW.57, IW.58, IW.60 and IW.71), who categorically admitted that testing of retention samples in the laboratories and equipment of the company revealed presence of Pyrimethamine in substantial quantities in Batch No.J093.

⁶ <http://www.npis.org/>.

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CAUSES OF DEATHS

7.1. According to the information provided to the Tribunal, there were 213 reported deaths of patients. About 1000 patients were admitted in different hospitals, who recovered at various stages and were discharged from hospitals, as a result of discontinuation of use and administering the antidote. The patients who died or were admitted to hospitals complaining of drug reactions had the following common factors:-



LAHORE, Jan 30: A pharmaceutical company supplied 20 cartons of a spurious medicine to the Punjab Institute of Cardiology and this drug might be one of the major causes of more than 100 patients' death

The caption and picture from daily Dawn 31st January 2012

- i) They were all cardiac patients;
- ii) They had received drugs from the Free Pharmacy of PIC;
- iii) Their symptoms started occurring between the first and second week of December, 2011. This was the approximate time when Isotab 20 mg from batches received on 8/10th of October, 2011, including Batch No.J093 was dispensed;
- iv) All patients had symptoms of bone marrow suppression, blackening of skin, low platelet levels and low white blood cell count.

7.2. Considering that dispensing of five suspected drugs was stopped on 12th January, 2012, an effort was made by PIC to contact patients whose telephone numbers were available in its data-base. Information was disseminated through the print and the electronic media and on 23rd January, 2012 onwards. A massive exercise was undertaken by

the Government of Punjab whereby its machinery was mobilized to contact patients all over Punjab. It was anticipated by medical experts that keeping in mind the half-life of the culprit contaminant, bone marrow suppression and its related symptoms were expected to stop by mid-February, 2012, which proved to be correct. This factor amongst many others, unmistakably points towards overdose of Pyrimethamine being the main cause of death.

7.3. It may also be kept in mind that after receipt of test reports involving other suspected drugs which were clear, PIC resumed dispensation of the same. However, neither any drug reaction nor drug reaction related death has been reported so far which lends further support to the argument that the drug reactions and the resultant symptoms either directly caused deaths of patients or contributed in a substantial manner towards causing deaths.

7.4. The Tribunal has also been informed that the Government of Punjab had constituted a committee headed by Professor Dr. Faisal Masud, Principal, Services Institute of Medical Sciences (SIMS) to verify the claims of legal heirs of deceased patients for the purposes of payment of compensation. The Committee verified such claims on the basis of records of hospitals, treatment, medical tests and other documentation and confirmed in 213 cases that death had been caused by the aforementioned drug reaction

7.5. During recording of statements of various experts summoned by the Tribunal, it was suggested that all the patients may not have died on account of adverse reaction to Isotab 20 mg which was contaminated by Pyrimethamine. It was pointed out that the other medicines including

Soloprin, Clopidogrel etc. may also have been responsible for excessive bleeding leading to death. In this regard it was pointed out that in some cases high doses of Asprin were prescribed on continued basis for months on end. One of the experts indicated that the internationally accepted dosage was between 70 to 80 mgs per day. However, there were other experts who stated that while excessive usage of aspirin and other similar drugs may cause bleeding, they do not cause symptoms like bone marrow suppression, darkening of skin and reduction of white blood cells. These were the symptoms reported in almost all cases where patients were admitted to hospitals as well as patients who died. Further, patients who were admitted to hospitals with symptoms of bone marrow suppression, low platelet counts and white blood cell count, recovered when they were administered calcium folinate, the anti-dote of Pyrimethamine as per information provided by MHRA. In the opinion of the Tribunal, these factors furnish sufficient basis to conclude that most of the drug reactions and deaths occurred in consequence of ingestion of the aforementioned contaminated medicine. This finding is also substantiated by the opinion of the special Medical Board set up by the Government of Punjab to process and verify claims of compensation.

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ROLE OF PHARMACISTS

8.1. During the course of proceedings before the Tribunal it has transpired that Pharmacists play a major role in the healthcare system. They also have a pivotal role in the process of manufacture of pharmaceutical products. They are supposed to oversee and supervise the process of manufacture and to ensure that cGMPs are strictly adhered to at all stages of manufacturing. Qualified pharmacists also man the regulatory agencies as Drug Inspectors and at other levels in order to ensure compliance with the provisions of the Drugs Act. Pharmacists, being experts of medicines, have a major role to play in hospitals. Their responsibilities include reviewing prescriptions, pointing out errors in prescriptions, if any, from the point of view of drug to drug and drug to food reaction and interaction, providing counseling to patients, doing rounds with doctors and performing services in the hospital's pharmacy. They are instrumental in detecting drug reactions at an early stage on account of their training and direct interaction with the patients.

8.2. Unfortunately in the health sector of Pakistan, pharmacists have not been assigned their due role. They have by and large (exceptions apart) been relegated to the position of storekeepers/dispensers. According to international standards for hospitals, one pharmacist should be available against every fifty beds. This ratio has been repeatedly accepted, approved and recommended in various reports written on the subject of healthcare as well as a Judgment of the Honourable Supreme Court of Pakistan. Unfortunately, the situation has not improved. In PIC, which is a 150-bed hospital, at the relevant time, there were only two pharmacists. Even they

were not performing any of the above functions. Their only role was limited to performing services in the storage area and dispensing of drugs. There is an urgent need to recognize the role of pharmacists at all levels of the health sector. Necessary legislation needs to be put in place to ensure that pharmacists are assigned their due role at every level of the health sector including manufacture, regulation, sale through drug stores/pharmacies and hospitals. In this regard reference may be made to a report submitted by the Special Committee of the Senate of Pakistan. The report dated March 18, 1991 is comprehensive and makes important recommendations in this regard (Mark IW-32/5). Some of the recommendations made in this report have been adopted from the said report. It is unfortunate that neither any heed has been paid to the said report nor has any effort been made to implement its recommendations. The National Health Policy announced in January, 1990 (Mark 32/4) also touched upon the subject of Pharmacists in the Health Sector. Unfortunately despite lapse of decades, successive governments have utterly and miserably failed to take any concrete steps in this regard. It is high time that this matter be seriously taken up and the order of the Hon'ble Supreme Court of Pakistan, recommendations of the Senate Committee as well as Health Policies announced by governments from time to time with special reference to Pharmacists be implemented immediately in letter and spirit.

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RESPONSE OF THE GOVERNMENT OF PUNJAB

9.1. Although patients had started trickling in different hospitals with adverse drug reactions in the second week of December, 2011, the numbers were small and the diagnosis vague. This did not ring alarm bells at the governmental level. As noted above, it took clinicians and doctors about a month to come to the conclusion that patients reporting to hospitals were not suffering from dengue fever and that it was possibly a drug reaction. In January, 2012, the number of patients approaching hospitals started increasing so did the number of fatalities. These events were picked up by the electronic and print media which also alerted the Government of Punjab. Till the later part of the first week of January, 2012, hospitals and doctors continued to treat the matter as a purely medical problem which did not need intervention by the Government of Punjab. In the first week of January, 2012, there was a broad consensus amongst doctors that the fatalities and symptoms were something other than dengue fever. At this stage the matter was taken up with the Health Department which got involved in the issue. Between 12th to 23rd of January, 2012, various steps were taken to deal with the situation. These included stoppage of prescribing the suspected drugs, sending samples to Drug Testing Laboratories for testing, seeking information from five manufacturers relating to the various ingredients and manufacturing practices adopted by such manufacturers and formation of one committee after another to look into, enquire, probe and investigate the matter with the object of dealing with the catastrophe. While the aforesaid efforts were largely unsuccessful,

they prepared some groundwork on the basis of which further work was undertaken by eight specialized committees which were commissioned on 23rd of January, 2012. The Tribunal noticed that while scattered efforts were made by individual experts, groups of experts and committees constituted by the government for the first few weeks of January 2012, there was neither coordination nor a systematic sharing of information and data. In this day and age of information technology, even the hospitals of Lahore did not have any medial information and knowledge sharing capability which may have helped focus, coordinate and streamline efforts to deal with the situation. There is a need to electronically connect the major hospitals of Lahore including Mayo Hospital, Services Hospital, Sir Ganga Ram Hospital, Jinnah Hospital, Sheikh Zayed Hospital, General Hospital and others so that information knowledge, experience etc. can be mutually shared to devise common strategies to deal with outbreak of epidemics, situations arising out of the drug reactions and similar catastrophes that occur from time to time.

9.2. It is also surprisingly noted that there is no system of adverse drug reporting (ADR), pharmaco vigilance and poison control in Pakistan. It is highly advisable and indeed necessary to put such systems in place on priority basis. The hospitals of Lahore must be interlinked as such systems can be put in place with minimal effort with the help and assistance from the Information Technology Board.

9.3. Between 23rd and 31st of January, 2012, when MHRA Laboratory established that Isotab Batch No.093 was contaminated by Pyrimethamine, efforts made by the Health Department were reasonable. However, it is evident that all steps taken were on the initiative of one

individual or the other. These were not based upon any system or standard operating procedures put in place to deal with emergencies of this nature. It is, therefore, not possible to predict how any future incident of a similar nature will be handled. This is a sad commentary on the weak structural and institutional base of our health sector which is most ill-equipped to deal with or handle situations of this nature.

9.4. We have been informed that the Government of Punjab announced compensation of Rs.500,000/- per patient who died from the drug reaction and Rs.200,000/- per patient for those who suffered drug reaction and survived. A committee of clinicians headed by Professor Dr. Faisal Masud was set up to confirm the claims filed by affectees of this catastrophe. The said committee examined the records produced before it, records of hospitals and other relevant information to process the claims. Those recommended by the committee received compensation. Anybody who was denied such compensation had the opportunity of approaching an appellate forum headed by Mr. Justice (Rtd) Saeed Akhtar, who reexamined the cases of each claimant and passed appropriate orders. The Tribunal has reason to believe that claims of most genuine claimants have been paid to a certain extent by the Government of Punjab. We are consciously restraining from commenting on the reasonability of the quantum of compensation offered by the Government of Punjab and the responsibility and liability of Efroze Chemicals, the manufacturer of the contaminated drug to compensate victims. The matter may be taken up before the appropriate forum by the affected parties.

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THE DISTRIBUTOR

10.1. The relevant consignments of Isotab 20mg consisting of Batch Nos.J091 to J096 were manufactured by Efroze Chemical Industries, Karachi and were supplied/delivered by Omar Trading Company vide delivery challan No.462 dated 08.10.2011 (delivery challan is Mark 14/6). The order in this regard had been placed with Omar Trading Company on 17.09.2011 by the Medical Superintendent, Punjab Institute of Cardiology for supply of 100,000 packs of Isotab 20mg with each pack containing 20 tablets (aggregate 2 million tablets) at the rate of Rs.7.60 per pack. The order stated that Omar Trading Company will pay the prescribed fee for testing of the drug by the Drug Testing Laboratory (DTL) and provide the receipt for payment of fee and samples of every batch to be sent to DTL. Strips/tablets were required to be marked as "PIC Property".

10.2. According to the invoice sent by Efroze Chemical Industries (Pvt.) Ltd. dated 30.09.2011, the consignment consisted of 06 batches i.e. Batch Nos.J091, J092, J093, J094, J095 & J096. Batch No.J093 consisted of 782 packs. Each pack contained 500 tablets and the entire batch consisted of 391000 tablets. The invoice also carried a warranty under Section 23(1)(i) of the Drugs Act, 1976 in the following terms:-

"I, Khurram Munaf, being a person resident of Pakistan, carrying on business on 146/23 Korangi Industrial Area, Karachi, Pakistan and Head office at 12-C, Block-6, Pechs Karachi, under the name of Efroze Chemical Industries (Pvt.) Ltd., do hereby give this warranty that the

drugs here above described as sold/indented/specified by me and contain in the bill of sale, invoice, bill of lading or other document describing the goods referred to here do not contravene in any way the provisions of Section 23 of the Drugs Act, 1976.”

10.3. The consignment was sent through New Karachi-Hazara Goods vide *Bilty* No.5966 dated 29.09.2011. The goods were delivered at the store of PIC on 08.10.2011 as is evident from the delivery challan as well as signatures of Zulfiqar Ali, Store Keeper Medicine, PIC, Lahore on the delivery challan. The delivery challan also contains a warranty in the following terms:-

“We do hereby give this warranty that the drugs described in this invoice as sold by us do not contravene in any way the provisions of Section 23 of the Drugs Act, 1976 as per the warranty of the manufacturer”

10.4. It is significant to note that there is a major discrepancy between the invoice sent by Efroze Chemical Industries and the delivery challan submitted by Omar Trading Company. While the invoice mentioned all six batches, the delivery challan prepared and submitted by the distributor mentioned only two batches i.e. Batch No.J092 & J095. More importantly, Batch No.J093, which was later found to be contaminated, was not mentioned in the delivery challan. Further, the invoice mentioned that the consignment consisted of packs containing 500 tablets per pack which

was contrary to the requirement of the supply order, which clearly mentioned supply in small packs of 20 tablets per pack. The delivery challan wrongly mentioned that the consignment was being delivered in 20 tablets packing and consisted of 100,000 such packs. Surprisingly, none of these discrepancies were either noted or objected to either by the Store Keeper or by the Inspection Committee, of PIC as is evident from the records produced before the Tribunal.

10.5. The partners of Omar Trading Company, which is a partnership firm, were summoned by the Tribunal. Mr. Tariq Rehman appeared as I.W.14 and explained that the firm is in the business of distribution of pharmaceuticals since 1986 and is the distributor of Efroze Chemical Industries since the past 05 years. The firm represents other pharmaceutical companies also and supplies pharmaceutical products to different hospitals including PIC. The procedure followed in the business is that the firm submits tenders for supply of pharmaceuticals to different hospitals. If a tender is accepted, the supply order is placed with the firm, which is communicated to the manufacturer, who manufactures the medicine and dispatches the same to the distributor alongwith the requisite documentation. When the consignment reaches Lahore, a representative of the firm goes to the Truck Stand, gets the consignment released and delivers it directly to the concerned hospital. Since the firm does not have a large storage area and operates in a three room office, the consignments are directly dispatched from the Truck Stand to the premises of the hospital, which had ordered the supply. In the year 2010-2011, the firm made two supplies of medicines in August and September, 2011. The same related to Batch Nos.J091 to J096 (total 06 batches) in the contract for the year 2010-

2011. Another supply was made in December, 2011, which consisted of Batch Nos.J098, J100 and J101. During his statement Mr. Tariq Rehman IW14 submitted that the delivery challan is generated by the firm, which contains the same information regarding batch numbers as is contained in the invoice sent by the manufacturer. He admitted that the delivery challan prepared by the representative of the firm namely Amjad was incorrect insofar as instead of mentioning 06 batch numbers, it just mentioned two batch numbers namely J092 and J095. He was unable to explain the reason why the delivery challan omitted to mention the other batch numbers including Batch J093. The only explanation he could offer was that the matter was overlooked by the representative of the firm. He further stated that although the consignment is received by the Store Keeper, subsequently, it is examined by the Inspection Committee, which is supposed to open each carton, examine the contents of the smaller boxes and tally batch numbers mentioned on the delivery challan. He submitted that no objection or complaint was received regarding the aforesaid omission either from the Store Keeper or the Inspection Committee of the Hospital. He further submitted that he never received any information or intimation from Efroze Chemical Industries relating to any defect or contamination in any of the batches supplied to PIC. Further, the firm was never requested to withdraw or recover any medicines from the batches of Isotab supplied to PIC. He claimed that he came to know about the omission of mentioning of certain batches and the fact that Batch No.J093 was found contaminated for the first time when the investigation agencies interrogated him in connection with an ongoing investigation into deaths of a large number of patients on account of drug reactions. He, however, submitted that failure to mention the correct batch numbers was an

accidental omission and was not intentionally made. The other partner of Omar Trading Company namely Muhammad Musharaf Rehman also appeared before the Tribunal as I.W.No.15. He reiterated the stance taken by his brother. Further, he added that every carton of the consignment contained a sticker on it mentioning the name of the medicine and its quantity. The smaller box packed in the larger container also mentioned other information about the medicine, its quantity as well as batch number. He stated that the consignment is received by a representative of the firm at the Truck Stand. He counts and verifies the same and provides the requisite information to the office of the firm, where delivery challan is prepared. In this respect, he contradicted I.W.No.16, who stated that he takes a blank delivery challan and fills it at the Truck Stand after randomly counting the number of cartons contained in the consignment. He admitted that there was omission of batch numbers in the delivery challan, but maintained that the same had happened by mistake. He stated that as a matter of general practice, some manufacturers mention the batch number on the outer carton while others do not. In case of Efroze Chemical Industries, he stated that sometimes, the batch number is mentioned on the outer carton and sometimes it is not and the practice is inconsistent. He submitted that in case of consignment consisting of Batch No.J091 to J096, batch numbers were not mentioned on the outer cartons. He failed to explain how he had this information because he admitted that he never saw the cartons in question. He admitted that the delivery challan given in the case of the relevant consignment did not provide the requisite information correctly. He submitted that at no stage was the firm informed of any defect or contamination in the medicine comprising Batch No J093. He also admitted that it was the responsibility of the firm to accurately mention

batch numbers in the invoice delivered to PIC. He did not deny the fact that the Inspection Committee relied on incorrect batch numbers supplied by the firm to conduct inspection of the medicines supplied, taking samples and sending the same to the Drug Testing Laboratory in accordance with the said batch numbers. He submitted that he and his brother were interrogated by the police, but Amjad, an employee of the firm, who had delivered the consignment and prepared the delivery challan, was not interrogated.

10.6 Amjad Iqbal, an employee of Omar Trading Company appeared before the Tribunal as I.W.16. He stated that the procedure of the firm is that when goods arrive at the Truck Stand, he or one of the other employees, goes to the Truck Stand, gets the consignment released and delivers it to the customer. He submitted that owners of the firm used to give him a blank delivery challan with instructions to fill batch numbers mentioned on the carton, get the consignment released and deliver it to the hospital. He admitted his handwriting and signatures on the delivery challan Mark I.W.14/6. He stated that batch numbers J092 and J095, which were lying in front of the stack of the Truck Stand, were written on the consignment, which consisted of 40 large cartons. According to him each carton contained a sticker containing the batch number. However, he did not check the batch number on each carton. Interestingly, in a subsequent part of the statement, the witness resiled from his earlier statement and stated that actually he had not checked the batch numbers at the Truck Stand. On the contrary, he had checked and entered batch numbers after the consignment had been stacked in the store of PIC. He also admitted that batch numbers were mentioned on each carton and he had mentioned Batch Nos.J092 & J095 on a random check. In this and many other

respects he contradicted the statements of IW-14 and IW-15 whose statements contradicted each other's.

10.7. The witness was shown delivery challan No.954 dated 21.11.2011 relating to supply of a subsequent batch of Isotab. He admitted his signatures on the document Mark I.W.15/3. The witness was asked how he had mentioned specific quantities of packs comprised in each package. He initially went quiet. He had no answer. After thinking for a while, he tried to give different and self-contradictory answers. He finally stated that since the Store Keeper of the hospital informed him that a consolidated challan would not be acceptable to the countersigning doctors, he divided the total number of the packs in the consignment into three parts and gave fictitious quantities on the delivery challan. The witness further admitted that Mr. Musharaf Rehman I.W.No.15 was informed by him that he had given fictitious information on the delivery challan. He failed to explain how he knew in advance that he would give two batch numbers on the delivery challan before even receiving the consignment and yet deposited fee of the Drug Testing Laboratory for two consignments. He also admitted that in case a batch number is not mentioned in the delivery challan, drug testing fee is not deposited for batches omitted in the delivery challan in consequence of which samples from the missing batch would not be sent for testing.

10.8. He also categorically admitted that the firm had no storage facility and acts as a "middle man" only. When the stock is received at the Truck Stand, it is shipped directly to the recipient institution/hospital. Further, it does not have any special arrangement for transportation and supply of sensitive drugs that are required to be transported in controlled

temperatures. He also admitted that the firms Omar Trading and Rehman Trading are operated through the same office and are owned by the same partners.

10.9. Further, despite knowing that the witness had prepared fictitious documents/delivery challan and submitted the same to PIC, no action was ever taken against the said witness. This points towards complicity of the three witnesses i.e. I.W.No.14, I.W.No.15 & I.W.No.16 in the matter. As pointed out above, there are glaring contradictions between the statements of the three witnesses and conscious effort has been made to conceal and distort the facts. Further, there is consensus amongst all three witnesses that all batch numbers in the consignment were not mentioned on the delivery challan, fee of the Drug Testing Laboratory was not paid for all batches, the Store Keeper as well as the Inspection Committee blindly relied upon information provided by the distributor and sent samples of only two batches for DTL testing and mention of batch J093 was omitted, which resulted in samples of the said batch not being sent for testing of DTL. Had the medicines not been retrieved and recovered from the patients, it would have been impossible to trace the culprit batch. Even otherwise, the distributor does not have any storage facilities and hence does not fulfill the conditions on the basis of which license has been granted to the firm to engage in the business of trading of pharmaceutical drugs. It is abundantly clear that deception was exercised in withholding batch numbers and mentioning only 02 batch numbers by specifically excluding 4 others including a batch, which was subsequently found to be tainted with pyrimethamine. The involvement of Omar Trading Company, as one of the players contributing towards occurrence of the

tragedy is clear and obvious from the record. The matter should be sent to D.G Health, Secretary Health and other competent authorities to take strict action against the firm in the facts and circumstances narrated above as may be permitted by the relevant laws.

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INVOLVEMENT OF THE POLICE AND CONDUCT OF INVESTIGATION

11.1. While the tragedy was still unfolding, patients were reporting to hospitals with drug reactions and a number of fatalities had been reported. On 24.01.2012, FIR No.47/12 was lodged at Police Station Shadman, Lahore. It was stated in the FIR that some cardiac patients of PIC had received drugs including Soloprin, Cardiovestin, Isotab, Alphagril and Corcont, from the pharmacy of PIC. Use of these drugs had caused adverse reaction and dozens of people had died while others are under treatment. One of the drugs namely Cardiovestin had been found to be substandard by the Drug Testing Laboratory. Therefore, the FIR was being lodged because a cognizable offence had been committed. The FIR was lodged under Section 322 of Pakistan Penal Code against manufacturers of the drug. The Tribunal has been informed that at a subsequent stage, Section 302 of Pakistan Penal Code was also added to the offences mentioned in the FIR. It is important to note that at this stage the focus of investigation was on Cardiovestin. On account of the fact that some samples had developed spotting and such samples were declared substandard because of spotting, by the Drug Testing Laboratory, the main suspicion for the drug reactions was narrowed down to Cardiovestin. However, the other medicines were also not cleared. A police investigation into the contaminant was initiated. Three manufacturing companies in Lahore were visited and the owners arrested and questioned. None of these factories were subsequently found to have supplied contaminated/sub-standard drugs which may have caused adverse reaction. One manufacturer was however found operating without a valid

manufacturing license. Investigations were also being carried out in Karachi by different agencies including the Federal Investigation Agency.

11.2 The investigation of the case was initially conducted by Inspector Abid Ali, Incharge Investigation, Police Station Shadman Lahore. However, subsequently, at the instance of the investigation officer, who stated that the case was of an important and sensitive nature, he was allowed to associate the concerned Drug Inspector for guidance in the matter. He also visited PIC alongwith Drug Inspector Saeed Iqbal IW-24 and met Store Keeper Zulfiqar Ali IW-21 and Pharmacist Muhammad Yousaf. He took into possession 10 DTL reports provided by Inspector Saeed Iqbal regarding medicines used by PIC patients and 06 documents regarding various companies, which supplied medicines/drugs to PIC

11.3. Subsequently, the investigation was transferred and entrusted to Major (R) Mubashar Ullah, DIG/Commandant Police Training School, Chung on 25.01.2012 on the recommendation of District Standing Board, Lahore as envisaged under Article 18(6) of the Police Order, 2002. During the course of investigation, the said officer visited PIC, met Drug Inspector Saeed Iqbal and Shaukat Wahab and also took into possession the stock register relating to indoor and outdoor patients. He also joined Deputy Medical Superintendent, Muhammad Waris, Store Keeper, Abid Niamat IW-10 and Muhammad Yousaf IW.13, Pharmacist in the investigation and also recorded their respective versions. He also obtained death certificates of Muhammad Rafique and Muhammad Shafi deceased. He also joined Professor Dr. Muhammad Azhar IW-1, Chief Executive of PIC, Dr. Muhammad Jaffar Saleem IW-12, Medical Superintendent, PIC, Dr. Abdul Hameed, Additional Medical Superintendent (Stores), Dr. Ali

Hassan IW-11, Deputy Medical Superintendent (Stores) and Dr. Hamid Mahmood, AMS (Stores) in the investigation and also directed Inspector Abid Hussain to collect record from the companies which had supplied medicines to PIC. He also visited the factory of Pharmawise, which supplied Soloprin to PIC, the owner of the factory namely Nadir was at that time in custody of FIA. In addition, Alflah Medicine Company owned by Muhammad Waseem and Mega Pharmaceutical owned by Tahir Azam were also visited.

11.4. It appears that FIA had also registered three separate FIRs bearing Nos.07/12, 8/12 & 9/12 under Sections 23/27 of the Drugs Act against the aforesaid companies. Further, the record of Rehmat Ali, a patient who had died in hospital on 28.01.2012 due to probable reaction of one of the aforesaid drugs was also taken into custody. Subsequently, his post-mortem report was also taken in possession.

11.5. Keeping in view the importance and sensitivity of the matter, at a subsequent stage, the investigation was transferred and entrusted to a team comprising of the following officers on the direction of the competent authority vide order dated 3.11.2011:-

Zulfiqar Cheema, DIG Elite Police Force,

Chairman

Muhammad Farooq Mazhar, DIG,

Member

Zulfiqar Hameed, AIG, Admin. PHQ,

Member

Inspector Abid Hussain Shah,

Member/Incharge Investigation.

11.6. The committee continued investigations, collected the postmortem reports, visited Punjab Institute of Cardiology, interviewed all concerned persons and also visited patients at the Service Hospital. It also visited the Punjab Drug Testing Laboratory and Chemical Examiner's Office to collect the requisite information. After a preliminary report had been received from U.K, according to which the tablet Isotab Batch J093 was found contaminated with anti-malarial product pyrimethamine, the investigating officers again visited PIC for procurement of record concerning the said medicine. They discovered that the PIC records did not mention receipt of Batch No.J093. However, on checking records of the distributor, supply of Batch No.J093 was found to have been made. On 01.02.2012, the owners of Omar Trading Company were interrogated and joined in the investigation.

11.7. The investigating officers also collected post-mortem reports prepared by the Special Medical Board, which opined as follows:-

“Postmortem findings on gross appearance in the GIT (Gastro Intestinal Tract) are suggestive of being caused by some toxic/irritant substance. This fact is also apparent from the

reports issued by the Histopathologist which reads as:

The stomach and small intestine sections reveal mucosal erosions and associated hemorrhagic necrosis.

The small intestine section reveals diffuse mucosal erosions and associated hemorrhagic necrosis.

Skin tissues reveal increased basal layer melanocytes.

This substance is also depressant to the Haemopoietic tissues i.e. the Bone Marrow. It may have caused suppression of the bone marrow due to its toxicity, a fact which is evident from the reports issued by the Histopathologist.”

The report of Histopathologist reads as “bone marrow dysplasia in the form of Myelodysplasia, Megakaryocytic aplasia, alongwith degenerative cellular changes” which is an evidence that the bone marrow is not producing the blood elements due to the effects of the toxic/irritant substance. After consulting the members of the Special Medical Board, it has been agreed upon that the effects of this toxic/irritant material in the body of the heart patients may lead to their deaths in due course of time.”

11.8. The Drug Testing Laboratory also gave a report to the Investigating Team relating to Tablet Isotab from Batch J093 stating that the said sample contained anti-malarial ingredient i.e. pyrimethamine. Hence the samples were found adulterated and substandard. The team also took into custody report of the Central Drug Laboratory, Government of Pakistan, Karachi verifying that the samples of Isotab 20mg from Batch J093 were contaminated with pyrimethamine. The team also went to Karachi and visited the factory of Efroze Chemicals. Subsequently, the investigation was entrusted to another team headed by Additional I.G. Mr. Aslam Tareen.

11.9. Some members of the investigation team including Additional I.G, Mr. Aslam Tareen, Mr. Abid Hussain Shah and Mr. Zulfiqar Ahmad Cheema, DIG Elite Police Force were summoned by the Tribunal. Mr. Zulfiqar Ahmad Cheema, also submitted his report and also answered questions of the Tribunal regarding material aspects of his investigation sharing the information available to him for assistance of the Tribunal. The statement of the said officer is Exh.I.W.31. The documents provided by the said witness are Mark 31/1 to Mark 31/08.

11.10. It is apparent that the investigation conducted by Mr. Zulfiqar Ahmad Cheema, DIG was ably conducted. Substantial information was collected by him, which is helpful in understanding the facts and circumstances in which this tragedy occurred. Further, the Tribunal is of the view that the investigation would have been more comprehensive and complete in case an expert Pharmacist or a qualified Drug Inspector had been associated with the investigating team at the very first instance. Further, the Heads of the Investigation was repeatedly changed, which

hampered the pace and direction of the investigation. The Tribunal recommends that in the first instance special expertise in investigating offences relating to drugs should be developed in the police organization as it is an important area of crime investigation, which has totally been ignored. Till such time as such expertise is developed, in the event of occurrence of an offence related to drugs, at the very first instance, duly qualified and experienced Pharmacists or persons specialized in this area should be associated with the investigation so that the matter is properly, systematically, technically and thoroughly investigated and culprits are brought to book at the earliest through successful prosecutions. In the instant case on account of frequent changes in investigation, lack of expertise, the matter of police investigation and prosecution lingered on for too long. We are consciously restraining ourselves from commenting on the criminal investigation lest it should prejudice the case of any of the parties in proceedings for determining criminal liability before courts of competent jurisdiction.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER -12-



**MANUFACTURER OF ADULTERATED DRUG EFROZE
CHEMICAL INDUSTRIES PRIVATE LIMITED KARACHI**

12.1 Efroze Chemical Industries Private Limited (Efroze) is a private limited company. It has been manufacturing pharmaceutical products for many years. It has its manufacturing plant in Karachi and also a separate godown in Korangi Creek Karachi. It manufactures a wide range of pharmaceutical products. These products are sold both locally in the market and to institutional consumers all over Pakistan. It is claimed that it also exports its products to many countries.



12.2. The company employs about 300 workers, out of whom only 25/30 are permanent and the rest are temporary workers provided by a contractor who are not employees of the company. They are hired through a contractor in order to work in various areas of the company. The number of temporary workers who are neither qualified nor trained to work in a pharmaceutical company is disproportionately high, fraught with risks, in utter violation of cGMPs and an obvious recipe for fatal mistakes, as seen in the present case. It appears that inaccurate information regarding the number of permanent and temporary workers was intentionally provided to the first commission which was re-verified by the second Commission and found to be incorrect. The second Commission found that 230 temporary

workers were employed to work in October, 2011. This trend has consistently been followed as is evident from the records of the Company and statements recorded by the Tribunal.

12.3 The workers provided by the contractor are daily wagers and work in various areas of the manufacturing facility. The company manufactures many pharmaceutical products. Besides other products, the company manufactures Isotab Tablet containing Isosorbide 5 Mononitrate. It also manufactures four other products containing a chemical called Pyrimethamine including Anti-Malarial medicine Maladar in tablet as well as syrup form. Pyrimethamine is not one of the ingredients of Isotab.

12.4. Manufacturing of pharmaceutical products is an extremely sensitive job. It requires strict adherence to Standard Operating Procedures (SOP) in order to ensure that there is no possibility of inter mixing and the probability of contamination is reduced to the minimum. Over the past many decades Good Manufacturing Practices (GMPs) and more recently Current Good Manufacturing Practices (cGMP)

http://search.who.int/search?q=GMP+guidelines&ie=utf8&site=default_collection&client=en&proxystylesheet=en&output=xml_no_dtd&oe=utf8) have been put in place all over the world in order to provide

guidelines and standard operating procedures to manufacturers of pharmaceuticals so that the products manufactured by them meet the highest standards of quality and risks of intermixing and



Medicine Testing Machinery

contamination are minimized. With this objective in mind great emphasis is placed on setting up systems of checks and counter checks, in-house testing, documentation at every stage of production, setting up of independent quality control and quality assurance departments, relying on known and reputable suppliers of raw material, and availability of requisite facilities within the manufacturer's premises which are required to be manned by qualified and experienced analysts and pharmacists. The Drugs Act, 1976 incorporates the GMPs which are required to be updated from time to time keeping in view the latest trends and discoveries.

12.5. It is also the primary responsibility of the regulator and more importantly the Drug Inspector as well as the Licensing Authorities which have the power to renew the licenses of pharmaceutical companies to conduct thorough and stringent inspections on periodical basis to ensure that manufacturers are fully cGMP compliant and are fulfilling all requisite requirements in letter and spirit. Manufacturing of pharmaceutical products is a serious matter and any lapse, intentional, un-intentional, negligent or careless can be disastrous as was seen in the present un-fortunate episode. Reference can be made to statements of D.G. Health, IW-65.Mr.Shahid Hussain Paichuho, DG, E&M Karachi IW-18 Saif ur Rehman Khattak, Inspector of Drugs, Karachi IW-19 etc. which shed light on the chain of events that resulted in the present fiasco.

12.6. In order to get a clear picture of the state of affairs at Efroze Chemical Industries, the Tribunal appointed two Commissions to visit the factory and submit reports. The Tribunal took the benefit of availability of 4 experts, 3 of whom were members of the Mission sent by WHO on the request of Government of Pakistan namely Mr. Michael Deats (IW-5),

Mohamed Bin Shahna (IW-6) and Syed Khalid Saeed Bukhari (IW-4). In addition Ms. Trudi Hilton (IW-7), who is a pharmacist by profession and was in Pakistan on the invitation of the Government of Punjab, was included in the first Commission to provide assistance to the Tribunal. The Commission visited the factory of Efroze on 17th and 18th of February, 2012. The Commission was accompanied by the Area Federal Drug Inspector and the Chief Analyst of the Central Drugs Laboratory Karachi. The Commission reported blatant violations at the factory.

12.7. Subsequently, a second local commission comprising the coopted Expert of this Tribunal again went to Karachi to conduct cGMP Compliance inspection of the factory and warehouses of Efroze. Both Commissions found serious violations and non-compliance of drug laws specially cGMP. Reports submitted by both commissions are significant in identifying causes of contamination and constitute an integral part of this report. Copies of the reports of both commissions are appended with this report.

**SOME OF PHOTOGRAPHS TAKEN BY THE
SECOND COMMISSION SHOWING cGMP VIOLATION**

Efroze Industry premises



Efroze passage area for workers





Efroze installed machinery



Efroze worst condition of steel pipes



Efroze installed machinery

Efroze worst condition of machinery



Efroze quarantine area



Efroze raw material store

Efroze raw material store



Worst condition of store



View of factory roof



WEAKNESS OF ENFORCEMENT, LAX INSPECTION CRITERIA AND REGULATORY FAILURES AT KARACHI

12.8. The law requires periodical inspections of plants and factories of manufacturers of pharmaceutical products, to ensure CGMP Compliance. A complete and comprehensive inspection is also mandatory at the time of renewal of license. Both commissions of experts sent by the Tribunal to visit and inspect the factory of Efroze Chemical Industries found serious violations of cGMPs and unanimously opined that the factory was not cGMP compliant. We find it very strange to note that Efroze Chemical Industries was repeatedly declared cGMP Compliant by the concerned Inspector and was issued a clean chit for renewal of its license. We specifically summoned Mr. Shahid Hussain Pachuhio (IW-18) and questioned him in this regard. We have serious reservations about the mode and manner in which such inspections were conducted and clearance reports issued. We also examined Mr. Saif-ur-Rehman Khattak (IW-19), Inspector of Drugs Karachi, who had recorded reservations regarding cGMP Compliance by Efroze at the time of renewal of its license. Strangely enough, he was replaced from the panel commissioned to conduct an inspection prior to renewal of the license of Efroze Chemicals. The reconstituted panel gave a clearance report and the license was renewed by the Drug Regulatory Authority.

12.9. It may be noted that cGMP Compliance is the only safety net between manufacture of drugs and their consumption by patients. Absence of this net (as was seen in the instant case) can expose patients to fatal risks. The laxity on the part of regulatory authorities in this case is an extremely serious matter and needs to be urgently probed, investigated and

addressed at all levels. Those found responsible must be proceeded against in accordance with law.

NON COMPLIANCE OF cGMPs BY EFROZE CHEMICAL INDUSTRIES

12.10. It was found by both commissions sent by the Tribunal that active and in-active raw materials arrived in the same warehouse which was part of the factory. All active pharmaceutical ingredients (APIs) were tested in-house to ascertain correct specification. In-active materials were sampled and tested randomly. The materials were thereafter moved to a designated store room on the first floor after API testing was complete.

12.11 The store room had shelves and also contained a small quarantine area. The Commissions were informed that when a requisition is received in the store room for ingredients required to manufacture a batch of medicine, such ingredients are moved to the dispensing area and weighed. Depending upon the quantum of demand, the ingredients are issued in the form of intact drums in which they were initially brought into the factory or placed in poly bags. The process of dispensing is supposed to be undertaken in the presence of a



Efroze raw material store

pharmacist, a representative of Quality Assurance ("QA") Department and a representative of production department who is accompanied by a worker. It may, however, be pointed out that only API is dispensed in the presence of the aforesaid staff. The practice is that the excipients/other ingredients

have already been dispensed when the aforesaid staff gathers in the dispensing area for dispensing of the Active Pharmaceutical Ingredients ("API"). As soon as the ingredients are complete, they are placed in a trolley and taken to the ground floor where there are a number of granulation rooms for the purpose of sieving (if necessary) and mixing. Once the ingredients reach one of the granulation areas, which are five in number, the process of granulation starts under the supervision of the Production Manager. The process of mixing is also supposed to be supervised by the Production Manager, however, the actual work is undertaken by a helper (statement of Muhammad Rizwan, IW-68). The practice at Efroze was that the active ingredient was put in the process of mixing in presence of the Supervisor while the rest of the ingredients were put in the machine by the helper, who completed the process of mixing.

12.12. The mixed ingredients were thereafter sent to the Compression Area for making tablets. During this stage samples were tested during in-process testing for weight, uniformity, disintegration and friability.

12.13. On completion of the batch the tablets are sent to the blistering area, where it is packed into blisters and the batch number and expiry date is embossed on each blister, which contains 20 tablets. The blisters are packed into a box containing 25 blisters (500 tablets) for institutional purchasers.



Efroze medicine machinery view

As per requirements of the PIC order, each blister is inkjet printed “PIC Property Not For Sale”.

12.14. Once the aforesaid process is complete, the finished tablets are submitted to the Quality Assurance Laboratory for testing using HPLC equipment. The said test is meant to ensure that the sample tablets contain the correct quantity of API as claimed in the label.

12.15. According to the copies of Batch Manufacturing Records which were submitted before the Commissions as well as the Tribunal, the manufacturing process of Batch No.J093 of Isotab started on 21.09.2011. By 26.09.2011, the entire batch was complete whereafter it was to be dispatched to Omar Trading Company on its way to PIC, the ultimate consumer.

12.16. According to the information provided to the Commission by the company including the documents placed on record Isotab consists of six ingredients. In order to manufacture a batch of 400,000 tablets following ingredients would have been required:-

Raw Material Requisition					
Date:	21/09/2011				
Product:	Nisid 20mg Tablet				
Batch No.:	J-093				
Batch Size:	400000 tablets / 80.00 kg				
Sl. No.	Q. C. No.	Name of Item	Quantity	Weight by	Checked by
1	1-053/12-g	Hydrochloride 5-Mononitrate 7550 Dilution (7% Overage)	11.658 kg	11/4	2/4
2	1-053/12-g	Pregelatinized Starch	26.800 kg	11/4	2/4
3	1-053/12-g	Avicel PH-102	26.800 kg	11/4	2/4
4	1-053/12-g	Talcum Powder	1.800 kg	11/4	2/4
5	1-053/12-g	Magnesium Stearate	0.571 kg	11/4	2/4
6	1-053/12-g	Aerocel 200	0.571 kg	11/4	2/4

View of raw material requisition

Ingredients	Batch Quantity
Isosorbide 5 Mononitrate	11.658 Kg
Pre-gelatinized Starch.	26.800 Kg
Avicel PH 102	26.800 Kg
Talcum Powder	1.600 Kg
Magnesium Stearate.	0.571 Kg
Aerosol 200	0.571 Kg

12.17. Out of the above ingredients, for Isotab Tablet, Isosorbide 5 Mononitrate was the active ingredient ("API"). However, all the ingredients were in the nature of white powder and an untrained eye could not appreciate the difference of one from the other. Owing to similarity of appearance it was of utmost importance that each movement, storage and use of each chemical ingredient used by the company in its factory was meticulously labeled, documented and supervised by professionals in strict compliance with SOPs and cGMPs in order to avoid the possibility of inter mixing or contamination. In the case of Efroze, it was found that such SOP's and CGMPs were either not in place or were not followed. In this regard reference may be made to the statement of Khurram Munaf, Director Technical Efroze Chemical IW-55, who stated as follows:-

"d) During the process of micronization, Pyrimethamine would have been taken out of its original drum, put in the machine for micronization and micronized

pyrimethamine would have been required to be collected in a bucket or drum. It is quite possible that the micronized pyrimethamine was collected in an empty drum of pre-gelatinized Starch, which contained a label to that effect. The said drum, which looks quite similar in colour with minor difference in shape, was returned to the store and kept in the storage area.”

12.18. Isosorbide 5 Mononitrate, Pre-gelatinized Starch and Avicel are supplied in 25 Kg Brown Cardboard Drums. The Tribunal has also been informed that Isosorbide 5 Mononitrate and Pyrimethamine are supplied in similar drums as are Pre-gelatinized Starch and Avicel. It was therefore fundamentally important that extreme care should have been taken to keep the said Chemicals segregated and clearly labeled to avoid any possibility of one being used instead of the other. This was obviously not done.

CIRCUMSTANCES AND CAUSES OF CONTAMINATION

12.19 In order to determine the circumstances and causes of contamination of Batch No.J093 of Isotab Tablets manufactured by Efroze Chemical Industries, we examined as many as 17 officials and employees of the company. They included most persons involved in various steps of the manufacturing process of Isotab. Most of them were either directly involved in the manufacturing process of Batch J093 or had direct knowledge about various material facts. Their testimony revealed some startling facts. While we do not wish to burden this report with reproducing their testimony, it will be useful to give a summary of the information and facts revealed by them. These amongst others furnish basis for the

conclusions drawn by us relating to fixing responsibility for contamination of the drug in question.

12.20 IW-54 Shakeel Ahmed General Manager Plant Operations stated that a 25Kg drum of Pyrimethamine which had been stored on the ground floor warehouse of the factory had been lost. This fact was discovered on 29-09-2011 when a batch of Maladar Syrup was required to be manufactured. This was reported to Mr. Abdullah Feroz on the telephone the same day and was followed up through email on 04-10-2011. He added that the batch of Maladar Syrup was manufactured by arranging 10 Kg of Pyrimethamine from Martin Dow Chemicals. He further stated that despite information provided to the head office regarding the missing quantity of Pyrimethamine no remedial action was taken by the head office. He however did not know if Retention Samples of Isotab or any other medicine manufactured by the company during this period were checked for mixing or contamination.

12.21. IW-55 Khurram Munaf, Director technical stated that on January 23/24 Nadir Khan Feroz IW-71, Deputy Managing Director asked him to get retention Batches of Isotab 098, 100 and 101 tested from the Karachi University. However the said exercise remained inclusive. However, on 31-01-2012, he was asked by Nadir Khan Feroz to reach the factory at around 11.30 pm for the purpose of testing samples of Isotab to check for Pyrimethamine contamination. He accordingly reached the factory premises where tests were conducted to detect presence of Pyrimethamine in retention samples of Batch nos. 098, 100 and 101 of Isotab which had been supplied to PIC. The said samples were not found contaminated. After midnight, Danish Feroz reached the factory. He looked panicked. He talked

to Nadir Khan Feroz and both left the factory. Before leaving Nadir Khan Feroz directed them to check retention samples of all batches of Isotab supplied to PIC. Therefore, retention samples of other batches were procured from the retention room and were tested one by one. The retention sample of Batch JO93 was found contaminated with Pyrimethamine. The test was repeated and the contamination was confirmed. He accordingly informed Nadir on the telephone. The said witness also testified that on 28/29 September 2011, Syed Razi Haider IW67 and Iftikhar Ahmed Shah IW63 had discovered that a 25kg drum of Pyrimethamine was missing. They informed Shakeel Ahmed Khan General Manager Plant IW54 and Waqas Hussain Shah, Supply Chain Executive IW64 about this fact. Some efforts were made to trace the drum, which were unsuccessful. A meeting of the concerned officers and workers was also called. Such meeting was not fruitful either. Mr. Abdullah Feroz was accordingly informed through an email dated 04-10-2011. No further testing, search and investigation was carried out. In his opinion the contamination may have occurred on account of mixing up of drums containing the chemicals in the warehouse/store.

12.22. IW.56 Fayyaz Ahmed, Senior Quality Control Officer of Efroze Chemical Industries informed the Tribunal that manufacture of Pharmaceuticals requires highly controlled systems. Testing methods are also established for specific active compounds as claimed in the label of the medicine. Chemicals used in manufacturing drugs are pre tested and kept under tight procedural controls. However, only (Active Pharmaceutical Ingredients) API's are tested and analyzed. He pointed out that the Quality Control Department ("QC") makes Standard Operating Procedures ("SOP")

for each product, with defined parameters including testing methods, which are required to be followed. He stated that Isotab has a single active ingredient namely Isosorbide 5 Mononitrate. He admitted that he tested a sample out of batch No. J093 according to the defined parameters using the prescribed testing method and did not find anything wrong with it. He submitted the test report along with the evidence (Chromatogram etc.) with the authorized person namely Mr. Atiq ur Rehman, the Quality Control Manager, IW.57. The Witness stated that Pyrimethamine was neither one of the ingredients of Isotab nor were the samples tested to detect the same. He stated that he did not receive any special instructions at any stage to run tests to detect presence of Pyrimethamine. The samples were tested as "Normal" samples and not "Complained" Samples. The witness further stated that Pyrimethamine has different properties than Isosorbide 5 Mononitrate and a different test and analytical method is required to be used to detect its presence in a drug. He added that it was not possible to detect Pyrimethamine by using the analytical method of Isosorbide 5 Mononitrate. He stated that he worked under the assumption that the samples sent for testing had been manufactured on the basis of formulation given in the pharmacopeia and could not even imagine that anything else would have been mixed in the formulation. The witness was shown a copy of the Chromatogram of the sample from Batch J093. He admitted that a small peak had appeared before the large peak indicating presence of Isosorbide 5 Mononitrate. However he stated that in his opinion the smaller peak could have been a solvent front or excipient and did not consider it necessary to probe it any further.

12.23. IW-57 Atiq-ur-Rehman, Quality Control Manager stated that samples of Isotab were tested on HPLC equipment. He was shown the Product Analysis Report of Batch J093 (Exhibit IW-4/8) dated 26-09-2011. He stated that although there was a small peak at 2 minutes appearing in the Chromatogram, such peak appeared to be on account of a solvent front or an excipient. He stated that as an analyst he was only required to look for the Active Pharmaceutical Ingredient ("API") and to ensure that such API was in the correct quantity as per the pharmacopeia. Since Isosorbide 5 Mononitrate was in the correct quantity in the testing sample of Batch J093 the same was approved. He did not feel the necessity to probe the peak that appeared in the Chromatogram.

12.24. The Witness testified that Khurram Munaf, the Director Technical, IW.55 called him on 31.01.2012 at around 11.30 pm and asked him to reach the factory for conducting some tests. When he reached the factory Khurram Munaf, Imtiaz Ahmed, QC Manager IW-58 and Nadir Khan Feroz (IW-71) were already there. They brought the retention samples of Isotab Batches J098, J100 and J101 from the Retention Room on the Second Floor of the Factory. Imtiaz Ahmed conducted tests to see if the samples had Pyrimethamine but nothing was found in the said samples. Later, Khurram Munaf told us that Nadir Khan Feroze wanted us to test all batches of Isotab supplied to PIC. He (IW-56) brought retention samples of Isotab of Batch Nos. J90 to J098 including those of Batch J093 from the retention room of the factory. During batch wise testing they found the retention sample of Batch No.J093 to be contaminated with Pyrimethamine. They repeated the tests a few times and the results were the same each time. They used the testing methodology for detecting Pyrimethamine for

conducting the tests. Khurram Munaf accordingly informed Nadir Khan Feroz about the same. The witness stated that the possibility of a helper negligently mixing pyrimethamine instead of Pre-gelatinized Starch during manufacturing process could not be ruled out. He admitted that there was room for improvement at the factory systems. HVAC systems needed to be installed, air handling units were not functioning. Further, a proper flow of the manufacturing process needed to be put in place. He pointed out that the raw material store had no receiving area. Incoming raw material was received on the ground floor and was stored on the ground floor as well as the first floor. Separate store rooms were not available for raw materials and finished goods, packaging material was also stored on the ground floor in the same storage area and the quarantine area was not segregated from the rest of the storage areas. He also admitted that according to his information no meeting of the top management took place after loss of a drum of Pyrimethamine was reported.

12.25. IW-58 Mohammad Imtiaz Ahmed, Manager Quality Control, Efroze Chemical Industries stated that at the time when samples from Batch No.J093 were first tested on 26-09-2011 he was Manager Quality Control and Research and Development. On 31-01-2012 he received a call from Khurram Munaf IW-55 who asked him to reach the factory to conduct some tests. Nadir Khan Feroz IW-71 also called him for the said purpose. When he reached the factory at about midnight, Nadir Khan Feroz, Khurram Munaf and Atiq ur Rehman were already there. Atiq and Khurram gave him samples from batch Nos.J098, J100 and J101 to run specific tests to detect presence of Pyrimethamine. He ran the standard tests for the said purpose on HPLC equipment in the Laboratory of the factory. The said

samples did not contain Pyrimethamine. Khurram Munaf then asked Atiq ur Rehman to bring Retention Samples of Batches starting from Batch No. J090 onwards from the Retention Room of the factory. He did so and gave him retention samples sequentially starting from Batch J090. He ran tests on HPLC Equipment for detection of Pyrimethamine. He found a large Peak on the Chromatogram of the sample of Batch J093 which indicated presence of significant quantities of Pyrimethamine in the sample. He was asked by Khurram Munaf and Atiq to repeat the test several times. The results were the same. He left the factory early in the morning leaving the flasks in which he had performed the tests in the Laboratory. He stated that prior to that, he was never asked to conduct any test to detect presence of Pyrimethamine in any sample of Isotab. He admitted that if an analyst conducted tests of different batches of the same medicine in a sequence, any abnormal peak in the Chromatograms should have been reported. He also admitted that if there was a suspicion that Pyrimethamine may have been mixed in a drug, an unexplained peak should have been seriously probed. He however submitted that in that case a test specific to Pyrimethamine would have been required to be conducted.

12.26. IW-59 Altaf Ahmed Qureshi, Production Manager appeared before the Tribunal and stated that in September 2011 it was reported that a 25 Kg drum of Pyrimethamine was missing. An effort was made to search for the drum. It was not found. The General Manager Plant, Shakeel Ahmed IW-54 called a meeting which was attended by the witness, Salman (Supply Chain Manager), Iftikhar Ahmed Shah, Store officer IW.63, Syed Razi Haider Kazmi Store Helper (IW.67), Syed Tabish Nomani, Production Executive (IW.60), Mohammad Rizwan, Production Helper (IW68). The

meeting was called to trace the missing drum of Pyrimethamine. During the meeting Razi Haider alleged that he had issued the drum to Rizwan for micronization which he had not returned. Rizwan denied the allegation. Syed Tabish Nomani also denied having instructed Rizwan to receive a drum of Pyrimethamine from the store for micronization. The witness also admitted that the drum appeared to have gone missing from the store. The empty drum was never found. The witness admitted that the storage area of the factory was not organized, there was no segregation of active ingredients and excipients, there was no separate quarantine area and there was no separate store for finished goods. He also admitted that now it had been established that pyrimethamine got mixed in the ingredients during production of Batch No.J093 of Isotab. According to the witness the error probably occurred in the Raw Material store where a drum of Pyrimethamine may have been issued instead of a drum of Pre-gelatinized Starch.

12.27. IW-60 Syed Tabish Nomani testified about the production facilities at factory of Efroze Chemical Industries and the procedures followed in the manufacture of Isotab. He stated that the Store Dispensing Staff may have committed an error in dispensing Pyrimethamine instead of Pre-gelatinized Starch. He stated that during the month of September 2011 there were heavy rains in Karachi and some of the drums got soaked in water. The ingredients of such drums were taken out and stored in other drums which were lying in the storage area. According to him, Pyrimethamine may have been put in an empty drum of Pre-gelatinized starch and the same was mistakenly issued as such. He came to know about the missing drum for the first time on 29-09-2011 when Pyrimethamine was required for production of Maladar Syrup and the store

staff could not find it. He admitted having attended the meeting called by Shakeel Ahmed Khan, General Manager Plant (IW-54). He categorically denied having asked for issuance of a drum of Pyrimethamine for micronization. He also denied having asked Mohammad Rizwan, Helper (IW-68) to do so.

12.28. IW-61 Amjad Javaid Lodhi, Production Executive testified about the production process. He stated that he did not detect anything unusual during production of Batch J093 during compression stage. The samples taken were found to meet the requisite parameters of hardness, thickness friability etc. and were sent to the Quality Control department which approved them. He stated that the Audit Department of the company conducts a monthly audit of the inventory of raw materials. They should have discovered that Pre-gelatinized Starch was in excess which would have easily led them to conclude that the missing 25kg Pyrimethamine had been used somewhere instead of 25 Kg Pre-gelatinized Starch. The witness stated that the error occurred at the dispensing stage in the storage area.

12.29. IW-62 Kashif Abdullah, Deputy Production Manager, Efroze Chemical Industries, Karachi deposed that at the relevant time, he was Incharge of the Suspension Section of the company, which amongst others produced Maladar Suspension. A batch of the said suspension was to be produced in the 3rd week of September, 2011. Accordingly, a request was sent for release of ingredients of Maladar, which included pyrimethamine. The said ingredient was not issued because it was discovered that a drum of pyrimethamine was missing. As a result, production of the batch was delayed. Efforts were made to find the missing drum, which were

unsuccessful. Ultimately, alternate arrangements were made to procure pyrimethamine from another company. He explained the various steps involved in the manufacturing process including the methodology adopted to receive ingredients from the store. He stated that the ingredients are received by the production staff and the excipients were weighed in the dispensing area. In case, ingredients of the entire drum were required and the same was intact, the production staff did not open the drum or check its ingredients. He also stated that in the area where liquid production took place, there was one permanent employee and the rest were daily wagers. He stated that he heard about contamination found in Isotab 20mg Batch J093 on 1st February, 2012.

12.30. IW-63 Iftikhar Ahmad Shah, Store Officer appeared and stated that he did not issue ingredients for Isotab Batch J093. The said ingredients were issued by Ms. Khadeeja, Dispensing Assistant, who did so in his absence. He claimed that there were two drums of pyrimethamine in the store. The first was released on 13.09.2011. The second was released on 20.09.2011 for grinding. However, there was no record either of its release or its return. When the second drum was found missing on 27.09.2011, he reported the matter to Shakeel Ahmad Khan, General Manager, Plants (IW-54) who took control of the matter of taking steps to find the missing drum which were not successful. On a query by the Tribunal, the witness stated that Ms. Khadeeja was a Pharmacist/Dispensing Officer and had since left the company. A person named Aqil undertook the actual dispensing while Syed Razi Haider Kazmi (IW-67) worked as a helper. There were three other helpers in the store. He stated that there was no separate quarantine area in the store. All active

ingredients were sampled and tested at the time of supply. However, excipients underwent random sampling. Once an active ingredient was tested and passed, it was placed in racks on the first floor or the storage area on the ground floor where space was available. Active ingredients were not stored in any particular order. He further stated that on 21.09.2011, when ingredients for Isotab Batch J093 were dispensed, he was out for lunch. Ms. Khadeeja, who was then on probation, dispensed all six ingredients in his absence. The witness deposed that in the month of September, 2011, there were heavy rains in Karachi and the ground floor (of the factory) was flooded. Further, on 10.09.2011/12.09.2011, a consignment of pyrimethamine and sulphadoxine was received in the factory. Some of the drums had fungus around the lid having been soaked in rain while lying at the Port. The said drums were discarded and the contents were shifted into blue plastic drums taken from the storage area. He further stated that the company did not always follow a written programme. On verbal instructions of the Production Manager, ingredients were dispensed without a written requisition.

12.31. On 27.09.2011, the Store Helper Razi Kazmi told him that he had given a drum of pyrimethamine to Muhammad Rizwan IW-68 for micronization and the same had not been returned. He had received a requisition for pyrimethamine for production of Maladar Suspension and a drum containing the said ingredients was missing. However, Muhammad Rizwan flatly denied having received the drum for micronization. He informed Salman Malik about the missing drum the same day. The next day Shakeel Ahmad Khan (IW-54) called a meeting regarding the missing drum. He was informed that the drum was missing since 20.09.2011. The witness

stated that since the drum was not found, the General Manager, Plant should have stopped all batches of medicines manufactured after 20.09.2011 for testing. According to him one or two days of search for pyrimethamine would have disclosed where it had been used. The witness admitted that there was sufficient time not only to detect presence of pyrimethamine in Batch J093 but also to stop the said batch from leaving the factory. According to him Isotab BatchJ093 left Karachi on 04.10.2011. He further deposed that the production process was undertaken by semi-literate workers who were daily wagers. Any of the said workers could have mistakenly put pyrimethamine instead of pre-gelatinized starch in the mixing machine. However, there was excess pre-gelatinized starch in the inventory, which should have alerted inventory control that some other ingredient had been put in a medicine instead of pre-gelatinized starch and thereby contamination in Isotab could have easily been detected.

12.32. IW-64 Syed Waqas Hussain Shah, Supply Chain Executive deposed that in the production plan for September, 2011, two batches of Maladar tablets, 04 batches of Isotab and one batch of Maladar Suspension were scheduled to be produced. He stated that he did not seek any authorization for issuance of any raw material for grinding. He submitted that there was enough ground pyrimethamine available in the store and there was no occasion for requiring further quantities of pyrimethamine to be ground. He stated that on 29.09.2011 Iftikhar Ahmad Shah (IW-63) came to his room and casually mentioned that a drum of pyrimethamine had been misplaced. Subsequently, Shakeel Ahmad Khan (IW-54) called a meeting to trace the drum, which was unsuccessful.

12.33. The witness further stated that in September, 2011, drums of Sulphadoxine and pyrimethamine imported from China got soaked on the port and developed fungus. The Quality Control Department opened the containers and shifted contents in empty containers, which are generally thrown on the roof. He admitted that the company did not initiate any serious internal inquiry/investigation to trace the missing drum of pyrimethamine. He also disclosed that the company also purchased excipients from the local market (which is not permitted in terms of cGMPs).

12.34. IW-66 Shoaib Ansari, Helper appeared before the Tribunal and stated that he was daily wage worker and was employed by a contractor. He did not work continuously at the factory and was given breaks in service at intervals. He did not always work in the same area. He stated that he worked in such area as the supervisor told him to work. He did not have any special training. He disclosed that there were five granulation areas in the factory where 26/27 daily wagers worked. There was only one permanent worker working in five granulation areas. He stated that in the 3rd week of September, 2011, Isotab Batch J093 was manufactured. At the relevant time, Syed Tabish Nomani (IW-60) was his supervisor. He stated that he did not know how many ingredients were used in the manufacture of Isotab. He went with his Supervisor to the storage area, received the ingredients on a trolley and brought them back to the granulation area. A worker named Ishaq came from the Quality Assurance Department, checked labels of containers in the trolley, signed the necessary documents and left. The Supervisor directed him to put the ingredients in the machine. The supervisor was not present all the time while the ingredients were being put in the machine. He admitted that he

did not examine the labels before putting the ingredients in the machine and poured the ingredients as per directions of the Supervisor, one after the other.

12.35. IW-67 Syed Razi Haider Kazmi, Helper Efroze Chemicals appeared before the Tribunal and stated that active ingredients and excipients were stored in two storage areas of the factory. Most of the raw materials were stored on the first floor warehouse. However, excess raw material was also stored in the finished goods store on the ground floor. He stated that where the raw material was delivered to the production staff for grinding, there was neither any documentation for release of the same nor receipt of the same on its return. He stated that there was no standard operating procedure to undertake the aforesaid exercise. He stated that he issued a drum of pyrimethamine for grinding on 18/20th September, 2011. However, he did not remember the specific date. He stated that he released the drum on being directed by Iftikhar Hussain Shah, Store Officer (IW-63) to do so. On 27.09.2012, a requisition for pyrimethamine was received for production of Maladar Suspension. The drum of pyrimethamine was not available in the store. He informed Iftikhar Hussain Shah that Rizwan had taken a drum for micronization and had not returned it. He asked Rizwan about the drum, but Rizwan denied having received the same. The matter was taken up with Syed Tabish Nomani, Production Executive. However, Tabish denied having asked for a drum of pyrimethamine for micronization. Subsequently, Shakeel Ahmad, General Manager, Plant (IW-54) called a meeting to trace the drum. However, the same could not be traced. The witness revealed that despite the fact that a drum containing 25 kg of pyrimethamine was not traceable, nobody thought of the scenario that the

drum may have been used in the manufacture of some other medicine. He further stated that in September, 2011, drums of Sulphadoxine and pyrimethamine imported from China got soaked on the port and developed fungus. The Quality Control Department took out the ingredients from the fungus affected drums and put them in blue plastic containers. He admitted that it was possible that in case an ingredient was taken out from its original drum and placed in some other drum, the same may have been returned to the store and issued by it subsequently on the basis of label outside the drum without checking its ingredients.

12.36. Muhammad Rizwan, IW-68 stated that at the relevant time, he was a daily wager. On 29.09.2011, Syed Iftikhar Shah, Store Officer (IW-63) came to him and informed him that a 25kg drum of pyrimethamine was missing. Iftikhar Shah asked him if he had taken the same for grinding, which he categorically denied. Later, Iftikhar Shah came with Syed Razi Haider Kazmi, Helper in the store who stated that he had handed over a drum of pyrimethamine for micronization to Rizwan allegedly on the request of Syed Tabish Nomani. Syed Tabish Nomani flatly denied having asked him or anybody else to receive a drum of pyrimethamine to micronize the same.

12.37. The witness stated that subsequently all concerned were called for a meeting by Shakeel Ahmad Khan, which did not result in tracing the whereabouts of the missing drum. The witness further stated that he had done his matriculation. He started as a helper, but subsequently learnt to operate machines and now worked in the granulation area. He pointed out that during the process of manufacturing, a Supervisor was not always present when excipients were being put into the mixer. He revealed that

workers at the factory worked under great pressure from the management to do things quickly and such pressure could lead to errors. He submitted that ordinarily raw material was sieved before being put in the mixer. However, when there was pressure of work, there were instances, where the process of sieving was bypassed and the material was directly put in the mixer. He further stated that because of the nature and properties of pre-gelatinized starch and avicel (which are ingredients used in the manufacture of Isotab), they could be put into the mixer without sieving.

12.38. The witness also stated that on account of heavy rains in Karachi in the month of September, 2011, some drums got soaked. Their ingredients were taken out and stored in other drums which may have found their way to the storage area. According to the witness, there was a possibility that an error had been committed. Instead of pre-gelatinized starch, a drum of pyrimethamine may have been issued. This could have easily occurred if a poly bag containing pyrimethamine taken out of a soaked drum had been placed in a drum containing the label of pre-gelatinized starch.

12.39. IW-69 Muhammad Saleem, Security Incharge/Administrative Officer, Efroze Chemicals appeared and stated that CCTV Cameras were installed in the production section, office areas and packaging sections of the company. He stated that he was directed by the management to visit the warehouse of Trash Contractors to recover discarded drums of pyrimethamine. Despite efforts, no drum out of the recent lot that may have mistakenly been used in the production of Isotab was found. He, however, admitted that nobody was interrogated or investigated for alleged theft of a drum of pyrimethamine.

12.40. IW-70 Abdullah Feroze, Managing Director, Efroze Chemical appeared and stated that he was the Managing Director of the company since 2007. He denied having any role in the day to day working of the factory. He also denied having any direct knowledge of the facts. He stated that for the first time he came to know about contamination of Isotab on 01.02.2012 from the electronic media.

12.41. IW-71 Nadir Khan Feroze, Deputy Managing Director, Efroze Chemical Industries, Karachi appeared before the Tribunal and stated that Shakeel Ahmad Khan (IW-54) was Incharge of operations of the factory. The top management did not visit the factory regularly. On 31.01.2012, he was informed by Ahsan Feroze that he had received a call from Dr. Muhammad Javed Akram, Principal Allama Iqbal Medical College, Lahore inquiring if Efroze Chemicals manufactured any medicine containing pyrimethamine. He stated that he went on line and checked the products of all six companies, which supplied cardiac medicines to PIC to find out if any of the six companies manufactured drugs with pyrimethamine as one of the ingredients. He discovered that only Efroze manufactured drugs containing pyrimethamine. This set off alarm bells in his mind. He called Khurram Munaf (IW-55) and Imtiaz Ahmad (IW-58) and directed them to reach the factory to run tests on Isotab. He alongwith his brother Fahad reached the factory at around 11:30 P.M. on 31.01.2011. Others reached later. He directed the said persons to take retention samples of Isotab Batches J098, J100 & J101 from the retention room and test them for presence of pyrimethamine. The said batches were found clear. In the meantime, he was informed that breaking news was being flashed on television networks that pyrimethamine had been found in samples of Isotab by MHRA

Laboratories in England. Simultaneously, he received calls from his home as well as sales staff to leave the factory for security reasons. He directed Khurram Munaf, Director Technical to test retention samples of all batches of Isotab supplied to PIC starting from Batch J090 onwards. At about 4:30 A.M. on 01.02.2012, he was informed on telephone by Khurram Munaf that pyrimethamine had been found in the retention samples of Batch J093. The tests were repeated a number of times in the laboratory of the factory with the same result. In the morning, the Federal Inspector of Drugs and FIA staff came to the factory and took into custody certain stocks as well as flasks containing solution of Isotab J093 prepared from retention samples of Batch J093, which had been left by the staff the preceding night. The witness stated that an internal investigation had been conducted, however, there were no conclusive findings as to how this contamination occurred. He admitted that retention samples of Batch J093 were tested in the Quality Control Laboratories of the factory and the samples of Batch J093 had been found contaminated with pyrimethamine. He stated that he was relying on the investigation agencies to get to the root of things as to who was involved in the mixing/contamination of Isotab with Pyrimethamine.

12.42. It is now known on the basis of the test reports initially prepared by laboratories in UK, Switzerland and USA, which were confirmed by the local laboratories that Batch No.J093 of Isotab 20 Tablet, which was found to be contaminated with about 50 mg of Pyrimethamine per tablet, would have required approximately 20/25 Kg of Pyrimethamine to contaminate the batch to the extent calculated by the laboratories.

12.43. It is also established and has not been denied by any witness including employees and owners of the company that a wrong

ingredient (Pyrimethamine) had been mixed in the ingredients for Isotab 20 Tablet when Batch No.J093 was being manufactured (See statements of IW-54, IW-55, IW-59, IW-60, IW-66, IW-67, IW-68 & IW-71. The question is where could such mixing take place. It may be emphasized that the fact of mixing is neither disputed nor denied. On the basis of evidence recorded by this Tribunal it is evident that the mix up occurred in the store room. It appears that instead of dispensing 26.800 Kg of Pre-gelatinized Starch, an intact drum containing 25 Kg of Pyrimethamine was dispensed and balance amount of 1.800 Kg of Pre-gelatinized Starch was dispensed separately in a poly bag from a different container. Once the fatal error had occurred, all subsequent processes were mechanically completed and the error was not discovered at any stage of manufacturing.

12.44. During the compression stage various in-process tests including testing for weight, uniformity, disintegration and friability should have been conducted.

http://search.who.int/search?q=GMP+guidelines&ie=utf8&site=default_collection&client=en&proxystylesheet=en&output=xml_no_dtd&oe=utf8.

The absence of pre-gelatinized starch could have been noticed at that stage on account of different behaviour of the tablet. However, in view of the fact that the process was mechanically being conducted minor deviations in behaviour of the tablet, if any, were not picked up.

12.45. On completion of the batch, Quality Assurance Laboratory carried out testing. Such testing is undertaken amongst others by using

HPLC (High Performance Liquid Chromatography) equipment. The Chromatograph provides indicators in the form of different peaks appearing at different points in time showing presence of different chemicals. In case of Isotab a peak appearing at a specific time would have indicated the presence of Isosorbide 5 Mononitrate in the sample. It is evident from the record that while testing batch J093, an unusual peak appeared in the Chromatograph which had not appeared during testing of other batches. On the basis of historical data available to the persons undertaking the testing, they should have noticed and investigated the out of trend (extraordinary) peak which appeared during testing before the principal peak in the same chromatographic condition, while testing batch No.J093 of Isotab. It is an admitted position that all six batches of Isotab required to be sent to PIC were tested and chromatograph of each was available. However, the abnormal peak was not investigated. Such investigation could have shown contamination and by withholding the contaminated batch the tragic loss of many lives lost on account of use of contaminated medicines of Batch No.J093 could have been averted.

12.46. According to the information brought before the Tribunal in the form of witnesses statements and documents, by 28th/29th of September, 2011, the company discovered that a 25 Kg drum of Pyrimethamine was missing. IW-55 and others testified before us that:-

“The absence of 25 Kg Drum of Pyrimethamine was discovered by Iftikhar, Store Incharge/ Razi, Store Helper, on 28/29.09.2011.”

12.47. This information allegedly came to light when a requisition for Pyrimethamine was sent to the store to commence production of a batch of Maladar. The store staff alleged that they had issued a 25 Kg drum of Pyrimethamine to the production staff through Rizwan Helper, who was then working as a daily wager and the same had not been returned. However, this allegation remained unproved.

12.48. There was no documentation either regarding issuance of said drum or return of the same. The matter of the missing drum was reported to the Production Manager. Search for the said container/drum was started within the factory as well as in the stores of the Trash contractor. The container/drum was allegedly never found. A meeting was convened by Mr. Shakeel Ahmad Khan IW-54, General Manager Plant Operations, which was attended by Mr. Tabish Nomani IW-60, Production Executive, Helper Rizwan IW-68, Store Officer Iftikhar IW-63, Store Helper Razi IW-67, Supply Chain Manager Salman Malik and Production Manager Altaf Qureshi IW-59. The allegation that the drum had been released to Rizwan and not returned could not be proved. The matter was reported to the top management by the Production Manager on the telephone and later on through e-mail. However, the drum in question could not be traced and it was presumed to have been stolen. As a matter of procedure and following the guidelines of cGMPs, the company should have tested all batches manufactured between 21.09.2011 to 29.09.2011 to ensure that the said missing quantity of Pyrimethamine was not mistakenly used in the manufacturing of any other medicine. This exercise could easily and conveniently be undertaken within a few hours because the retention samples of all batches including Batch No.J093 were in possession of the

Company. Unfortunately, this was not done. This act of gross negligence and callous disregard for human lives cost about 200 precious lives.

12.49. There is another way to look at this scenario. Even if for the sake of argument, it were to be assumed that 25 Kg drum of Pyrimethamine had been stolen, there should have been an increase in the quantity of available Avicel or Pre-gelatinized Starch which was supposed to have been used and was not used in the manufacture of Isotab. This clearly shows a failure of inventory control system which was not maintained in accordance with cGMPs (Inventory Reconciliation System). In view of the fact that a certain quantity of Pyrimethamine was alleged to have been stolen or had disappeared or wrongly used, the company should have immediately taken inventory of at least the missing ingredients as well as Avicel and Pre-gelatinized Starch. This could easily have been done, but regrettably was not done on account of negligence, carelessness and complete disregard of cGMPs on the part of the management of the company.

12.50. The Tribunal is also perturbed to note the extreme carelessness, utter irresponsibility and criminal negligence on the part of senior officers and management of the company, who were fully aware that a 25 Kg of Pyrimethamine was missing and the possibility of the said ingredient being mixed with any other medicine in which it was not supposed to be present, could not be ruled out. They had discovered this fact on 29.09.2011 and had sufficient time to test batches manufactured between 21.09.2011 and 29.09.2011, but did not care to do so. The ease and simplicity of the testing procedure is evident from the fact that they managed to test more than 10 batches of Isotab within a span of few hours

in their own laboratory on the night of 31.01.2012 and were able to discover that Batch J093 of Isotab 20 Tablet was contaminated by Pyrimethamine. But by that time, it was too late and the damage in terms of loss of hundreds of precious lives had already been done.

RESPONSIBILITY FOR CONTAMINATION AND ITS CONSEQUENCES

12.51. It may be noted that the consignment of Isotab which included Batch J093 was shipped from the factory to Lahore after 29.09.2011. It reached PIC on 08.10.2011 and was formally entered in its relevant register on 10.10.2011. By that token the company had more than a week to stop the supply before it reached PIC and a number of days after that when they could have contacted PIC and restrained them from dispensing the batch in question. Even after that they had a whole month to inform PIC that there was contamination of Pyrimethamine in Isotab 20 mg Tablets supplied to it. The batches could have been withdrawn. However, unfortunately the company decided to ignore its responsibility let commercial and financial considerations override patient safety and waited for the damage to be done in the form of loss of precious lives and serious medical complications for more than 1000 Cardiac Patients, who fell seriously sick on account of ingestion of the contaminated drug.

12.52. According to the information provided to the Tribunal by various witnesses including the Federal Drug Inspector, who visited the factory of Efroze on 01.02.2012 after identification of Isotab contamination by Pyrimethamine by MHRA Laboratories, an effort was also made by the

company to tamper with and conceal evidence. Efroze Chemical Industries was required to maintain retention samples of each batch of medicines produced by it. An attempt was made to manipulate the retained samples by embossing Batch No.J093 and its expiry date on retention samples of other batches which, to the knowledge of the company, were not contaminated. This attempt at manipulation and thereby misguiding the investigation did not succeed on account of the crudeness of the attempt at embossing Batch No.J093 on strips on which different batch numbers had already been embossed. Further, strips of Isotab from Batch No.J093 had also been recovered from the patients, who had either died or had suffered symptoms. It is also clear and admitted by various employees of Efroze that on the night of 31.01.2012 and 01.02.2012, when test results provided by MHRA were televised by various channels confirming presence of Pyrimethamine in samples of Isotab, members of the management, staff and analyst went to the factory and carried out urgent test of retained samples of Isotab. They found the retained samples of Isotab Batch J093 to be contaminated by Pyrimethamine. Remnants of these tests in solution form were still present in the testing flasks, which were taken into custody and delivered to CDL after following procedural requirements. After conducting the requisite tests, CDL confirmed, that the solution made from retained samples of Isotab Batch J093 contained substantial quantities of Pyrimethamine.

12.53. There is overwhelming evidence in the form of oral testimony and documents available on record to establish that the contamination in Isotab Batch J093 with pyrimethamine occurred within the factory. Almost all witnesses including the Director Technical, Production Executive, Quality

Control manager and the Deputy Managing Director have admitted the said fact. This Tribunal is, therefore, in no manner of doubt that the first and foremost responsibility for this tragedy, which has cost about 213 lives and medical complications for over 1000 cardiac patients squarely lies on the management and senior officers involved in production and supply of Batch J093 of Isotab 20 Tablets to PIC. The Drug Regulatory Authorities and law enforcement agencies need to take strict legal action against the Company, its management and staff in accordance with law.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER

-13-

RECOMMENDATIONS



**CONSOLIDATED
RECOMMENDATIONS****13.1. RECOMMENDATIONS RELATING TO MANUFACTURERS / PRODUCERS OF DRUGS.**

- a) In view of our finding that the first and foremost responsibility for this tragedy lies on Efroze Chemical Industries, we strongly recommend strict legal action against the Company, its management and others involved, under the Drugs Laws as well as the relevant provisions of the Pakistan Penal Code, in view of findings recorded in this report, the reports submitted by the two Commissions appointed by the Tribunal and investigation carried out by the investigating agencies.
- b) During the course of proceedings before the Tribunal it has transpired that a large number of manufacturers engaged in manufacture of pharmaceuticals in Punjab and other provinces may not be in compliance of provisions of Drug Act, 1976. Further, we have reason to believe that an equal number of manufacturers all over the country are not cGMP compliant. This is an alarming situation for the reason that the only safety net against errors, omissions, defects, contamination etc. of the drugs and preventing such drugs from reaching the hospitals, markets and patients is at the stage of manufacturing. Compliance with cGMP requirements minimizes the possibility of the defective or injurious drugs reaching the hospital, markets or patients. Once a defective, contaminated or injurious drug comes out of the factory, it is extremely difficult to detect the same and where an exercise of such detection is undertaken, it takes time, effort and resources, which in most instances are not available in Pakistan, as was highlighted in the present episode. This is an all the more reason to stress on strict compliance of cGMP requirements.

- c) With the aforesaid in mind, the Tribunal recommends that a task force comprised of adequate number of qualified experts in the field of pharmaceutical manufacturing be constituted in order to undertake thorough and detailed cGMP compliance audits of all manufacturers in Punjab.
- d) The task force must be provided a target date within which the entire exercise is required to be completed. The Tribunal is mindful of the fact that the number of manufacturing facilities runs into hundreds while the number of experts available and willing to undertake such audit may be limited. It is, therefore, recommended that in the first instance, the Government of Punjab should constitute a core committee, which should identify experts of pharmaceutical manufacturing and production in sufficient numbers.
- e) cGMP auditors must be provided the requisite facilities, back up, equipment, staff and the legal support in order to undertake the aforesaid exercise and complete their job within the shortest possible time.
- f) A standard and detailed form for undertaking such inspection based on points system must be developed in consultation with experts in the field to facilitate the work of cGMP Inspectors and to introduce standardization of such inspections.
- g) The Inspectors must issue certificates relating to cGMP compliance in a standard format. The veracity of such certificates may be counterchecked by random surprise inspections through independent cGMP Audit Teams. In case such certificate is found to be false or deficient, strict disciplinary action against the inspector issuing such certificate should be taken in accordance with law. The requisite legal framework to support the aforesaid actions must be put in place on top priority.

- h) Appropriate orders must be passed directing those companies which are manufacturing drugs despite major and critical deficiencies from the point of view of cGMP compliance, to suspend production till such time that such major and critical deficiencies are removed and a clear cGMP compliance certificate is issued by the concerned authorities.
- i) Depending on the size and capacity of the manufacturer, it must be made obligatory on manufacturers to employ duly qualified Pharmacists as properly trained workers in sufficient numbers in all necessary areas of the manufacturing process. Under no circumstances temporary workers should be allowed to work in manufacturing and allied activities.
- j) Companies manufacturing drugs despite minor deficiencies pointed out during inspections must be given a specified time to remove such deficiencies to the satisfaction of the concerned authorities. In case such deficiencies are not removed within the time frame granted, such companies may be directed to suspend production till such time that they remove the deficiencies and obtain a clear cGMP compliance certificate.
- k) During the course of proceedings, it was brought to our notice that the structure of drug regulation in the province has deteriorated considerably over a period of time. Provincial Drug Inspectors do not ordinarily visit factories or conduct inspections from the point of view of cGMP compliance. The said work is left to be conducted by the Federal Drug Inspectors who are limited in number and are unable to cope with the level of man hours required to be invested in undertaking the aforesaid inspections on regular basis. The Tribunal, therefore, recommends that the duties and powers of Provincial Drug Inspectors may be re-vitalized by re-activation of the office of the Chief Drug Inspector,

Provincial Drug Inspectors etc. This can be done by providing them the requisite facilities and placing responsibility of conducting periodical inspections of Pharmaceutical Companies within their areas of jurisdiction. They should also be obligated to submit their reports in the aforementioned Standard Point based formats with the Chief Inspector of Drugs and other official departments in the hierarchy. Such certificates should also be subject to counterchecking by way of surprise random cGMP Compliance audits.

- l) All workforce involved in the production of drugs, should mandatorily be at least matriculates and proficient enough to read labels in English.

13.2. RECOMMENDATIONS REGARDING DISTRIBUTORS.

- a) The Tribunal recommends strict legal action against partners and employees of the Distributor in accordance with law.
- b) The Drug Inspectors should be tasked with the responsibility of visiting the distributors of the pharmaceuticals in their areas of jurisdiction. They must ensure that the licensed distributors possess all requisite storage facilities of proper size and with necessary environmental control equipment. Once such inspections have been completed each inspector must issue a certificate that such inspection has been conducted and the distributor fulfills all legal and procedural requirements.
- c) In case the distributor is not found compliant with the legal requirements, proper action under the law must be initiated with the object of ensuring compliance or in case of failure, for cancellation of license. The inspectors must also be required to ascertain the number of permanent qualified staff employed by the distributor for the purpose of ensuring proper storage and distribution of the drugs. Since the law requires at least one full time pharmacist on the staff of the

distributor, compliance with the said requirement must be ensured.

- d) The distributors must be obligated to provide accurate information and data regarding the drugs distributed by them including quantity, batch numbers, storage requirements, date of manufacturing, expiry date etc. to the hospitals and other purchasers. It must be made obligatory for the distributor to maintain a proper computerized system of inventory control, so that the inventory, source and the recipient of the drugs and other requisite information can conveniently be retrieved as and when required.
- e) The suppliers/distributors must be obligated to maintain and use specialized vehicles for transportation of heat sensitive drugs. The present system of transportation of drugs through ordinary trucks, which have no temperature control, must be dis-continued forthwith.
- f) Present system of supplying medicines on the basis of delivery challans generated by the distributor and receipt of the consignment by the hospital on the basis of such delivery challan only must be dis-continued immediately. If at all delivery challan is to be submitted, it must be accompanied by a detailed invoice sent by the manufacturer together with the statutory warranty as required under the provisions of the Drugs Act, 1976. It goes without saying that all personnel involved in this business need to have bare minimum education.
- g) The Tribunal also recommends that a standard form may be developed for the purpose of conducting periodical inspection of the premises and stores of the distributors. Points system should be introduced relating to various facilities that the distributor is required to have in his premises for storage of products. The Drug Inspector be provided such forms on the basis of which periodical

inspections must be conducted. It must be made obligatory that in order to act as a distributor, the distributor must be compliant with all requirements and must score a certain minimum marks, failing which its distribution license should be suspended till such time that it improves the facilities to come up to the requisite standards.

13.3. **RECOMMENDATIONS FOR INVESTIGATING AGENCIES:**

- a) During the course of its proceedings, the Tribunal examined various investigating officers, who investigated the matter after FIR was lodged on 24.01.2012 with Police Station Shadman, Lahore. The most glaring deficiency found in the investigating process was that it lacked direction and expertise. The Drug investigation is a highly specialized area of investigation. Owing to the growth of the pharmaceutical industry, the Tribunal feels that cases may arise from time to time requiring criminal investigation. It is, therefore, recommended that specialized investigators having expertise and training in undertaking investigation involving drug related offences should be set up on the lines of Special Investigative Units for white collar crimes, cybercrimes etc. Till such time that such specialized teams are put in place, individuals with qualification and experience in the field of pharmaceuticals must be associated with investigation to advise and assist in various aspects of investigation.
- b) It is also observed that one of the reasons the police investigation lacked direction and coherence was that the investigation as well as the investigating officers were frequently changed. This practice needs to be avoided in order to ensure that issues arising out of drug related offences must be addressed swiftly, expeditiously, transparently and professionally.

13.4. **RECOMMENDATIONS REGARDING PHARMACO VIGILANCE AND POISON CONTROL CENTERS:**

- a) Introduction of system of yellow slips for reporting Adverse Drug Reaction to the Hospital Committees set up for the said purpose.
- b) Setting up of Pharmacovigilance Centers at the level of the Health Department to process and share information regarding Drug Reactions and other related matters with health professionals/hospitals.
- c) Setting up of Poison Control Center at the level of the Health Department to maintain a database relating to poisons, data of medicines relating to adverse reaction, drug interaction data and other such information. The poison control center should be accessible to health professionals and hospitals. All major hospitals should be electronically linked inter se as well as with this center in order to share information of this nature.
- d) The Poison Control Center/Pharmacovigilance Center should have access to international database and should continuously update its database and information.

13.5. **RECOMMENDATIONS REGARDING PIC:**

- a) We recommend that an internal inquiry may be initiated within PIC and departmental action may be taken against those found responsible in the matter of receiving, verifying and sending the batches received for testing, in accordance with law.
- b) A proper and well organized storage facility within the premises of PIC must be set up within the shortest possible time.
- c) A computerized inventory control and documentation system must immediately be introduced.

- d) A therapeutic committee consisting of top medical consultants of each discipline along with a pharmacist should be set up to develop a standard formulary, which should be updated from time to time.
- e) The ratio of pharmacists viz a viz patient must be increased to one pharmacist for each 50 beds in the hospital.
- f) The role of pharmacist needs to be specified and enhanced. The pharmacist must be given the responsibility to countercheck the prescription written by the consultants/medical doctors and conduct rounds of the wards with the consultants.
- g) The role of pharmacist in the pharmacy as well as the store needs to be specified and in this regard SOPs need to be put in place.
- h) The job descriptions of pharmacist should be specified in writing and handed over to the pharmacists performing functions in different departments in line with duties assigned to pharmacists internationally.
- i) The pharmacist should also play a major role in the process of acquisition, receipt and storage of medicines for the hospital. He must be a responsible member of the Committee.
- j) In case the hospital decides to set up a committee to pre-qualify suppliers, the Chief Pharmacist of the hospital must head such committee.
- k) There should be a separate hierarchy and service structure of pharmacists. It is also recommended that Government of Punjab should set up a separate directorate of Pharmacy to deal with service structure and all related matters involving pharmacists.

- l) An air conditional storage area for medicines should be set up within the hospital

13.6. **RECOMMENDATIONS REGARDING ACQUISITION OF MEDICINES:**

- a) The procedures prescribed in PPRA Rules may be followed with modifications designed to acquire medicines for hospitals.
- b) There must be emphasis on ensuring that the intending suppliers meet the minimum criteria of cGMPs compliance and are pre-qualified for that purpose before they are pre-qualified to submit bids for supply of medicines to the hospitals.
- c) Special committee should be set up in the hospitals headed by the Chief Pharmacist, consisting of end user and other consultants, not only to examine cGMP compliance, capacity, capabilities and quality of the plant where the medicines in question are manufactured as a process of pre-qualification.
- d) In case of specific products, the committee must issue a certificate that the manufacturer not only has the requisite facility but also the equipment, processes and capacity to manufacture particular medicines required by the hospital.
- e) Only those companies, which meet the aforesaid criteria should be allowed to submit financial bids.
- f) The committee should also reserve its right to ask for financial information regarding the price mechanisms adopted by the supplier.
- g) It has been noticed that the free pharmacy being run by the hospital is unduly stretching the resources, manpower and time of the hospital staff. Owing to the growing number of

patients who visit the free pharmacy to collect free medicines, the system is not feasible. It is, therefore, recommended that free pharmacy should be separated from the hospital. It should be an independent unit with its own independent hierarchy of administrative staff, pharmacists, IT systems, and administrative structure.

- h) There should be close coordination between the hospital and the free pharmacy. The role of hospital must be limited to providing health care facilities, examining the patients and writing prescriptions. The pharmacy should run independently under its own administrative structure which should be provided adequate funding and administrative back up by the Government of Punjab.
- i) There is a need to invest in Information Technology by providing requisite hardware and software to the pharmacy to maintain records of patients, inventories of incoming medicines, dispensed medicines and other relevant data. The doctors and the pharmacy should be electronically linked so that the prescription written by the doctors should be electronically available to the pharmacy where the medicines are to be dispensed. The system of inventory control needs to be modernized. The requisite software needs to be developed/introduced in the interest of automation and efficiency.
- j) In view of the volumes involved, the free pharmacy should be an independent unit with its own independent store and staffed by professional pharmacists and qualified and trained store keepers who constitute a part of the free pharmacy. The store should be of adequate size and have the necessary environmental control and other necessary equipment required for storage of medicines of various nature.

- k) The store of PIC should only be used for storage of medicines used by PIC for the hospital. The said store should also be of adequate size with the requisite environmental control, equipment and should work under the supervision of PIC management, and trained pharmacists.
- l) The Tribunal strongly recommends, having seen the present storage conditions in PIC to take immediate steps to provide a new store for medicines with the aforesaid facilities in it. This needs to be done on top priority basis owing to the importance of proper storage of medicines.
- m) The Agha Khan Hospital in Karachi which operates the most well organized pharmacy in Pakistan comparable to the standards maintained internationally may be requested to provide consultancy service for establishment of a model hospital pharmacy in PIC. The said model can then be replicated in all major hospitals of Punjab. In this regard a manual be compiled with assistance from Agha Khan Hospital on the subject of hospital pharmacy service for implementation and observance in all major public and private sector hospitals.
- n) The pre-qualification procedures and criteria adopted and followed by Agha Khan Hospital for acquisition of drugs may be studied and adopted in order to ensure that the emphasis shifts from price to quality.

13.7. RECOMMENDATIONS REGARDING ADMINISTRATION OF HOSPITALS:

- a) The Tribunal is of the opinion that Administration of the hospitals should be undertaken by the professional administrators who have no direct responsibility towards clinical work. In this regard the hospital administration should consist of existing career officers in addition to specialized administrators who should constitute a team to run the

administration of the hospitals in an efficient and professional manner. In this regard it is recommended that consultants be hired to recommend a proper, streamlined and modern organizational structure, prepare an organogram, provide detailed job descriptions for each member of the administrative staff and the mechanism for mutual coordination and interaction.

- b) The Tribunal has also noticed that although de-centralization has the potential of increasing efficiency, de-centralization undertaken in Punjab has not yielded the requisite results. The issue needs to be re-visited, and re-examined, the trouble areas identified and steps taken to eradicate/rectify the defects and shortcomings.

13.8. **RECOMMENDATIONS REGARDING MONITORING AND UPGRADING TESTING LABORATORIES:**

- a) A visit to Drug Testing Laboratory has indicated that the same is ill-equipped, under-staffed and not able to cope with current and projected workload in the next few years. It is, therefore, recommended that substantial funds be allocated for the purpose of acquiring the latest equipment, hiring more qualified professionals and increasing its capacity manifold. In this regard the example of Forensic Science Agency may be kept in mind.
- b) It is recommended that specialized equipment for specific tests required to be conducted for testing of drugs may be acquired and provided to Drug Testing Laboratory. Up-gradation of Drug Testing Laboratory must be carried out on the same pattern as adopted by the Government of Punjab for up-gradation of Forensic Science Agency. The Drug Testing Laboratory also needs to have professional administration in addition to a separate cadre of professionals who undertake professional functions as

analysts. The Drug Testing Laboratory must be headed by a professional who specializes in the specific field and has the requisite experience in the field of Drug Testing.

- c) The fee structure for testing of drugs needs to be revised/enhanced upwards to generate enough funds to meet the running costs of Drug Testing Laboratory. It may be kept in mind that the testing costs are required to be paid by the manufacturer, who can afford to pay such costs. Such obligation should be incorporated in the contract for supply of medicines.
- d) In view of the fact that it would practically not be possible for a hospital to get each batch tested from DTL, it is recommended that the suppliers must be asked to provide not only the warranty in terms of Drug Act, 1976 but also a certificate to the effect that the medicines being supplied meets all quality standards and criteria and are fit for human consumption. Such certificates must be systematically retained in the records of the hospital.
- e) The interaction of the Tribunal with the Provincial Drug Inspectors has indicated that there is much to be desired in terms of training, know how, technical education, motivation and capacity to undertake the functions that they are required to perform. It is recommended that serious efforts should be made towards capacity building of the Provincial Drug Inspectors and related staff. Their technical know how needs to be updated and their training is required to be improved on regular basis by conducting workshops, training seminars and continuing education to keep them abreast of the latest trends in the field. It may be pointed out that role of the Drug Inspectors is of pivotal importance in ensuring safety of manufactured drugs. The administrative structure needs to be improved and, the Drug Inspectors need to be given reasonable work load in order to ensure that the

inspections conducted by them are thorough and in line with internationally accepted standards.

- f) It is also recommended that a standardized and detailed point based proforma may be developed for use by the Drug Inspectors, when they undertake inspections of a Drug Manufacturer from the point of view of cGMP compliance. It may, however, be emphasized that the inspection should not be restricted to the items identified in the proforma and the inspector should be free to inspect any other areas, systems, equipment, storage areas etc. as he may deem appropriate. Zero tolerance policy for non-compliance or violation of cGMPs must be adopted.
- g) A strict system of accountability must be ensured so that an improperly conducted cGMP inspection or a compliance certificate issued without proper and thorough inspection would attract strict penal consequences in accordance with law. The system of checks and counter check needs to be put in place in order to ensure that the same factory is checked by at least two to three inspectors at different intervals to avoid the possibility of the inspectors being approached for issuing favourable reports. The areas of jurisdiction of inspectors need to be periodically rotated in order to avoid the inspectors developing relationship/familiarity with the manufacturers in their areas of jurisdiction
- h) The inspectors need to be provided requisite powers, transportation and facilities including security arrangements in order to enable them to perform their functions freely, honestly and without fear.

13.9. RECOMMENDATIONS REGARDING LICENSING

- a) The provisions of the Drug Act, 1976 regarding issuance of manufacturing Licenses must be strictly implemented. Further the licenses to produce molecules must be sparingly

issued considering the capacity, capability, and cGMP Compliance of the intending manufacturer. It has been brought to our notice that such licenses have indiscriminately been issued in the past without meeting the necessary requirements. We recommend that licenses of companies which are not actually manufacturing the licensed molecules may be cancelled. A Committee of experts may be constituted to examine this issue and make recommendations within the shortest possible timeframe.

- b) The Tribunal was informed that the tenure of the manufacturing license issued by the Licensing Authority used to be two years. On expiry of two years, the license could be extended if after a proper and satisfactory inspection by a panel of inspectors/experts, the factory/manufacturing facility was found to be cGMP compliant. For reasons not clear to the Tribunal the tenure was extended to five years. The experts appearing before this Tribunal have opined that period of five years is too long for the pharmaceutical industry. Two years is just the right period of time after which the license should come up for renewal and undergo a rigorous process of inspection for cGMP Compliance. We recommend that the validity of all future licenses be reduced to two years. Necessary modifications in the existing law, rules and regulations may be made without further delay.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

CHAPTER
-14-
CONCLUSION



CONCLUSION

14.1. The terms of reference of the Tribunal and the conclusions drawn have elaborately been discussed in various chapters of this report. However, for ease of reference the same are summarized below:-

i) **To ascertain the cause(s) of death(s) and ailment(s):**

The causes of deaths of 213 patients of PIC and adverse symptoms suffered by about 1000 other patients, who reported to different hospitals are attributable to the use of Isotab, Batch J093, which was found contaminated by substantial quantities of pyrimethamine;

ii) **To determine if any such cause is related to the drugs administered and procured from the PIC, Lahore:**

Isotab Batch J093 was administered by PIC to its patients in the month of November/December, 2011. Immediately thereafter, the patients complaining of adverse drug reaction symptoms started reporting to different hospitals of Lahore and other areas. Such adverse symptoms stopped when the medicine was discontinued, its half-life expired or when the anti-dote (folonic acid) suggested by MHRA for over dose of pyrimethamine was administered. It is, therefore, concluded that the causes of the ailments had a direct link to Isotab Batch J093 administered and procured from PIC;

iii) **If the drug reaction is established as the cause of death and /or ailment, to determine the source, manufacturing, processing, storage, dispensing and dosage of such drugs:**

The manufacturer of the drug Isotab 20mg was Efroze Chemical Industries, Karachi where the contaminated Batch J093 was manufactured and processed. Upon supply, the same was stored by PIC. The dosage prescribed for use of the drug was within acceptable medical parameters. The same medicine from other batches, which were not contaminated, was prescribed in the same dosage to patients, who did not have any adverse reactions;

iv) **To fix responsibility of lapse at each stage:**

a) The first and the foremost responsibility for lapses lies on Efroze Chemical Industries, its top management and its officials, who had a legal obligation to ensure that the drug supplied by them was fit for human consumption, did not contain any ingredient, which was not prescribed in the pharmacopeia and the drug was manufactured and tested in strict compliance with cGMPs. The said company miserably failed to fulfill any of its aforementioned obligations. Therefore, the direct responsibility as has been discussed in this report, for the tragic loss of lives lies on the manufacturer of the drug;

b) The distributor of the drug i.e. Umar Trading Co. and its partners are also

held responsible insofar as they committed acts and omissions, which resulted in incorrect documentation being provided to PIC by omitting mention of Batch J093 in the delivery challan. Consequently, the records of PIC did not reflect that Batch J093 had been received by it and samples from the said batch were not sent for testing to the Drug Testing Laboratory. All three witnesses, two of whom are partners of Umar Trading Company admitted this fact. Had medicines dispensed by PIC from Batch J093 not been recovered directly from some of the patients, it would have been impossible to discover the cause of drug reactions would surely have led to loss of many more human lives.

- c) The inquiry conducted by the Tribunal has exposed major structural weakness and loopholes in the administrative processes and procedures of PIC. The mode and manner in which medicines are procured, received and stored, documented and dispensed is not in consonance with the requirements of running an organized and efficient hospital. Further, the Free Pharmacy of PIC, its storage area, its staff working in the store room, inventory control and supervising staff including doctors, who checked and approved the consignment, but missed the presence*

of Batch J093 are liable to answer for their actions.

d) The inquiry has also brought into focus complete absence of systems at the level of the Health Department to handle situations like these. Although the Health Department and the Government of Punjab made efforts took steps to take remedial action by mobilizing all available resources to control the damage and prevent further loss of human lives, the response was neither structured nor based upon standard operating procedures already in place to handle situations like these. It was a shot in the dark. It was by sheer good luck that the contaminated drug was swiftly identified in a matter of weeks and an anti-dote found by laboratories of MHRA in U.K. The system needs to be revamped to be prepared to offer and organized a structured response to any future eventuality of this nature.

v) **To make recommendations for averting such like incidents in future:**

This report contains detailed recommendations in the last chapter covering the areas of manufacture/production of drugs, distributors, investigating agencies, improvement of regulatory framework and improvement of enforcement, establishment of pharmaco vigilance and poison control centers,

administration of hospitals generally and PIC in particular and upgrading testing faculties.

14.2. It is our earnest hope that the conclusions drawn, responsibilities fixed and recommendations made in this report will result in appropriate action by the competent authorities in accordance with law. The Government of Punjab may share this report with the Federal Government/Drug Regulatory Authority whose involvement for implementation of recommendations made herein is necessary and expedient. This report should act as an eye opener for all concerned, who must take immediate steps to implement existing laws in their letter and spirit, introduce fresh legislation where required, frame new rules and regulations, put in place efficient, effective and modern systems and administrative structures as suggested herein so that the lives lost in this tragic incident would not have been lost in vain.

A copy of this report complete with its Schedules, Appendices and the entire record shall be retained in the Judges Library of the Lahore High Court.

This report is officially handed over to the Home Secretary, Government of Punjab by the Registrar of the Tribunal at the Judges' Library, Lahore High Court, Lahore this _____ day of December, 2012.

JUSTICE IJAZ UL AHSAN
CHAIRMAN

SYED SHAHID NASIR
CO-OPTED EXPERT

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

-SCHEDULES-



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REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

**SCHEDULE
-1-**





GOVERNMENT OF THE PUNJAB
HOME DEPARTMENT
Ph.No.042-99210113
Dated Lahore the 30th January, 2012.

NOTIFICATION

NO.SO (JUDL-III) 9-84/2012. Whereas numerous deaths have been reported prima-facie due to bone marrow suppression amongst patients registered with Punjab Institute of Cardiology, which is of public importance and has caused unrest among the people.

2. **WHEREAS**, the above incident has been flashed in media and attracted public attention and it is expedient to determine the full facts of the incident.

3. **NOW THEREFORE**, in exercise of the power conferred under section 3 of the Punjab Tribunal of Enquiry Ordinance, 1969 [II of 1969], the Government of the Punjab is pleased to appoint **Hon'able Mr. Justice Ijaz ul Ahsan as Tribunal of Inquiry**. The Tribunal may co-opt any expert and or person for the purpose of this inquiry.

4. The terms of reference shall be as follows:-
- To ascertain the cause(s) of death(s) and ailment(s).
 - To determine if any such cause is related to the drug(s) administered and procured from the PIC, Lahore.
 - If the drug reaction is established as the cause of death and or ailment, to determine the source, manufacturing, processing, storage, dispensing and dosage of such drug(s).
 - To fix responsibility of lapses at each stage.
 - To make recommendation for averting such like incidents in future.

5. The enquiry report is to be completed within thirty days of the issuance of this Notification and furnished to the Government.

BY ORDERS OF THE GOVERNOR
HOME SECRETARY

NO. & DATE EVEN

A copy is forwarded for information and necessary action to:-

1. **Hon'able Mr. Justice Ijaz ul Ahsan.**
2. Registrar Lahore High Court, Lahore.
3. Syed Ali Akbar Shah, Additional Registrar [Establishment]
Lahore High Court, Lahore w/t to letter No.2755/Gaz-II dated 30.01.2012.
4. Inspector General of Police, Punjab Lahore.
5. Director General, Public Relation, Punjab Lahore.
6. Superintendent, Government Printing Press, Punjab Lahore.

(M.ASAD ULLAH SAJID)
SECTION OFFICER (JUDL-III)

NO. & DATE EVEN

A Copy is forwarded to:-

1. Chief Secretary Punjab Lahore.
2. Principal Secretary to Chief Minister Punjab Lahore.
3. Secretary to Government of the Punjab, Health Department, with the request to provide secretariat and all others support and facilitation the Tribunal of Inquiry may required upon nomination and notification.
4. Additional Secretary (Judicial) Home Department.
5. Additional Secretary (IS) Home Department
6. Deputy Secretary (Law & Order) Chief Minister Secretariat Punjab.
7. P.S to Secretary Home, Punjab Lahore.

(M.ASAD ULLAH SAJID)
SECTION OFFICER (JUDL-III)



GOVERNMENT OF THE PUNJAB
HOME DEPARTMENT

Dated Lahore the 10th February, 2012.

NOTIFICATION

NO.SO (JUDL-III) 9-84/2012. In pursuance of Lahore High Court, Lahore letter No. 2804/Gaz-5/V.B dated 08.09.2012 **Mr. Irfan Ahmad Saeed, District & Sessions Judge (Estt.)** is hereby appointed as Registrar of the Defective Drugs Inquiry Tribunal (DDIT) as already notified vide notification of even number dated 30.01.2012.

SECRETARY TO GOVERNMENT OF THE PUNJAB
HOME SECRETARY

NO. & DATE EVEN

A copy is forwarded for information and necessary action to:-

1. Hon'able Mr. Justice Ijaz ul Ahsan Tribunal of Inquiry, Lahore High Court, Lahore.
2. Registrar Lahore High Court, Lahore.
3. Mr. Irfan Ahmad Saeed, District & Sessions Judge (Estt.), Registrar, Defective Drugs Inquiry Tribunals.
4. Syed Ali Akbar Shah, Additional Registrar (Establishment), Lahore High Court, Lahore with reference to letter referred above.
5. Secretary to Government of the Punjab, Health Department with the request to provide an official vehicle alongwith petrol and driver as admissible to Grade 21- Learned Judicial Officer and other necessary assistance required by the Inquiry Tribunal.
6. Director General, Public Relation, Punjab Lahore.
7. Superintendent, Government Printing Press, Punjab Lahore.
8. P.S to Home Secretary, Punjab Lahore.
9. P.S to Additional Secretary(Judl) Home Department.

10/2/12
to
to
to
(SOHAIL NASIR)
Registrar

SECTION OFFICER (JUDL-III)

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

**SCHEDULE
-2-**



ORDINANCE II OF 1969
WEST PAKISTAN TRIBUNALS OF INQUIRY ORDINANCE, 1969

An Ordinance to provide for the appointment of Tribunals of Inquiry and for vesting such Tribunals with certain powers

[Gazette of West Pakistan, Extraordinary, 14th April 1969]

No.Legis.3(2)/69.---The following Ordinance (was promulgated on 10th April 1969) by the Governor of West Pakistan is hereby published for general information :---

Preamble.--- Whereas it is expedient to provide for the appointment of Tribunals of Inquiry and for vesting such Tribunals with certain powers; Now, therefore, in pursuance of the Martial Law Proclamation of 25th March 1969, read with the Provisional Constitution Order, the Administrator of Martial Law, Zone A, in exercise of the powers of the Governor West Pakistan conferred on him by the Chief Martial Law Administrator, is pleased to make and Promulgate the following Ordinance:---

1. *Short title extent and commencement.* --- (1) This Ordinance may be called the West Pakistan Tribunals of Inquiry Ordinance, 1969.

(2) It extends to the whole of the Province of West Pakistan, except the Tribal Areas.

(3) It shall come into force at once.

2. *Definition .*---In this Ordinance, unless the context otherwise requires, the following expression shall have the meanings hereby respectively assigned to them:-

(a) "Government means the Government of 1[North-West Frontier Province.]

(b) "Prescribed" means prescribed by rules made under section 13: and

(c) "Tribunal" means a Tribunal appointed or deemed to have been appointed under section 3, and includes a Commission or Committee of Inquiry appointed under the said section.

3. *Appointment of Tribunal, commission or committee of inquiry* --- (1) Government may, if it is of opinion that it is necessary so to do, by notification in the official Gazette, appoint a Tribunal, Commission or Committee of Inquiry for the purpose of making an inquiry into any definite matter of public importance and performing such functions arid with in such time as may be specified in the notification, and the Tribunal, Commission or Committee so appointed shall make the inquiry and perform the function accordingly.

(2) The Tribunal may consist of one or more members appointed by Government, and where the Tribunal consists of more than one member, one of them may be appointed as the President or Chairman thereof.

4. *Power of tribunal.*--- The Tribunal shall have the powers of a civil court, while trying a suit under the Code of Civil Procedure, 1908, in respect of the following matters, namely:—

- (a) summoning and enforcing the attendance of any person and examining him on oath;
- (b) requiring the discovery and production of any document;
- (c) receiving evidence on affidavits;
- (d) issuing commissions for the examination of witnesses or documents.

5. *Additional powers of tribunal .*---(1) Where Government is of opinion that, having regard to the nature of the inquiry to be made and other circumstances of the case, all or any of the provisions of sub section (2) or sub-section (3) or sub-section (4) or sub-section (5) or sub-section (6) should be made applicable to a Tribunal, Government may, by notification in the official Gazette, direct that all or such of the said provisions as may be specified in the notification shall apply to that Tribunal, and on the issue of such a notification, the said provisions shall apply accordingly.

(2) The Tribunal shall have power to require any person, subject to any privilege which may be claimed by that person under any law for the time being in force, to furnish information on such points or matters as, in the opinion of the Tribunal, may be useful for, or relevant to, the subject matter of the inquiry.

(3) The President or the Chairman of the Tribunal, or any officer, not below the rank of a gazetted officer, specially authorised in this behalf by Government may enter any building or place where the Tribunal has reason to believe that any books of account or other documents relating to the subject matter of the inquiry may be found, and may seize any such books of accounts or documents or take extracts or copies there-from subject to the provisions of section 102 and section 103 of the Code of Criminal Procedure, 1898, in so far as they may be applicable.

(4) The Tribunal shall be deemed to be a civil court and when any offence as is described in section 175, section 178, section 179, 180 or section 228 of the Pakistan Penal Code, is committed in the view or presence of the Tribunal, the Tribunal may, after recording the facts constituting the offence and the statement of the accused as provided for in the Code of Criminal Procedure, 1898, forward the case to a magistrate having jurisdiction to try the same and the magistrate to whom any such case is forwarded shall proceed to hear the complaint against the accused as if the case had been forwarded to him under section 482 of the Code of Criminal Procedure, 1898.

(5) Any proceeding before the Tribunal shall be deemed to be a judicial proceeding within the meaning of section 193 and 228 of Pakistan Penal Code.

(6) The Tribunal shall have the powers of a civil court, while trying a suit under the Code of Civil Procedure, 1908, in respect of requisitioning any public record or copy thereof from any court or office.

6. *Statements made by persons to the tribunal .*---No statement made by a person in the course of giving evidence before the Tribunal shall subject

him to, or be used against him in, any civil or criminal proceeding except a prosecution for giving false evidence by such statement:

Provided that the statement—

- (a) is made in reply to a question which he is required by the Tribunal to answer; or
- (b) is relevant to the subject matter of inquiry.

7. *Tribunal to cease to exist when so notified* .--Government may, if it is of opinion that the continued existence of Tribunal is unnecessary, by notification in the official Gazette, declare that the Tribunal shall cease to exist from such date as may be specified in this behalf in such notification, and thereupon, the Tribunal shall cease to exist.

8. *Procedure to be followed by the Tribunal* .---The Tribunal shall, subject to any rules that may be made in this behalf, have power to regulate its own procedure (including the fixing of places and times of its sittings and deciding whether to sit in public or in private) and may act notwithstanding the temporary absence of any member or the existence of a vacancy among its members.

9. *Protection of action taken in good faith* .---No suit or other legal proceedings shall lie against Government, the Tribunal or any member thereof, or any person acting under the direction either of Government or of the Tribunal in respect of anything which is in good faith done or intended to be done in pursuance of this Ordinance or of any rules or orders made thereunder or in respect of the publication, by or under the authority of Government or the Tribunal, of any report, paper or proceedings.

10. *Members ,etc, to be public servants* .---Every member of the Tribunal and every officer appointed or authorised by the Tribunal to exercise functions under this Ordinance shall be deemed to be a public servant within the meaning of section 21 of the Pakistan Penal Code.

11. *Conferment of powers* .---(1) Government may, by notification in the official Gazette, and subject to such conditions or restrictions, if any, as may be mentioned in the notification confer upon the Tribunal the power to order a police investigation into any matter coming before it.

(2) In conducting an investigation ordered under sub-section (1) the police shall exercise the powers conferred on the police in respect of a cognizable case by Chapter XIV of the Code of Criminal Procedure, 1898.

12. *Act to apply to other inquiring authorities in certain cases* .---Where any authority (by whatever name called), other than a Tribunal appointed under section 3, has been or is set up under any resolution or order of Government for the purpose of making an inquiry into any definite matter of public importance and Government is of opinion that any of the provisions of this Ordinance should be made applicable to that authority, Government may, by notification in the official Gazette, direct that the said provisions of this Ordinance shall apply to that authority, and on the issue of such

notification, that authority shall be deemed to be a Tribunal appointed under section 3 for the purpose of this Ordinance.

13. *Powers to frame rules.*--- Government may by notification in the official Gazette, make rules to carry out the purposes of this Ordinance.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

SCHEDULE
-3-



CONFIDENTIAL



**World Health
Organization**

**Report
Of
WHO Mission to Pakistan**

**Lahore Medicine Contamination
6th -19th February 2012**

Syed Khalid Saeed Bukhari, WHO Country Office, Islamabad

Mohamed Bin- Shahana, WHO EMRO, Cairo

Michael Deats, WHO HQ, Geneva

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INTRODUCTORY NOTE

This report has been prepared by the World Health Organization at the request of the Federal Government of Pakistan and the Government of the Punjab. Information contained in this report is provided by the Organization on a purely voluntary basis and without waiver of any of the privileges and immunities which it enjoys pursuant to the Convention on Privileges and Immunities of the Specialized Agencies 1947, to which Pakistan acceded, with respect to the Organization, on 23 July 1951, as well as by virtue of Article V of the Basic Agreement for the provision of technical advisory assistance concluded between Pakistan and the Organization in 1960.

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INTRODUCTION

On the 23rd January 2012 the World Health Organization began monitoring press reports of suspected serious adverse drug reactions in patients presenting to hospitals in Lahore, Pakistan. The WHO country office liaised with the Punjab health authorities who reported that a contamination in one of a number of medicines was suspected.

On the 25th January 2012 the Federal Government of Pakistan and the Government of the Punjab requested the World Health Organization to deploy a mission to Lahore to assist in the investigation of a series of fatalities suspected to be caused by a reaction to substandard medicines. They also requested that the WHO make recommendations on the prevention of similar incidents in the future.

Since mid-December 2011 over 120 patients have died and a further 800 have suffered from a suspected adverse drug reaction in the City of Lahore, Punjab, Pakistan. It was quickly established that all of the patients were receiving treatment and medicines from the Punjab Institute of Cardiology (PIC).

Five medicines were common to these patients and the Punjab Government took immediate steps to have them tested both in Pakistan and at a number of International laboratories.

Samples of the five medicines suspected of being contaminated were sent to laboratories around the world, including London, facilitated by International Health Partners (IHP) UK, a British registered charity working in Pakistan. On the 31st January 2012 the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK identified that one of the medicines, an anti-anginal with the brand name Isotab, had tested positive for large doses of pyrimethamine used commonly as an anti-malarial drug. Pyrimethamine overdose was known to cause the symptoms being exhibited by the patients in Lahore. The Punjab authorities were immediately notified, replicated the analysis, and a treatment regime was urgently implemented. Most patients began to respond positively. However, tragically, over 120 patients have died as a result of taking the contaminated medicine.

A WHO mission was deployed to Pakistan on the 6th February 2012 consisting of Mr Michael Deats, WHO HQ Geneva, joined on the 7th February by Mr Mohamed Bin-Shahna, WHO Eastern Mediterranean Region Office (EMRO) and assisted throughout by Dr Syed Khalid Saeed Bukhari of the WHO Country office Islamabad.

The focus of the mission was to establish the root cause of this contamination and make recommendations on both the management of the incident and steps to prevent a re-occurrence.

The WHO mission has been afforded every assistance in Pakistan from both the Punjab and Federal Government. Grateful thanks goes to all of those persons, from the highest Government officials to the laboratory technicians, doctors, pharmacists, and nursing staff caring for those affected. Their professionalism,

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determination and personal commitment in reacting to this tragic set of circumstances has shone through.

It is hoped that this tragic loss of life will result in Pakistan taking this opportunity to implement the recommendations set out in this report, and take the appropriate and proportionate steps to ensure that medicines and medical products manufactured, distributed and supplied in Pakistan are of a nature and quality demanded by Internationally recognised standards and can be relied upon with certainty as to their safety, quality and efficacy.

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Executive Summary

This mission has examined the circumstances leading to this incident and has reviewed the gaps currently in existence which have allowed this tragic event to occur.

The Pakistan Government implemented amendment 18 to the Pakistan Constitution on the 30th June 2011. This amendment was designed to devolve more responsibility to the Provincial states. The Department of Health at a Federal level was one of a number of Government departments disbanded, and responsibility passed to the Provincial Governments. However, the Provinces were not yet prepared for the transition and in essence temporarily suspended the regulation of medicine. There has effectively been an absence of medicine regulation since 30th June 2011 at the Federal or Provincial level.

This incident appears to have been caused by the contamination of a batch of medicine during the manufacturing process. Internationally recognised standards of current Good Manufacturing Practice (cGMP), when adhered to, minimise the risk of this type of accident taking place. cGMP requirements provide for an extensive system of checks and balances, and require that every precaution is taken to prevent mistakes in the manufacturing process. Ensuring strict compliance with these legal requirements is an essential and critical element in minimising the risk of manufacturing errors. Proportionate and timely action should be taken in cases of non-compliance with the statutory requirements. This function should be carried out as part of the normal regulatory process.

This mission has found that both Healthcare professionals and the Government reacted quickly to the surge of adverse reactions in patients in Lahore. The common denominators amongst patients were quickly identified and suspected medicines tested. The contaminant was discovered and an effective treatment regime implemented. The retrieval of medicines from 46,000 patients was commenced utilising all means and resources. This combination of actions and co-ordination amongst Hospitals, the Punjab Government and International bodies undoubtedly saved lives.

However, the absence of a well-resourced and functioning National Medicine Regulatory regime created an environment that was ripe for an incident of this nature. Pakistan has over 500 pharmaceutical manufacturers currently operating without proper regulation. There are in excess of 60,000 registered medicines being produced and Pakistan exports medicines to 26 countries, a trade worth in excess of \$170,000,000 per annum.

This incident has reduced confidence in the medicines manufactured in Pakistan. Media reporting subsequent to this incident has suggested consumers have been demanding medicine produced outside of Pakistan, and countries are threatening to suspend all imports of medicines produced in Pakistan.

Perhaps more importantly this incident has led to the public losing confidence in their medicine with evidence suggesting some patients suspending their treatment altogether.

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There is an urgent need to establish a National Medicine Regulatory Authority (NMRA) and implement internationally recognised standards in the registration, production, distribution, supply and use of medicines and medical products in Pakistan.

The Agency should be Independent and autonomous, funded from the fees generated through its normal functions. It should be led and staffed by properly qualified and experienced personnel, recruited on merit, properly rewarded and strictly absent of any conflict of interest. Good corporate governance should be strictly adhered to and the Agency subject to regular external audit.

Lessons should be learnt from existing stringent regulatory authorities from around the world, and staff from the new Agency exposed to the international bodies that exist to harmonize the recognised standards.

Political will and finance to establish a National Drug Regulatory Authority needs to be followed up by the appointment of a well-qualified Chief Executive with both technical skills and managerial experience at a senior level within an existing stringent drug regulatory authority, and the drive to ensure the implementation of regulation throughout Pakistan. That person must have the political support at both Federal and Provincial levels to carry out their regulatory responsibilities recruit the best qualified staff and collaborate internationally with the minimum of political interference. However, that person should report to a Government minister and apply the health policy and strategies of Pakistan.

The tragedy that has occurred in Lahore is a clear signal of the consequences of non-compliance with recognised norms and standards. The evidence and opportunity now present themselves to the Government of Pakistan to invest in implementing measures to ensure access to safe, efficacious, quality and affordable medicines for all. Doing so will minimise the risk of similar incidents re-occurring, improve national and international confidence in medicines manufactured in Pakistan and establish the country with a reputation for maintaining a well regulated environment within the pharmaceutical sector.

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ADR	Adverse Drug Reaction
API	Active Pharmaceutical Ingredient
CDL	Central Drug Laboratory
DCO	Drug Control Organisation (Federal)
DTL	Drug Testing Laboratory (Punjab)
EMRO	Eastern Mediterranean Regional Office (WHO)
FTIR	Fourier transform Infrared Spectrometer
GCMS	Gas Chromatography Mass Spectrometer
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonization
IHP	International Health Partners UK
INN	International non-proprietary names
LCMS	Liquid Chromatography Mass Spectrometer
MHRA	Medicines and Healthcare products Regulatory Agency
MOH	Ministry of Health
NDRA	National Drug Regulatory Authority/Agency
NMRA	National Medicines Regulatory Authority (also known as NDRA)
PIC	Punjab Institute of Cardiology
WHO	World Health Organization

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Part 1. Drug Contamination Incident, Lahore, Pakistan

In mid-December 2011 patients began to present themselves to hospitals in Lahore exhibiting symptoms of bleeding, nausea and darkening of the skin. Further investigation quickly identified that all patients had recently received a range of 5 medicines from the Punjab Institute of Cardiology. One batch of one of those medicines was contaminated with an additional active pharmaceutical ingredient causing a severe overdose and leading to in excess of 120 fatalities and 800 other patients suffering adverse reactions.

1.1 Detection of Adverse Drug Reactions (ADR's)

In 2011 the City of Lahore suffered a serious outbreak of Dengue fever. This incident led to the death of over 320 patients, and placed the health services under severe strain. This situation led the Government of Punjab to implement increased surveillance and monitoring for patients presenting themselves to hospitals with symptoms suggesting infection of Dengue fever. It also led to the establishment of an expert panel to closely monitor the situation. This serious event and the implementation of enhanced vigilance is judged to have contributed to the early detection of patients suffering from the subsequent drug contamination in December 2011.

Some of the symptoms exhibited by patients were similar to those experienced when suffering from dengue fever (bleeding and low white blood cell count) and were quickly reported. By the end of December a surge in deaths involving over 50 reports was identified. However experts were concerned that the normal vectors for dengue were diminishing whilst the suspected cases were increasing. Some of the usual symptoms associated with Dengue, particularly a high fever were absent. Further investigation was carried out and patients were consistently exhibiting a reduced white blood cell count, reduction in platelets and importantly suppressed bone marrow. These findings began to suggest some type of toxic reaction either by drug overdose or contamination.

The arrival of patients at the Punjab Institute of Cardiology suffering from nausea, bleeding and darkening of skin and their referral to the Jinnah, Services, Mayo and other local hospitals continued to increase dramatically and was confined almost entirely to the City of Lahore. It was soon established that the key common denominator present was that all of the patients had recently been dispensed a range of 5 medicines by the Punjab Institute of Cardiology, Lahore and this dispensing was estimated to have occurred during the first week of December 2011.

The detection of this incident was assisted by a number of factors.

- The patients exhibited some dengue like symptoms
- The outbreak of dengue fever in 2011 had increased systematic vigilance for further cases.
- The contaminated medicine was only distributed through one hospital
- The patients presented to hospitals almost exclusively in Lahore
- This geographic concentration enabled the identification of common denominators and co-ordination between hospitals within a period of 2 weeks.

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When considering the possibilities had the contaminated medicine been distributed more widely, and patients had presented to hospitals throughout Pakistan, it is doubtful that a link would have been made as quickly, or indeed at all. In the absence of any link being established between the cases, and the cause identified, an effective treatment regime would not have been implemented. In these circumstances the risk of a much larger number of fatalities could realistically have been expected.

1.2 Clinical Response

This mission has visited the Jinnah, Services and PIC hospitals in Lahore and spoken to staff at all levels responsible for the administration of the hospital, procurement of medicine, Doctors, Pharmacists and laboratory staff. It is abundantly clear that they were placed under intense pressure as a result of this incident, in addition to their already heavy workloads. Their commitment, professionalism and pride in their work were clearly evident.

Several hospitals noted a surge in patients presenting with what initially appeared to be Dengue fever during mid-December 2011. This was as a result of a number of patients initially returning to PIC complaining of nausea, bleeding and darkening of the skin. PIC specialising in cardiology therefore referred them to the nearest general hospitals. The hospitals each investigated and soon co-ordinated with each other. On the 12th January 2012 dispensing of 5 medicines suspected to be the possible cause was stopped by the PIC.

The General Hospitals were trying different methods of treatment including steroids, vitamin B12 and Folate, these treatment regimens were consistent with the symptoms they were encountering. One of the hospitals was using what turned out to be the correct antidote (folinic acid) but because the patient was still taking Isotab batch J093 the treatment was failing to work.

Following the identification of the contaminant on the 31st January 2012 as pyrimethamine overdose a treatment regime was initiated within hours. Most patients began to respond within 2 days and their platelet and white blood cell count began to increase. Those patients whose bone marrow had been more seriously suppressed did not respond to treatment leading to approximately 120 fatalities.

This incident was first recognised in Mid-December and initially suspected to be a second outbreak of Dengue fever. By late December other causes including adverse drug reaction were suspected. On the 12th January 2012 the suspected medicines were identified and dispensing ceased. Samples were sent to the UK by personal envoy on 25th January 2011 and the contaminant identified on the 31st January 2011. Treatment regimens involving the administration of folinic acid were implemented on the following day. Measurable and sustainable improvement in the majority of patients could be seen after 48 hours.

Despite the tragic loss of life it can be considered that this contaminant was identified very quickly, had this not been the case many more fatalities are likely to have occurred.

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The co-ordination between the various hospitals clinicians involved in the treatment of patients was both timely and effective.

1.3 Government of the Punjab Response

The first priority of the Government in these circumstances must be to protect public health. The Government of the Punjab concentrated effort on establishing the cause, putting in place an effective treatment regime, and recalling suspected medicines from patients.

The second priority was carrying out an investigation to determine cause and culpability and taking the necessary proportionate action. Close co-ordination is required between all of those responsible for both priorities with the Chair Person fully sighted of all developments.

On the 23rd January 2012 The Health Secretary convened a meeting during which a series of specialist committees were established to advise on particular aspects of the incident in Lahore. It should be remembered that at this stage the numbers of fatalities were rising, no contaminant had been discovered and no successful treatment regime identified, the situation was extremely serious and getting worse. The committees drew upon recognised and highly qualified specialists from across a range of disciplines. The following committees were established;

Analysis Committee
Post Mortem Board
Drug Retrieval Committee
Epidemiology Committee
Clinical Guidelines Committee
Legal Committee
Production Surveillance Committee
Information Dissemination Committee

The focal point for the work of these committees was the Special Secretary for Health supported by an additional secretary. The purpose was to examine every aspect of what was now a very serious and escalating incident and urgently identify the cause and solution.

A Judicial Commission was established at the end of January 2012 sitting at the Lahore High Court to determine the facts of this incident. This WHO mission was invited to attend and gave evidence to the Commission. A copy of this report will be forwarded for their attention.

1.4 Punjab Institute of Cardiology (PIC)

The PIC has been operating since 1988. The Hospital is a specialist cardiac facility. It treated over 219,000 outpatients, 21,000 inpatients of which over 96,000 were emergencies in 2011. PIC was dispensing five medicines which were common to the patients reporting adverse reactions. They were;

No.	Active Pharmaceutical Ingredient	Brand Name	Indication	Manufacturer
1	Aspirin 300mg	Solprin	NSAIDs	Pharmawise Lab, Lahore

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2	Atenolol 100mg	Atenolol	Beta Blocker	Zafa Pharmaceuticals, Lahore
3	Amlodipine besylate 5mg	Concont	Ca Channel Blocker	Swiss Pharmaceuticals, Karachi
4	Isosorbide-5-mononitrate 20mg	Isotab	Anti-Anginal	Efroze Chemical Industries, Karachi
5	Simvastatin 20mg	Cardiovastin 20mg	Anti-Lipidemic	Mega Pharmaceuticals, Lahore

PIC maintains an electronic patient record which showed that between the 11th December 2011 and the 11th January 2012 46,000 patients were being dispensed a combination of the medicines listed above. This record included where available telephone contact numbers enabling some patients to be reached quickly.

Once Isotab 20mg was identified as the contaminated medicine the hospital confirmed they had been dispensing the medicine to patients with instructions to take them 2 or 3 times per day.

The hospital had been sourcing Isotab 20mg for the past 2-3 years from a well known pharmaceutical distributor known as Omar Trading based in Lahore. The PIC awarded a contract to Omar Trading in 2011 for the provision of 8.8million doses of Isotab 20mg. The hospital would place orders throughout the year for quantities of the medicine in line with their needs and storage capacity. It is known that PIC issued a purchase order to Omar trading on the 17th September 2011 for 100,000 packs of Isotab 20mg containing 20 tablets per pack (2,000,000 doses) at a cost of 760,000 Pk Rupees (7.60 per pack, Rs 0.38 per dose) for delivery within 30 days.

The Isotab was delivered to PIC on the 8th October 2011. The delivery note and invoice show two batches of Isotab J092 and J095 containing 52,550 packs (1,051,000 doses) and 47450 packs (949,000 doses) respectively. It has been established that Isotab is manufactured in batches of 400,000 doses in which case these documents appear questionable. It should be noted that distributors are liable for the medicine laboratory quality control testing fees. This may provide an incentive to reduce the number of batches shown on any invoices and delivery notes, thus reducing the cost of their fees. It is considered a strong possibility that batch J093 and J094 were also contained in this delivery.

The PIC submitted samples of batches J092 and J095 to the Punjab Drug Testing Laboratory which were received on the 19th October 2011, tested between the 26th - 29th October, and confirmed to contain the correct amount of the expected Active Pharmaceutical Ingredient, Isosorbide-5-mononitrate. In accordance with their standard operating procedures they performed the test for the label claim. They were not asked to test for any other substances and used the internationally recognised testing methods.

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The PIC have to predict their requirements for medicine some time in advance to enable delivery and subsequent testing, which can take up to 60 days.

A quantity of medicines seized by the authorities and sealed in a store room at PIC have not been seen by this mission. It is not known if this contains further quantities of batch J093. The authorities have also seized all paperwork from PIC to assist in their criminal investigation.

A number of staff from PIC have been suspended and some arrested in connection with this incident, although some members of staff have now been reinstated.

1.5 Recall of suspected medicines

The Lahore case involved a contaminated medicine supplied by a Government hospital. Patients who were dispensed this medicine would have had a high degree of confidence that the medicine was safe, of the appropriate quality and would treat their illness effectively. These patients were not obtaining their medicine without a prescription or from an unlicensed source. In their minds they were taking no risks.

This was recognised by the Punjab Government. Once the Punjab Institute of Cardiology was identified as the common source of medicines taken by those suffering serious adverse reactions, a monumental effort was commenced to retrieve the suspected medicines. It was established that 46,000 patients had been prescribed a combination of 5 medicines suspected to be contaminated.

On the 12th January 2012 dispensing of the suspected medicines ceased.

On the 23rd January 2012 personnel were mobilised from a range of different departments to visit the patients. Lists of patients were drawn up based upon the location of their address and each was visited. The medicines were recovered and a questionnaire completed by the patient. This represented an immense task and was organised and carried out in a short period of time. The quantity of medicine recovered during the recall process has not been aggregated so no judgement can be made on the effectiveness of the recall. Patients were also contacted by telephone wherever possible.

The Punjab Institute of Cardiology and other hospitals set up a dedicated office and 'hot lines' within the hospital, staffed by qualified pharmacists to receive enquiries from patients and telephone enquiries. They have dealt with thousands of patients, recovering the suspected batches of medicine where necessary. The hospital maintains an IT database including full details of patients with telephone numbers, and their medication. It was this system that identified 46,000 patients as having received the 5 medicines which were originally suspected in this case.

The media was widely reporting details of the suspected medicines, once the investigation had identified which medicine and which batch/lot number of that medicine was contaminated, it was then possible to release this specific information. However there is of course no editorial control of exactly what the press choose to publish, the level of detail or the accuracy.

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The attempts to safeguard patients by recovering the suspected medicines was impressive but, in every well regulated pharmaceutical sector efficient recall procedures are established and implemented. It is quite clear that at present in Pakistan there is no effective system for recalls present and that any similar future event with serious quality failures can lead to similar devastating results.

1.6 Punjab Drug Testing Laboratory (DTL)

Once the PIC was identified as a common denominator in Patients suffering adverse reactions, and 5 medicines were common to the patients involved, there was an obvious desire to rapidly test the samples. They were sent to the Punjab Drug Testing Laboratory. It is the task of this laboratory to test the medicine to ensure it is what it claims to be in terms of the presence of the declared active pharmaceutical ingredient in the right quantity. They do this using the standards set in the International, US, or British Pharmacopeia's, and a technique known as High Performance Liquid Chromatography (HPLC). This technique is commonly used in both government and quality assurance laboratories worldwide. They do not, and cannot identify other unknown ingredients beyond suspected impurities related to the declared API's on the label. A medicine could be contaminated with any one of millions of substances, it is possible for the laboratory to identify the presence of a substance, but not the identity of that substance without using Gas chromatography mass spectrometry (GCMS). The DTL do not have this facility. The DTL were asked to confirm the presence of the correct active ingredient, in this case Isosorbide-5-Mononitrate, they did confirm its presence and in the correct quantity. In this case they tested the suspected medicines and confirmed that they contained the correct active ingredient, they could not identify any unknown ingredients with the range of testing available to them.

It should also be noted that the DTL were not provided with batch J093, later proved to be the culprit. They were provided with batch numbers 92,94,95,98,100,101 which were all proved to be of the correct standard, not only by DTL but also by other International laboratories. It should be repeated that the Punjab Drug Testing Laboratory were only submitted Batch J093 for testing AFTER the MHRA had identified the contaminant as pyrimethamine. The Punjab Drug Testing Laboratory were informed of the contaminant and were then able to retest the batch using their own equipment in the presence of senior Government officials and confirmed the contaminant as pyrimethamine.

Submission of samples to Punjab Drug Testing Laboratory			
Date	Submitted by	Batch number	Result
19/10/11	PIC	J092	Contains correct API in correct quantity
19/10/11	PIC	J095	Contains correct API in correct quantity
29/12/11	PIC	J098	Contains correct API in correct quantity
29/12/11	PIC	J100	Contains correct API in correct quantity
29/12/11	PIC	J101	Contains correct API in correct quantity
31/10/12	Drug Inspectors following receipt of result from MHRA	J093	Contaminated
31/10/12	Drug Inspectors	J094	Contains correct API in correct quantity

The head of the laboratory has been suspended in connection with this incident.

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Finally, it should be underlined that quality control testing of medicines is not a substitute for other regulatory measures such as effective inspection of production facilities and full assessment of product dossiers. Used as a stand alone measure it has obvious limitations and cannot protect from such incidences.

1.7 International Laboratory Analysis

The Health Secretary took immediate steps to send products to laboratories all over the world. A personal envoy was dispatched to the UK and with the assistance of International Health Partners UK, a British Charity active in Punjab and Pakistan, they submitted a number of samples to the London School of Pharmacy. Their testing revealed that one of the medicines Isotab 20mg, an Anti-Anginal medicine containing 20mg of isosorbide-5-mononitrate also contained a significant quantity of an unknown ingredient. All of the samples were sent to the laboratory of the UK Government Drugs regulator, the Medicines and Healthcare products Regulatory Agency (MHRA) for more advanced analysis. It was quickly identified that the unknown ingredient was pyrimethamine with each tablet containing approximately 50mg. Pyrimethamine is used for a number of purposes but is commonly used as an anti-malarial drug. The normal dose for pyrimethamine is 25mg per week for 3 weeks. The patients that had been prescribed Isotab by PIC were taking 2 to 3 tablets per day. They were therefore taking between 100-150 mg of pyrimethamine each day instead of 25mg per week. This equates to between a 4-6 weeks dose of pyrimethamine every day.

The method used to identify the contamination of batch J093 by the MHRA laboratory was as follows

A. Gas Chromatography/Mass Spectroscopy (GC/MS) - This separates the ingredients and allows identification by comparing the mass spectrum of any peaks detected to a spectral library.

B. Liquid Chromatography/Mass Spectroscopy (LC/MS) - This separates the ingredients and allows identification by comparing the mass spectrum of any peaks detected to the mass spectrum of corresponding peaks from a reference standard. Based on the GC/MS library match, the standard of pyrimethamine was injected to confirm by LC/MS.

C. The samples were also tested by Infrared Spectroscopy (FTIR) - this gave a Spectral match to the reference standard to pyrimethamine.

The batch of Isotab which tested positive for pyrimethamine was batch number J093 labelled as manufactured by Efroze Chemical Industries, Karachi, Pakistan. The MHRA laboratory also tested 2 other batches of Isotab supplied by PIC which tested negative for pyrimethamine.

The techniques used by the MHRA are more commonly used in forensic chemistry laboratories.

1.8 Investigation

In parallel with the investigation into the contaminant and protection of public health a criminal investigation was taking place. Three manufacturing companies

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in Lahore were visited and the owners arrested and questioned. None of these factories were subsequently found to be the cause of the adverse reactions, although one was operating as an unlicensed manufacturer and ceased trading.

Investigations were also being carried out in Karachi where three more manufacturers were visited. Once the cause of the adverse reactions was identified as Isotab manufactured by Efroze Chemical Industries, Karachi, that factory was visited by Drug Inspectors and sealed to prevent further trading.

Police have also recommended prosecutions against a number of staff from Efroze, Omar Trading, and PIC although at this stage it appears that no decisions have yet been made. The nature of the evidence against these entities has not been examined by this mission and is a matter for the Police and prosecutors who have conduct of this case.

1.9 Efroze Chemical Industries, Karachi

Efroze Chemical Industries have been manufacturing pharmaceuticals in Pakistan for almost 40 years. They occupy a manufacturing plant in Karachi and were last re licensed as a manufacturer by the Federal Drug Inspector in May 2010. They manufacture a large range of products and export to over 20 countries including;

Afghanistan, Belarus, Ghana, Kyrgyzstan, Myanmar, Yemen, Uzbekistan, Malaysia, Singapore, Sudan, Sri Lanka, Vietnam, Bangladesh, Cambodia, Philippines, Nigeria and Kenya.

They employ over 350 staff, 150 of which are permanent and 200 contracted. Most of the latter have apparently been employed for 2-3 years.

The company produces in the same factory Isotab containing isosorbide-5-mononitrate and four products containing pyrimethamine.

Active and inactive raw materials arrive in their warehouse which is part of the factory. All active pharmaceutical ingredients (API's) are tested in house to ascertain correct specification. Inactive materials are sampled and tested randomly. The products are then moved upstairs to a designated store room once testing of API is complete and satisfactory.

The store room is shelved and also contains a small quarantine area for smaller quantities of product awaiting test results. When a request is received in the store room for the precise quantities of ingredients required for a batch of medicines they are moved to a dispensing area and are weighed and if necessary placed in bags.

Once complete the batch specific ingredients are taken downstairs to a granulation room for sieving and mixing. These should be the only ingredients in the granulation room.

The next process involves the compression of the tablets during which stage samples are tested for weight, uniformity, disintegration and friability.

On completion the batch is ready to be placed into blisters, sealed and the batch and expiry date embossed on the blisters. The blisters each contain 20 tablets

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which are packed into boxes containing 25 blisters (500 doses). Each blister is ink jet printed 'PIC Property Not for sale'.

At the conclusion of the process the finished product is submitted to the quality assurance laboratory for testing using HPLC. The batch should not be released until quality assurance controls have been carried out.

According to copies of the Batch Manufacturing records seen by this mission, the manufacturing process for batch J093 was commenced on the 21st September 2011 and the batch was concluded on the 26th September 2011. Omar trading would have arranged collection of the batch sometime after that date.

Isotab 20mg contains six ingredients which for a batch of 400,000 tablets would require the following;

Ingredient	Batch Quantity	Tablet Quantity
Isosorbide-5-mononitrate	11.658 kg	29.145 mg
Pregelatinized starch	26.800 kg	67.000 mg
Avicel PH-102	26.800 kg	67.000 mg
Talcum Powder	1.600 kg	4.000 mg
Magnesium Stearate	0.571 kg	1.428 mg
Aerosil 200	0.571 kg	1.428 mg

The products listed above are described as white powders. Active Pharmaceutical Ingredients (API's) and some excipients are supplied in 25kg brown cardboard drums. Both isosorbide-5-mononitrate and pyrimethamine are supplied in similar drums as are starch and Avicel.

It is suggested that batch J093 which has shown to be contaminated with approximately 50 mg of pyrimethamine per dose would have required approximately 20-25 kg of pyrimethamine to contaminate the batch to the levels established.

If the wrong ingredient had been mistakenly included at the exclusion of one of the correct ingredients then this could only have occurred in the store room, dispensing room, on the way to the granulation room or in the granulation room. At the time of compression the contamination had already occurred.

Further laboratory testing should be carried out to determine and confirm the presence and quantities of the other ingredients that should have been included in this batch.

During the compression stage various tests are carried out to determine the uniformity and disintegration levels of the tablets, the absence of some of the ingredients could have been expected to have shown up at that stage.

On completion of the batch the quality assurance laboratory within Efroze carried out testing, their chromatogram was carried out using standard HPLC methodology which confirmed the correct level of Isosorbide-5-mononitrate. The purpose of their testing was to establish the presence of the correct API in the correct quantity.

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Within a few days Efroze discovered that a 25kg drum of Pyrimethamine was missing from the store. An internal investigation failed to identify the whereabouts of the drum.

Information provided to the mission by the FIA and Federal drug Inspectors who attended Efroze premises on the 1st February 2012, following the identification of Isotab contaminated with pyrimethamine as the suspected culprit revealed some potentially serious discrepancies

The manufacturer is required to maintain a 'retained sample' of each batch of medicine they produce. The investigators seized the retained samples and tests were carried out in the factory. Batch J093 was found not to contain pyrimethamine, whereas samples of the same batch retrieved from patients did reveal the contaminant. On careful examination the embossing of the batch number and expiry date on the blisters of Isotab recovered from Patients was slightly different from the embossing on the retained sample. Further examination of this anomaly is suggested as this may indicate some manipulation of the retained samples. The mission were also informed by the FIA and local drug inspectors that on the night of the 31st January / 1st February staff and analysts attended the factory and carried out urgent testing of the retained samples, remnants of these tests were still in the quality assurance laboratory when the Inspectors arrived.

All retained samples have been passed to the Central Drug Testing Laboratory (CDL) Karachi where full analysis of each of the batches produced by Efroze for PIC should be carried out. This laboratory holds the most complete set of samples of Isotab and careful analysis should be carried out to determine that only batch J093 is contaminated, and which other ingredients in which quantities are contained in batch J093. This mission has visited the laboratory and been informed that testing is still taking place but expected to confirm that only one batch contained Pyrimethamine.

Efroze and some of their management and staff are under investigation by the Pakistan authorities.

Based upon the records available at Efroze and compared to the prescribing information provided by PIC sufficient medicine was produced in Batch J093 (400,000 doses) to treat approximately 4,500 – 6,500 patients (depending if they were prescribed 2 or 3 tablets daily). It is not known if all of the medicines were dispensed and how much has been recalled from patients. It is known that there have been approximately 1000 patients affected. Reconciliation of the data is recommended to make a more accurate assessment of the numbers potentially affected, why all of the patients were not affected or if indeed the entire batch was dispensed.

1.10 Communication/ Media Handling

The Lahore contamination generated widespread national and international public interest. An incident of this type is emotive and touches vulnerable sections of society. It naturally attracts widespread concern amongst the public, press, Government and the International community.

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However the handling of communication is critical to minimising the detrimental effects of the incident on the community. A careful balance needs to be achieved between protecting public health and preventing disproportionate panic, undermining confidence in health systems and medicines, resulting in a greater threat to public health than the current matter being addressed.

The media were widely reporting that the public had stopped taking medication due to a loss of confidence in all medicines, or demanding medicines that were not produced in Pakistan. This may ultimately lead to further more serious health issues.

The Health Secretary initially in charge of this case clearly requested that only evidence based information was disseminated to the media, and done so in a timely fashion.

It is suggested that one spokesperson only is nominated wherever possible, all members of the management committee handling the incident, members of any subcommittee and advisors refrain from commenting to the press. If appropriate pre-arranged structured press conferences should be scheduled regularly according to the speed with which the event is unfolding, attended and fronted by the dedicated spokesperson. In a serious incident as experienced in Lahore this would represent a full time task and should be allocated to a suitably trained and senior person with access to the management team. This model allows those handling and managing the incident to proceed with their tasks with minimum interruption and disruption from a demanding press corps, whilst controlling as far as possible the release of information to accurate, evidence based data accompanied by strong and honest messages of re assurance to the public.

Co-ordination between non-government entities involved in the incident should be achieved wherever possible. Consistency in the delivery of information and message to the public from all stakeholders is key to reducing confusion, fear and panic. The management of the incident should be handled in a transparent, open manner providing reassurance and advice in a clear consistent way to all those potentially affected utilising all appropriate forms of media.

The demands of the media are distracting when handling a serious incident and can lead to the diversion of finite resources, but they can be used to great advantage if facilitated properly. Failure to invest time and resource to the effective communication of the incident can lead to irresponsible reporting generating widespread fear, misconception and panic.

The Punjab Institute of Cardiology has reported a 30% reduction in patients since the adverse publicity resulting from this incident. This hospital is one of the leading cardiac facilities in Punjab and has been so since 1988. The PIC has unsurprisingly suffered reputational damage and this has made patients nervous. It is not yet known if these patients have attended other hospitals or have stopped receiving treatment altogether.

Maintaining public confidence in medicines and the way they are obtained is central to providing effective healthcare. Communication of incidents involving substandard or spurious medicines involves a careful balancing act of protecting public health whilst not frightening the public to the extent they stop taking safe

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medicines resulting in further health problems and increased pressure on stretched healthcare facilities.

1.11 Timeline

Date	Event	Comment
17/09/11	PIC issue a purchase order to Omar trading for 2,000,000 doses of Isotab	Omar Trading is the distributor for Efroze
21-26 /09/11	Efroze manufactures Batch J093	Containing 400,000 doses
27/09/11	Efroze discover that a 25kg drum of Pyrimethamine is missing from the store	
08/10/11	Omar trading deliver 2,000,000 doses to PIC	Invoice shows Batches J092 and J095 only but quantity of doses exceeds those two batches
19/10/11	Drug Testing Laboratory receives samples of J092 and J095 from PIC	
26-29/10/11	Drug testing laboratory confirm batches confirm 20mg of Isosorbide-5- mononitrate	J092 and J095
1-7/12/11	Estimated date of dispensing by PIC to patients of batch J093	
9/12/11	First cases of adverse reactions presenting to hospitals	PIC and Jinnah
Mid December	Hospitals begin to collaborate, different treatment regimens implemented without success	Dengue fever or variant suspected
12/01/12	PIC cease dispensing five medicines suspected of causing adverse drug reaction including Isotab	
23/01/12	WHO Geneva pick up emerging media reports of suspected drug contamination and contact WHO Islamabad	
23/01/12 – 06/02/12	WHO Islamabad liaise closely with all Pakistani authorities and conduct daily conference calls with WHO HQ and WHO EMRO	
23/01/12	Health secretary convenes a meeting of experts and establishes 8 committees to investigate cause and treatment	Also a number of other responsibilities
23/01/12	Government of Punjab instigate a recall of the suspected medicines from 46,000 patients	
25/01/12	Federal and Government of Punjab request a WHO mission to Pakistan to assist	
25/01/12	Secretary of Health arranges for samples of suspected medicines to be taken to laboratories around the world for further testing	

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25/01/12	International Health Partners UK facilitates submission of samples to the London School of Pharmacy who discover an unknown abnormality in Isotab batch J093.	
27/01/12	Samples passed to MHRA laboratory for forensic analysis	
31/01/12	MHRA lab establish Isotab Batch J093 contaminated with Pyrimethamine and inform Government of the Punjab and WHO	
31/01/12	Batch J093 tested at Punjab DTL and confirmed presence of contaminant	Once DTL knew what to look for their equipment could verify MHRA findings
01/01/12	Antidote administered to patients	Folinic acid
03/02/12	WHO Issue a Global drug alert for Isotab Batch J093	
06/02/12 - 19/02/12	WHO mission deployed to Pakistan, daily conference calls undertaken with WHO HQ	

1.12 Finding

On examination of the data made available to this mission (which does not include all of the documentation seized by the authorities as part of a criminal investigation) it is concluded that in all probability an error occurred during the manufacturing process. Pyrimethamine was being stored together with the ingredients of Isotab and manufacturing of both products was taking place within a few days of each other. This error was made more difficult to identify through the quality assurance testing as the presence of the correct active ingredient in the correct quantity provided assurance that the medicine was as intended and described.

The discovery that a 25kg drum of pyrimethamine was missing shortly after batch J093 was manufactured should have led to a thorough internal investigation and re checking of the retained samples of recently manufactured batches of medicines for the presence of the potential contaminant. This then followed by a pro-active recall of any suspected contaminated batches initiated by the manufacturer.

Some inconsistencies in the documentation have been apparent. The invoice from Omar trading to PIC appears to have not included all batch numbers, and the retained sample of batch J093 appears inconsistent with the samples of batch J093 recovered from patients.

The mission has not conducted a GMP Inspection of the factory or an investigation into who may be responsible, these are matters left to the Drug regulators and Police.

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Part 2. Drug Regulation in Pakistan

Drug regulation in Pakistan is legislated under the Drugs Act 1976 and Good Manufacturing practice was introduced the same year. Some responsibility sits with the Federal Government and some is the responsibility of the Provincial Governments. The National Drug Regulatory Authority was part of the Ministry of Health until June 2011.

2.1 Federal Responsibility

The Drug Control Organisation (DCO) has responsibility for regulating the following;

- Importation and Export
- Manufacture
- Registration
- Pricing
- Pharmacopeia
- Quality testing laboratory (Karachi)
- Clinical Trials
- Advertising and promotion of medical products

The DCO has a headquarters in Islamabad and offices in the Provinces. They have a staff of 76 posts of which 36 are technical staff and 13 are GMP Inspectors, with an operating budget of 80-85 million Pk rupees per annum (around \$1 million). They are expected to regulate 532 manufacturing sites inspecting each annually, including 26 manufacturers sites owned by 17 multinational companies

Between 60-65,000 medical products are registered in Pakistan. This is due to the brand being registered as opposed to the molecule. Over 100 new dossiers are submitted for registration each month. No in depth evaluation is carried out. Five assessors are allocated to this work. One assessor can deal with 2 dossiers per week. There is a current backlog of 12-13,000 dossiers awaiting registration. There are only 11-1200 different formulations in Pakistan but each manufacturer requires their own 'branded generic' placing enormous strain on finite resources.

The Federal Government place a 1% levy on pharmaceutical manufacturers profit before tax. This fund should be used for research and development purposes but although some small projects existed, little evidence of R and D remains now.

Usually bioequivalence studies are required for generic medicines as the only surrogate for their safety and efficacy. Minimal capacity for bio equivalence studies exist in Pakistan today with only two or three universities providing limited services.

The Central Drug Testing Laboratory (CDL)

The CDL in Karachi is the Federal Laboratory, the main functions of CDL are Qualitative & Quantitative Analysis of Drugs & Medicines and to convey results of the analytical reports to the concerned authorities in the stipulated period.

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Besides the administration section the CDL consists of three sections, Chemical Section (Wet Chemistry and Instrument Sections), Microbiological Section (Sterilization, Inoculation and Incubation Sections) and the Stores (Chemical, Glassware and Auxiliary stores).

The CDL processed 3000 to 4000 tests annually during the period 2008-2010, and 1556 in 2011, this is due to a decrease in budget in addition to defective equipment, during the visit of the mission all HPLC apparatus were out of order.

Marketing Authorisation:

In Pakistan, legal provisions require a marketing authorisation (registration) for all pharmaceutical products on the market. Explicit and publicly available criteria exist for assessing applications for marketing authorization of pharmaceutical products. Legal provisions require the NDRA to make the list of registered pharmaceutical products publicly available. Currently, the existing data is under the process of computerisation, which has not been finalised. Medicines are registered by their INN (International Non-proprietary Names) or Brand name + INN. Legal provisions require a fee to be paid for Medicines Market Authorization (registration) based on applications.

Regulatory Inspection

In Pakistan, there are legal provisions allowing for the appointment of government pharmaceutical inspectors. Legal provisions exist permitting inspectors to inspect premises where pharmaceutical activities are performed and requiring inspection to be performed. Inspection is a pre-requisite for licensing facilities. Inspection requirements are the same for public and private facilities.

Import Control

Legal provisions require authorisation to import medicines. Laws exist that allow the sampling of imported products for testing. Legal provisions require importation of medicines through authorised ports of entry. Regulations or laws exist to allow for inspection of imported pharmaceutical products at the authorised port of entry.

Licensing

Legal provisions require importers, wholesalers and distributors to be licensed, and pharmacists and private pharmacies to be licensed. National Good Pharmacy Practice Guidelines are not published.

Medicines Advertising and Promotion

In Pakistan, legal provisions require the control of promotion and/or advertising of prescription medicines. The Drug Control Organisation is responsible for regulating the promotion and/or advertising of medicines. There are legal provisions prohibiting direct advertising of prescription medicines to the public and requiring a pre-approval for medicines advertisements and promotional

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materials. Guidelines/Regulations are in place for advertising and promotion of non-prescription medicines.

A national code of conduct exists concerning advertising and promotion of medicines by marketing authorisation holders, but no enforcement or control is in place.

Clinical Trials

There are legal provisions requiring authorisation for conducting Clinical Trials by the NDRA. Laws require the agreement by an ethics committee or institutional review board of the Clinical Trials to be performed. Registration of the clinical trials into a registry is required by law.

Controlled Medicines

Pakistan is signatory to the:

- Single Convention on Narcotic Drugs, 1961
- 1972 Protocol amending the Single Convention on Narcotic Drugs, 1961
- Convention on Psychotropic Substances 1971
- United Nations Convention against the Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988

Laws exist for the control of narcotic and psychotropic substances, and precursors. The annual consumption of Morphine is 0.006 mg/capita.

Pharmaco Vigilance

There are legal provisions requiring the Marketing Authorisation holder to continuously monitor the safety of their products and report to the NDRA. Laws about monitoring Adverse Drug Reactions (ADR) are in place and an official standardized form for reporting ADRs exists, but a national Pharmacovigilance centre linked to the NDRA does not exist in the country.

2.2 Provincial Responsibility

Provincial responsibility includes,

- Distribution
- Sale and supply
- Quality Control labs (4)
- Post market surveillance

Medicines are available to the public in Pakistan mainly through Hospitals, Pharmacies and Drug stores. Over 95% of medicines in Pakistan are dispensed without prescription some through pharmacies and some through drug stores which have some limitations on the medicines they can supply. The remaining medicine is supplied through hospitals against prescription. Non-compliance with regulations can be prosecuted through dedicated and specialist drug courts that specialise in breaches of the Drug Act 1976. One of the four provincial Drug Testing Laboratories (DTL) is the Punjab Drug Testing Laboratory, which processes over 25,000 samples each year, the existing staff are qualified and skilled analysts who are specifically experienced and familiar with the testing of

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medicines. They are specialists and represent a significant resource which would benefit from enhanced training and engagement with existing international laboratory fora. However the laboratory requires significant investment in terms of further staff and additional equipment in order to cope with the volume of work. Seriously over stretched analysts processing up to 3 times the work recommended will leave the process vulnerable to errors. The work of this laboratory is critical to providing assurance that medicines procured by the Punjab Government are of the specified quality.

2.3 Regulatory Vacuum

Since the 18th amendment to the constitution was implemented on the 30th June 2011 a number of responsibilities were devolved to the Provinces. This led to the abolition of the post on Minister of Health and the Health department. Health responsibilities have fallen to the Cabinet Secretary who has a large portfolio of responsibilities including defence.

The Provinces were not prepared for this devolution of responsibility and in effect the drug regulatory system has been suspended. The Federal Drug Control Administration has ceased to operate and all functions have ceased.

This vacuum has led to what the DCO state is 532 manufacturing sites and the Pakistan Pharmaceutical Manufacturers Association state is closer to 650 sites operating without any form of regulatory supervision.

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Part 3. Recommendations

This incident has provided the opportunity for Pakistan to learn from this tragedy and implement measures to minimise the risk of repetition of a tragedy of this kind.

3.1. The Lahore Contamination – Recommendations

- a) A national Pharmacovigilance Centre for an effective adverse drug reporting scheme should be established and implemented. Health professionals and patients should be actively encouraged to report suspected adverse reaction to drugs, enabling signals within the population to be detected at the earliest opportunity and the appropriate investigation carried out;
- b) It is undesirable for hospitals to find it necessary to test medicines on receipt from distributors. This increases bureaucracy and causes delay in dispensing to patients. Standards should be raised within the Pakistan Pharmaceutical Industry and supply chain to ensure confidence in the safety and quality of products before reaching hospitals, other health facilities and end users.
- c) Pharmacists are being under used in roles inconsistent with their qualifications in hospitals, and were too few in number. Examples included operating the stores and keeping ledgers. Pharmacists should be more closely engaged with Clinicians and Patients to help ensure the safe, effective, evidence based and economic use of medicines. i.e. Establishing clinical pharmacy and drug therapeutic committees in hospitals;
- d) The procurement and tendering procedures used by hospitals should be reviewed with a focus and clear emphasis on firstly obtaining quality medicine and secondly doing so at an appropriate cost.
- e) The urgent and thorough review of the existing Central and Provincial Drug testing laboratories should be conducted in terms of staff levels, qualifications, training and equipment. WHO prequalification for Drug quality control laboratories and accreditation to other international standards should be sought and co-ordination with the International network of quality control laboratories should be established;
- f) As soon as a serious incident is suspected a clear management structure should be implemented, reporting to the Secretary for Health and widely communicated to all stakeholders. Clarity on who is operationally managing the incident on behalf of the Secretary for health is vital at the earliest stage.
- g) The establishment of a Medicine Information and National Poison centre with 24/7 help lines should be established staffed by properly qualified experienced professionals.
- h) Where an incident crosses Provincial borders an early decision should be made concerning primacy and responsibility and that decision communicated to all parties, the media and the public.
- i) The Legal framework should be reviewed and necessary provisions about the obligations of different parties in executing efficient recalls should be implemented. Standard Operating Procedures dealing with the recall of

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medicines should be established including consideration of advertisements in the print, broadcast and electronic media in order to ensure editorial control and accuracy rests with the Secretary for Health.

- j) A drug alert should be communicated to all hospitals, clinics, pharmacies and drug stores in Pakistan when a defective drug is identified. Wider dissemination outside of Pakistan should be considered where necessary and where evidence of export exists.
- k) Suspected defective drugs should only be disseminated to international laboratories capable of carrying out the required tests. Customs regulations should be considered and a careful record maintained of which batches of medicines have been provided to which laboratories.
- l) Investigations concerning defective drugs and manufacturing processes is complex and outside of the knowledge of most Police investigators. Consideration should be given to establishing a team of Police, Drug Regulators and laboratory scientists at the outset of an investigation of this type to work closely together throughout.
- m) Reconciliation of the numbers of Isotab batch J093 recovered from patients and seized at PIC should be compared to the number of packs produced to ensure that all contaminated medicines are recalled and cannot endanger further patients.
- n) The early allocation of one person to act solely as media liaison to deal with all media enquiries should be considered.
- o) Strict instructions should be provided to all those involved in handling the incident not to communicate with the media other than through or with the nominated spokesperson
- p) Consideration should be given to holding regular press conferences dependent on the scale and escalation of the incident
- q) Ensure and agree with all stakeholders e.g. Federal Government, Provincial Government, Police, Hospitals, Pharmaceutical industry, supply chain and International organisations that they are communicating a consistent message to the public to avoid confusion, misinformation, speculation and the provision of conflicting information to patients.

3.2 The Pakistan Drug Regulatory System - Recommendations

The preliminary findings of this mission have established that when considering all of the circumstances the hospitals and Government reacted in a timely and effective manner to this incident.

However, this incident was caused by a complete system failure facilitated by the absence of an effective, independent, national medicine regulatory regime.

- r) This WHO mission strongly recommend the investment of continuing political will and resources to establish a fully functional National Drug Regulatory Authority.
- The NDRA should be autonomous and independent. Allowed to implement the National medicine and health policies whilst reporting directly to a Government Minister or Prime Minister

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- It should be led by a properly qualified and experienced senior manager with both technical knowledge and managerial skills gained with an Internationally recognised stringent drug regulatory authority
- All NDRA staff should be appointed solely on merit and be properly qualified, experienced professionals, strictly devoid of any conflicts of interest and rewarded in a manner commensurate with their skill, experience, qualifications and responsibility
- The NDRA should be self-financing from fees generated from the registration, licensing, inspection and testing processes. All accounts should be subject of regular external audit
- The NDRA whilst reporting directly to Government should be permitted to function with minimal political interference

The principal regulatory responsibilities of an NDRA include the regulation of human and veterinary medicine, vaccines and other biological products, traditional medicine and medical devices. Key functions include:

- Licensing: manufacturers, importers/exporters, wholesalers/distributors, supply chain, and pharmacies / drug stores
- Registration of medicines and granting of marketing authorisations
- Regulatory Inspections of all licensed entities
- Quality control laboratory
- Post Marketing surveillance and safety monitoring
- Regulation of medicines promotion and advertising
- Pharmacovigilance (Adverse drug reaction monitoring)
- Licensing of clinical trials
- Enforcement of regulations and handling non compliance
- Control of narcotics, psychotropic substances and precursors
- Registration of Pharmacy personnel and the establishment of pharmacy services
- International co-operation and harmonization

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Part 4. A Regulatory Roadmap

4.1 Previous WHO and other regulatory assessments

Attention is drawn to three previous assessments conducted by the WHO since 2003. All of these assessments provide detailed proposals for establishing a National Drug Regulatory Authority in Pakistan

The first assessment was conducted in 2003(Pakistan Drug Regulatory Authority as an Integral Part of Pakistan National Drug Policy, December 2003) the team provided detailed recommendations and reported the following:

"The recommendations were shared informally with the Management Services Wing of Establishment Division. Which was of the view that under Rule 68 of "Secretarial Instructions" it was obligatory on all the Ministries / Divisions to refer all the cases / proposals for restructuring / reorganizing / creation of new organization / expansion etc. to the Management Services Wing for consultation / technical evaluation."

In addition to that MoH prepared a report on the basis of the WHO report and submitted it to the Management Services Wing of Establishment Division which then prepared a joint report with the MoH.

The second was published in 2005 entitled 'Establishing a Drug Regulatory Authority in Pakistan'. The authors recommended the following;

"The team are proposing a fully empowered Drug Regulatory Authority to make technical, administrative and financial decisions; guided by National development objectives and National Health Policy; responsible for implementing National medicine Policy based on essential medicines concept in order to ensure equitable, reliable, and sustainable access to safe, efficacious, affordable medicines of ensured quality and their appropriate use"

The third assessment was conducted in 2009 (Towards a National Therapeutic Goods Regulatory Agency for Pakistan) and recommended the following;

"The project team recommends Pakistan should establish a Regulatory Agency, The Therapeutic Goods Regulatory Agency, the TGRA, to be the National Regulator for the supply and distribution of all therapeutic goods. The TGRA should be established along the lines recommended by WHO and report directly to the Minister of Health. This is the model used in Countries with well developed regulatory systems for medicines and other therapeutic goods. Such regulatory agencies are an arm of Government and not totally independent Authorities e.g. Food and Drug Administration (FDA) of USA, the Health Products and Food Branch (HPFB) of Canada, the UK Medicines and Healthcare products Regulatory Agency (MHRA), and the Therapeutic Goods Administration (TGA) of Australia"

In addition to the above in 2005 the Ministry of Health commissioned Sarfaraz K. Niazi, Ph.D. to submit a framework for a Drug Regulatory Authority in which he sets out the vision, mission and objectives of a modern regulatory agency.

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This mission draws on the work carried out by those assessment teams and endorses their recommendations. The Lahore drug contamination case has starkly highlighted the essential need for the early implementation of all recommendations.

4.2 Short term objectives, 1 – 6 months

a. A detailed and thorough assessment is required of the existing capacity in each of the regulatory functions using the existing WHO assessment tool, including the Drug Testing Laboratories.

b. Establish the legal basis for the creation of an independent and autonomous National Medicine Regulatory Authority.

c. Identify a team of the best National / International experts to co-ordinate and facilitate all preparatory work required for the establishment of a National Medicine Regulatory Authority and develop a plan of action. This team should be led by a person with experience of working with International stringent regulatory authorities.

4.3 Mid-term objectives, 6 – 18 months

d. The Pakistan National Medicine Policy should be thoroughly reviewed, updated and implemented

e. A thorough analysis of the legal framework for medicines regulation should be carried out with clear recommendations for improving the legal framework on all levels.

f. The establishment of a pharmacovigilance centre to monitor the safety of medicines on the market and receive reports of adverse drug reactions.

g. The establishment of a National Poisons Centre and medicine information centre

h. Implementation of the findings from all assessments of the components required to fulfil the responsibilities of a fully functioning NMRA equipped with the necessary powers for enforcement.

4.4 Long term objectives, Over 18 months

i. Implement a quality assurance system, inspection and enforcement regime to ensure internationally recognised standards are applied throughout the pharmaceutical supply chain

j. Implementation of c GMP, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, and WHO norms and standards in all areas of medicine regulation.

4.5 Desired outcomes

- Ensure that safe, quality and affordable Health technologies are accessible to all.

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- Improve and maintain national and international confidence in medicines and medical products manufactured and available in Pakistan
- Establish Pakistan as a country maintaining internationally recognised standards in the field of Medicine Regulation

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Appendices

Appendix-I WHO terms of reference, mission to Lahore, Pakistan 2012

Terms of Reference

1. To provide technical support in assisting the authorities and the Country Office in the investigation of the suspected substandard medicine incident in Lahore, through

- Provision of expertise in regulatory related investigations to assist in the detection of the root cause for this or any future incident;
- Assistance in identifying any further measures that might be necessary to protect the patients exposed;
- Assistance in enabling links and coordination between the investigating committees, the authorities and the WHO collaborating centre in Uppsala regarding related ADR data as well as medicine information and poison centre(s) regarding the symptoms;
- Assistance in providing a mechanism for collaboration among the forensic and quality control laboratories within and outside the country for testing medicines and trace elements, as needed.

2. To conduct a comprehensive analysis and enquiry into the Lahore incident, identifying all issues, and developing best practice guidance, identifying structures, guidelines and standards that would need to be implemented to avoid, identify and react to serious incidents in the future

3. Based on the findings of the mission and on recent assessments carried out by WHO, propose key recommendations and a road map for further interventions and WHO missions for improving pharmaceutical policy aspects such as :

*strengthening of regulatory capacity e.g. The development of a pharmacovigilance system; the pre-qualification of quality control laboratories; the establishing of a drugs/ therapeutic goods regulatory authority.

*the development of a systems for rational use and monitoring of medicine use, along with mechanisms for selection and procurement, to improve access to quality medicine in the country.

*CONFIDENTIAL***Appendix-II WHO Global Alert, Isotab batch J093****Alert No. 125****03 February 2012****Contaminated Isotab® (isosorbide mononitrate) incident in Lahore Pakistan**

Increased vigilance is requested for batch/lot number J093 of Isotab® 20 mg (isosorbide mononitrate) labelled as being manufactured by Efroze, Karachi, Pakistan.

A serious incident occurred in Lahore (Punjab, Pakistan) involving the deaths of 107 patients with serious adverse reactions in more than 450 patients. The incident is currently being investigated.

At the request of the Department of Health Government Punjab, samples of the suspected tainted medicines were sent to different laboratories for testing in Pakistan and abroad, including two European laboratories of national regulatory authorities.

The results of those tests are being communicated, both to the Punjab Health Authority and to WHO. The analysis from the first of those tests are now available. The Punjab Health Authority and WHO have been informed that one of the medicines tested, an antianginal medicine (isosorbide mononitrate) contained pyrimethamine in quantities large enough to cause a substantial overdose. The effects caused by the overdose of this medicine are consistent with some of the symptoms exhibited by the patients who have been admitted to hospital in Lahore.

The product concerned is Isotab® (isosorbide mononitrate 20 mg) which contained a significant amount of the pyrimethamine. From the information available to date, the contamination has only been found in the production batch J093 of Isotab labelled as being manufactured by Efroze, Karachi, Pakistan. Samples of the same medicine tested from other batches have not shown any contamination with pyrimethamine to date.

The Department of Health Government Punjab has taken steps to contain the supply of the suspected medicines and according to the Pakistan authorities, the medicines concerned have only been delivered to The Punjab Institute of Cardiology in Lahore.

However, this alert is issued as a precautionary announcement, and a preventive measure, in the event that this batch of medicine has been more widely distributed.

Further investigations are ongoing. Updates will be issued in case further enquiries reveal that other batches and/or other medicines are involved.

If this specific batch of medicine has been imported, distributed or dispensed in your country please notify Mr Michael Deats (deatsm@who.int) and Dr Lembit Rago (ragol@who.int)

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WHO Pharmaceutical Profile, Pakistan. 2010

WHO Assessment, Towards a National Goods Regulatory Agency for Pakistan, 2009

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Acknowledgements

The Government of the Islamic Republic of Pakistan
Cabinet Secretary
Ministry of Inter Provincial Coordination
Planning Commission
The Drug Control Organisation
The Government of the Punjab
Secretary for Health, Health Department
The Judicial Commission in to the Lahore Drug Contamination
International Health Partners UK
Punjab Institute of Cardiology
Jinnah Hospital AND Allama Iqbal Medical College
Services Hospital and Services Institute of Medical Sciences
Punjab Drug Testing Laboratory
Punjab Forensic Sciences Laboratory
Central Drug Testing Laboratory, Karachi
Federal Drug Control Authority
Provincial Drug Inspectors, Sindh
Provincial Drug Inspectors, Punjab
Pakistan Pharmaceutical Manufacturers Association
Pakistan Pharmacists Association
WHO Country Office, Islamabad

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

SCHEDULE

-4-



REPORT REGARDING INSPECTION OF M/S EFROZE CHEMICAL INDUSTRIES KARACHI ON 14.05.2012 AND 15.05.2012.

In pursuance of order dated 09.05.2012 passed by the learned Defective Drugs Inquiry Tribunal, inspection of M/s Efroze Chemical Industries was carried out on 14.05.2012 and 15.05.2012. The following persons took part in this inspection.

- 1) *Mr.S.S. Nasir, Co-opted Expert.*
- 2) *Mr.Irfan Ahmad Saeed, D&SJ/Registrar of the Tribunal.*
- 3) *Mr.Abad ur Rehman, Private Secretary of the Tribunal.*
- 4) *Dr.Shahid Hussain Pechuho, Federal Inspector of Drugs, Karachi.*
- 5) *Dr.Obaid Ali, Chief Analyst, Central Drugs Laboratory, Karachi.*
- 6) *Mr.Akbar Balouch, Assistant Director FIA, Karachi.*

Following persons from Efroze Chemical Industries represented the company in the said inspection.

- 1) *Mr.Nadir Feroz, Deputy Managing Director.*
- 2) *Mr.Shakeel Ahmad Khan, General Manager, Plant.*
- 3) *Mr.Kashif Abdullah, Deputy Production Manager.*

OBJECTIVES OF THE INSPECTION

To observe and evaluate the overall cGMP (Current Good Manufacturing Practices) and GLP (Good Lab Practices) compliance by the company.

To investigate the lapses and lack of controls and weaknesses in the procedure adopted, which could have led to addition/contamination of Batch No.J093 of Isotab Tablets with Pyrimethamine. The contamination of this batch with Pyrimethamine has been clearly established by testing of the samples of this batch by MHRA and London School of Pharmacy.

TOTAL AREA OF THE FACTORY

Efroze Chemical Industries is located at 146/23, Korangi Industrial Area, Karachi. Total area of the plot is 2777.77 Square Yards

(Approximately 5.5 Kanals). The total covered area as reported by the management is 25,239.5 Square Feet.

REGISTERED PRODUCTS IN THE NAME OF THE COMPANY

The company has registered 179 different products under the Drugs Act, 1976 but they are manufacturing only 90 products whereas the other 89 products are not being produced.

(Reference Annexure-A. The products being manufactured are highlighted in yellow in this annexure).

According to the record provided by the company 1763 batches of solid and liquid products were produced between July, 2009 to June, 2010, whereas between July, 2010 to June 2011 1713 batches of these dosage forms were produced. The breakdown is as follows:-

July, 2009 to June, 2010.

Tablets	1397
Liquids	265
Capsules.	51

July, 2010 to June, 2011.

Tablets	1467
Liquids	266
Capsules.	30

Further according to the information provided by the company the following quantities were produced in the years mentioned below:-

Dosage Form	Year	Quantity
Tablets	July, 2008 to June, 2009	466.3 millions
	July, 2009 to June, 2010	486.9 millions
	July, 2010 to June, 2011	467.5 millions
	July, 2011 to December, 2011	268.4 millions

Dosage Form	Year	Quantity
Liquids	July, 2009 to June, 2010	291,000 Liters
	July, 2010 to June, 2011	336,400 Liters
	July, 2011 to December, 2011	172,567 Liters
Capsules	July, 2009 to June, 2010	6.4 millions
	July, 2010 to June, 2011	5.8 millions
	July, 2011 to December, 2011	5.7 millions.

It is noteworthy that the company, in addition to the domestic sale is also exporting their various products to different countries. The export value is given below:-

Country.	Year	Value of Exports in US Dollars
Vietnam	2009-2010	19,000/-
	2010-2011	92,650/-
	2011-2012	64,210/-
	2011-2012 (WIP)	40090/-
	Total 2011-2012	149,700/-
	Projected sale for 2012-2013	185,020/-
	Projected sale for 2013-2014	203,522/-
Cambodia	2009-2010	11500/-
	2010-2011	52,150/-
	2011-2012	86950/-
	2011-2012 (WIP)	0/-
	Total 2011-2012	100850/-
	Projected sale for 2012-2013	105,380/-
	Projected sale for 2013-2014	115,918/-

Country.	Year	Value of Exports in US Dollars
Sri Lanka	2009-2010	24,371/-
	2010-2011	84,704/-
	2011-2012	39895.5
	Projected sale for 2012-2013	50123/-
	Projected sale for 2013-2014	55135/-
Myanmar	2009-2010	43120/-
	2010-2011	69010/-
	2011-2012	91,250/-
	2011-2012 (WIP)	28700/-
	Total 2011-2012	124,750/-
	Projected sale for 2012-2013	135,493/-
	Projected sale for 2013-2014	149,042/-
Singapore	2010-2011	30659/-
	2011-2012	13443/-
	Total 2011-2012	21,383/-
	Projected sale for 2012-2013	23,521/-
	Projected sale for 2013-2014	25,873/-
Hong Kong.	2010-2011	675/-
	2011-2012	1350/-
	Total 2011-2012	1350/-
	Projected sale for 2012-2013	1485/-
	Projected sale for 2013-2014	1634/-

Country.	Year	Value of Exports in US Dollars
Bangladesh	2010-2011	57619/-
	2011-2012	51000/-
	Projected sale for 2012-2013	56100/-
	Projected sale for 2013-2014	61710/-
Kyrgystan	2011-2012	4875/-
	Projected sale for 2012-2013	16250/-
	Projected sale for 2013-2014	17875/-
Nigeria	2009-2010	99,465/-
	2010-2011	87,880/-
	2011-2012	51,840/-
	Projected score for 2012-2013	57,024/-
	Projected score for 2013-2014	62,726/-
Kenya	2009-2010	234,972/-
	2010-2011	142,666/-
	2011-2012	87,405/-
	Projected score for 2012-2013	162,163/-
	Projected score for 2013-2014	178,380/-
Sudan	2009-2010	2091234
	2010-2011	1810335/-
	2011-2012	1187114/-
	Projected score for 2012-2013	1289330/-
	Projected score for 2013-2014	1418263/-

Country.	Year	Value of Exports in US Dollars
Yemen	2009-2010	192300/-
	2010-2011	153400/-
	2011-2012	128897/-
	Projected score for 2012-2013	174,019/-
	Projected score for 2013-2014	191,422/-
Uzbekistan	2009-2010	200720/-
	2010-2011	43120/-
	2011-2012	81852/-
	Projected score for 2012-2013	125471/-
	Projected score for 2013-2014	138017/-

In addition to the above, the company also intends to export their products to Ghana, details of which are as under:-

Country.	Year	Value of Exports in US Dollars
Ghana	Projected sale for 2012-2013	3700/-
	Projected sale for 2013-2014	4070/-

RAW MATERIALS (ACTIVE PHARMACEUTICAL INGREDIENTS (APIS) AND EXCIPIENTS)

According to the stock report of the company dated 31.12.2011, the total number of APIs used by the company for their various products is 75 items, whereas the total number of excipients is 141 items, and the total number of various packaging materials is 1052 items.

FINISHED PRODUCTS:

Domestic Sale Total number of Products	76
Export Total number of Products	16
Physician's Samples.	47

STAFF COMPLIMENT:**Temporary Workers:**

The company is utilizing the service of temporary workers to carry out their production and packaging activities, who are hired through three contractors namely Shirazi Engineers, Shah Traders and Al-Zahid Corporation. The details are given as under:-

Name of the Contractor	Month	Number of workers
Shirazi Engineers	May, 2012	43
	July, 2011	80
	August, 2011	65
	September, 2011	70
	October, 2011	67
	January, 2012	67
	February, 2012	59
Shah Traders	May, 2012	48
	July, 2011	72
	August, 2011	64
	September, 2011	69
	October, 2011	75
	January, 2012	62
	February, 2012	48
Al-Zahid Traders	February, 2012	60
	January, 2012	61
	October, 2011	88
	September, 2011	89
	August, 2011	69
	July, 2011	70

The total Number of Workers hired through these three contractors in the months mentioned below are as follows:-

Month	Shirazi Engineers	Shah Traders	Al-Zahid Traders.	Total
May, 2012	43	48	-	91
July, 2011	80	72	70	222
August, 2011	65	64	69	198
September, 2011	70	69	89	228
October, 2011	67	75	88	230
January, 2012	67	62	61	190
February, 2012	59	48	60	167

Permanent Staff:

Number of permanent workers are as follows:-

Manufacturing Department	12
Packaging Department.	9
Warehouses. (Raw Material Store	4
Packaging Material Store and Finished Goods Store)	

This is a matter of concern that in a sensitive trade like pharmaceutical manufacturing, the company has on its permanent pay roll only 25 workers to carry out the work in the warehouses, manufacturing and packaging. Whereas according to the above figures of contractual workers, for seven months, a minimum of 91 contract workers (May, 2012) and maximum of 230 contract workers (October, 2011), worked in the factory. According to the agreements with the contractors, there is no condition of minimum literacy and education level. According to the management, these temporary workers frequently change and there is no concept of in house training of these workers. It is note worthy that these temporary workers take part in the sensitive warehousing, manufacturing and packaging activities.

VISIT TO THE FACTORY PREMISES**ENTRANCE:**

The workers' entrance to the production area is through a passage adjacent to the security guard room. In this passage, dirty clothing presumably of the workers were seen hanging on the wall and also dirty drums and other miscellaneous items were seen haphazardly stored, after this the workers pass through an open space through a canteen and temporary dining area meant for the workers. It was observed that cooking was being carried out in the open space and also utensils were being washed in this area. Some benches and chairs were placed in the open where the workers have their lunch. A lot of flies and insects were seen in this area.

From there the workers enter the wash rooms. The condition of the wash rooms was found un-satisfactory. No soaps and towels were seen for hand washing. The toilets were dirty with stained tiles, accumulated with dust and dirt. The hot air hand dryer was out of order.

CHANGE ROOMS:

Workers' factory uniforms and their personal clothing were seen hanging on the same wall without any identification or surety about their cleaning and allotment to the workers. Under these conditions, the workers must be wearing each others uniforms which is not acceptable. There is no separate place for the workers to change their clothes. Furthermore, there is no proper ventilation or temperature control in this area. The temperature was found to be extremely high. The shelves meant to store factory shoes were found full of dust. In the whole area only one fan is installed. The electricity wiring is open. The tube lights are hanging type and were seen covered with dust. The door between the production area and change room is of wood and very old. Air curtain installed above this door meant to prevent entry of insects in the production area is old and out of order. The tops of the lockers allocated to the workers were full of dust.

Similar conditions were seen in the female change room.

PRODUCTION CORRIDOR (GROUND FLOOR):

The false ceiling of the production corridor is patterned. It should be plain and smooth. The patterned ceiling has the potential to collect dust. There is no ventilation or temperature control in this corridor. The temperature was very high and the atmosphere in this area was suffocating.

RAW MATERIALS STORE/FINISHED GOODS STORE (GROUND FLOOR):

The area of raw material store on the ground floor is only 880 Square Feet. It does not have any proper receiving bay and de-dusting area. The access is directly outside to a dirt road. There is no air curtain installed on the gate to prevent entry of insects and dust in this sensitive storage area. This store does not have any proper ventilation or air conditioning which is mandatory for the storage of raw materials and finished goods. The store does not have any quarantine area or bounded area for storage of rejected materials. The other gate of this store also opens directly in an uncovered passage. According to the management, finished goods are also stored in this premises and these are transported out for shipment from this gate. A small air curtain is installed on this gate, but it does not totally cover the gate so it has no utility for the intended purpose. The store was fully occupied by raw materials. There were only 14 empty spaces for further incoming raw materials. At this time no finished goods were seen stored and according to the management they had been moved for storage at Korangi Creek Warehouse. It should be noted that according to the requirements of drug laws, there should be a separate and exclusive store for finished goods. The company does not have this facility.

RAW MATERIALS STORE (FIRST FLOOR):

This store has three rows of racks on which raw materials are stored. These raw materials include active and non-active ingredients. There is no air conditioning/temperature control in the store and high temperature and humidity was observed. According to the store incharge 25 active pharmaceutical ingredients (APIs) and 60 different excipients were stored in this area at that time. The store was fully occupied and only two empty spaces were available for further storage. Sugar, Macrogol,

Acetone, Chloroform, Sorbitol and Glycerin were stored in a space adjacent to the material lift outside the store under high temperature conditions. The drums of Sorbitol and Glycerin had temporary hand written labels fixed with scotch tape, which can easily result in mix ups. There is no proper dispensing area in this store. A so called dispensing area has been created with Aluminum Partition. There is no temperature control and ventilation in this partitioned dispensing area. The balances in the dispensing area have resolution of 1 gram and these balances are not suitable for weighing active ingredients. The readability of these balances is only upto 2 decimal spaces, which is not as per requirement. (For example, in the manufacturing of Isotab Tablet quantity of Isosorbide 5 Mononitrate for a batch of 400,000 tablets is 11.658 Kgs.) This quantity cannot be weighed on the aforesaid balances. The management had no answer as to how they were carrying out this type of weighing. On account of lack of space, three different ingredients namely Methyl Paraben, Propyl Paraben and Croplovidone XL were stored together in one shelf. This can easily lead to wrong issue. Furthermore, controlled substances like Diazepam, Pseudoephedrin and Tramadol Hydrochloride were stored in the open, these materials should be stored under lock and key.

As per the stock report dated 31.12.2011, the company had in stock 92 finished products, 75 Physician's Samples of various products, 31 different finished products, 75 different Active Pharmaceutical Ingredients and 141 excipients. According to the Stock Movement report dated 14.05.2012, 1052 packaging materials were in stock.

M/s. Efroze Chemical Industries has at its disposal two warehouses, one for raw materials with covered area of 880 Sq. Ft, the other store with a covered area of 1232 Sq. Ft. is a combined store for raw materials, packaging materials and finished goods. The following quantities of materials are to be stored in this very limited storage space.

Finished Products.	92
Physicians' Samples.	75
Finished Products in Quarantine.	31
APIs	75

Excipients.	141
Packaging Materials	1052

Due to this shortage of space, obviously, there is no other choice with the company than to dump these goods in a congested and disorganized manner. This kind of storage can lead to mix ups and wrong issues, which can result in serious consequences as it happened in the case of addition of Pyrimethamine in Batch No.J093 of Isotab 20 Tablets.

KORANGI CREEK WARE HOUSE:

Due to acute shortage of space within the factory, M/s.Efroze Chemical Industries have rented a warehouse located at Plot No.224/2, Sect.39 Korangi Creek Karachi, exclusively to store finished products manufactured by Efroze Chemical Industries. In this regard they have obtained a Drugs Whole Sale License No.2142 dated 26.10.2010. This license is exclusively to sell stock and exhibit for sale and distribute drugs by way of wholesale. However, in violation of the conditions of this license, this premises is also being used to store raw materials, packaging materials and promotional materials of the company. This violation is serious as the company has no authorization/approval by the Health Authorities to store these items in a warehouse meant and authorized for distribution of drugs by way of wholesale. This is also in violation of the Drugs Act, 1976 and the rules framed there-under. Accordingly, the raw materials/packaging materials have to be stored by the manufacturer within the premises for which license to manufacture by way of formulation has been issued by the Health Authorities.

There should be adequate space within the factory to store the materials (e.g. Active Ingredients, Raw Materials and Packaging Materials etc.) in accordance with Schedule B(2)(i) of Rule 16 of Drugs (L.R.A) Rules, 1976.

This rented warehouse at Korangi Creek does not even meet the requirements. The store does not have a receiving and dispatching bay. There is no de-dusting area or air lock. The main gate of the store directly opens towards outside. Furthermore, there is no environmental control in the store (e.g. provision of any ventilation, air conditioning or humidity

control). No temperature and humidity gauges are installed. The temperature was found extremely high with suffocating atmosphere.

MANUFACTURING FACILITIES:

Following is the detail of the facilities available for manufacturing of various dosage forms:-

A. Tableting Facility.

As per management the area of this facility is as under:-

Tablet Section-1	440 Sq. Ft.
Tablet Section-2	880 Sq. Ft.
Tablet Section-3	880 Sq. Ft.
Tablet Section-4	400 Sq. Ft.

The minimum area required for each tablet section by the drug laws is 900 Sq. Feet.

During the inspection critical deficiencies were noted in the tablet manufacturing Section, which are as follows.

- I- The partitions between the compression machines are of wood. Cabinets for the machines are also of wood and the main entrance doors are of wood. Wooden material is not acceptable according to the latest cGMP (Current Good Manufacturing Practices) requirements.*
- II- There is no proper HVAC system and separate Air Handling Units (AHU) for each compression machine, only Split Units are installed.*
- III- Proper negative pressure for each cabin is non-existent, this will lead to cross contamination of the products being manufactured simultaneously.*
- IV- The electrical wiring is not concealed. It is in open conduit pipe and there is accumulation of dust leading to cross contamination.*
- V- There are no thermometers installed to monitor the temperature in the areas.*

- VI- *The cabin for powder mixing is of Aluminum. This Aluminum partition has a tendency to accumulate dust leading to cross contamination.*
- VII- *As there is no Air Conditioning in the area, high temperature of 32° C without any proper ventilation was observed.*
- VIII- *All the tray dryers are very old and rusted, these dryers do not have any probes installed inside the chamber for proper monitoring of the temperature in different areas of the dryers. There is no directly connected exhaust on all these dryers.*
- IX- *In the General Tableting Section, there is a 10 Inch X 18 Inch common exhaust installed inside the room on the wall leading to the outside which is highly undesirable because this heats up the area.*
- X- *Preparation of coating solution is carried out in an open vessel, which does not have a cover. This is not a good practice, as this can lead to dust contamination of the solution or even entry of insects.*
- XI- *The Fluidized Bed Dryer is also very old and rusted. Common bags are being used for all products, which is not acceptable as this can lead to cross contamination, these bags should be dedicated product wise. There is no Standard Cleaning Procedure for the Fluidized Bed Dryer. In the absence of this procedure there is no assurance about the proper cleaning of the equipment. This can also result in contamination of one product with another.*
- XII- *Standard cleaning procedures for majority of the machines are not available. For some machines, they have been developed but there are no cleaning records available, which could reflect that cleaning of the machines is being carried out as a routine by the company. These reports should be detailed recording stepwise cleaning and verification of the same by the person carrying out the steps and the supervisor. This is a serious cGMP violation, as there is no assurance that the machines are being properly cleaned between manufacturing of different products. Improper cleaning can lead to cross contamination*

/mixing of active ingredients of one product into the other, which can lead to very serious consequences.

- XIII-** *Four tablet compression machines are very old and rusted and are not compliant with cGMP (Current Good Manufacturing Practices) requirements.*

B. Psychotropic Tablet Manufacturing Section:

- I- In this area the partitions are of Aluminum, which has a tendency to collect dust. This accumulation of dust can lead to cross contamination.*
- II- The cabin for the tablet compression machine indicated positive pressure instead of negative pressure. In the cabin for Cone Mixer, there was no pressure at all. The requirement is negative pressure. Similarly at the main entrance to the Section, there exists positive pressure instead of negative pressure.*
- III- The workers' entrance to this area is too small and cannot accommodate a cabinet for the storage of uniforms. So the changing of the uniforms becomes questionable.*
- IV- HVAC System in this area is not effective.*

C. Hormone Manufacturing Section:

- I- The partitions are of Aluminum. These Aluminum partitions tend to accumulate dust leading to cross contamination.*
- II- Cross over bench to this area is of small size with open spaces on both sides, these open spaces are big enough for a person to pass through without crossing over the bench.*
- III- There is no HVAC system installed in this section, which is a must for sensitive hormonal products.*
- IV- It was noticed that two compression machines were installed in a room without any partition between them, both these machines should be in separate cabins considering the sensitive nature of the hormonal products manufactured in this area.*
- V- No validated standard cleaning procedures were available.*
- VI- The hormonal product manufacturing area should have a dedicated blister packaging machine, which was not available.*

It is worth noting that both dedicated Psychotropic Tablet Manufacturing Section and Harmonal Products Manufacturing Section have been recently approved by the concerned Health Authorities and critical deficiencies and cGMP (Current Good Manufacturing Practices) violations mentioned above have not been taken into consideration.

D. Liquids Manufacturing Section:

- I- *There was no HVAC system in this section, only two Split Units were installed. The atmosphere in the area was hot and suffocating.*
- II- *Standard Cleaning Procedures were available for some of the machines but their authenticity and effectiveness remains questionable as these procedures have not been validated.*
- III- *No detailed cleaning reports are on record.*
- IV- *One open type drain was seen in one corner of Liquid Manufacturing Area, this drain should be cGMP compliant having a completely closed cover, through this open drain insects etc. can enter into this sensitive production area.*
- V- *There is a wooden entrance door to the Liquid Manufacturing which is not permitted.*
- VI- *The source of water for production is city supply and in case of shortage, the requirement is met through purchase of water brought in through tankers. The water after storage is not chlorinated. Since this treatment is not being carried out, there exists a big risk of microbial contamination of the products being produced specially with injurious pathogenic bacteria and fungus etc.*

Treatment of the water with ultra violet light is ineffective for removal/killing of micro organism.

E. Quality Control Department.

- I- *The department did not have proper ventilation. Fans and window type air conditioners were being used in this laboratory. Fans are not acceptable at all as per the latest cGMP requirements. Window Air Conditioners are also not acceptable as they have a tendency to intake dusty air from outside.*

- II- The laboratory had Aluminum partitions, wooden furniture and cabinets etc. which is not acceptable.*
- III- Electrical wiring was not concealed and was fixed on the wall in open conduit pipe.*

Although the equipment in the quality control laboratory was sufficient for testing but some of the equipment was very old. The availability of spare parts and after sale service for the old equipment is questionable.

F. Microbiological Testing Facility:

This sensitive area did not meet the cGMP (Current Good Manufacturing Practices) requirements, as it did not have installed HVAC system, which is a must for this laboratory. Because of non availability of HVAC system there was no positive pressure in the laboratory. Only a split air conditioning unit was provided, which does not meet the requirements.

G. Storage of Junk Items at Roof Top:

- I- The company stores miscellaneous items, such as empty cardboard and plastic drums of raw materials, rejected blisters and cartons on the roof top.*
- II- Some of the witnesses during the inquiry of the Tribunal, revealed the fact that these empty drums are re-used in the production to store in-process materials or portions of the batches. The original labels on these drums were intact, which is hazardous. If these drums are re-used in the warehouse or production to store in-process materials, there can be a mis-judgment about the contents of the container and the label. It was stated by some of the witnesses who appeared before the Tribunal that Pyrimethamine, after micronization, may have been stored in a drum of pre-gelatinized Starch.*
- III- Furthermore, it was revealed by the management that the drums, rejected cartons and blisters are sold to the junk dealers in their original condition e.g. without removing the labels of the raw material from the drums. This situation is not acceptable as these labeled drums can be mis-used.*

H. Isotab 20 Tablets:

- I- Isotab tablets are being manufactured by Efroze Chemical Industries with a batch size of 400,000 tablets. In the formulation they are using an overage of 2% of Isosorbide-5 Mononitrate, there is no justification at all to add this quantity. The management could not produce any document that they have approval for the same from the Health Authorities.*
- II- During the course of inspection of the quality control laboratory, the concerned staff was asked to produce batch records of any 3 batches of Isotab tablets for examination by the team. Records of Batch No.J077, J078 and J079 were made available, according to the staff it is a regular routine that the chromatograms of the tested batches are studied and attached with the batch record and it is also a regular routine that the analyst/quality control managers study the chromatograms before approval of a particular batch.*
- III- It was observed that the chromatograms of above mentioned three batches did not show any additional undesirable peaks, whereas the chromatogram of the contaminated batch i.e. J093 prominently showed an additional peak. This additional peak should have raised an alarm and the matter should have been investigated further instead of out rightly approving the batch.*

I. General Comments:

- I- The factory premises of M/s.Efroze Chemical Industries, located at 146/23, Korangi Industrial Area, Karachi, is more than four decades old and in the meantime there have been major changes in the requirements for Pharmaceutical Plants. This factory premises of Efroze Chemical Industries does not meet cGMP requirements.*
- II- Factory of M/s.Efroze Chemical Industries has been built in a very limited space. The total area of the plant is 2777.77 Square Yards approximately 5.5 Kanals. The covered area is only 25,239.5 Square Feet. In the meantime the production of M/s.Efroze Chemical Industries has increased manifold*

rendering the plant deficient for producing the large volumes in a proper manner. Presently the company has 179 different registered products out of which they are actively producing 90 items in this small plant.

- III- The company has inadequate and very limited space for storage of raw materials, packaging materials and finished goods in the factory premises. There should be separate stores for each of these items. The number of active pharmaceutical ingredients in active use is 75, whereas the total number of excipients is 141, packaging material quantity is 1052 items and 90 different products are required to be stored. The company simply does not have available space to store these large quantities in an orderly manner with proper segregation to avoid mix ups and wrong issues, as happened in the case of issuing Pyrimethamine in the manufacturing of Batch No.J093 of Isotab 20 Tablets.*
- IV- The situation has been compromised by renting a warehouse which is located approximately 5/6 KM from the factory, this store is not suitable for the purpose for which it has been taken because the storage conditions are not proper. There is no environmental and temperature control. Further, the company is not authorized to store raw materials and packaging materials in this warehouse.*
- V- M/s.Efroze Chemical Industries is heavily dependent upon contractual workers. These contractual workers even work in the manufacturing departments. The turnover of the temporary workers is frequent, these temporary workers are not imparted any training nor the company has any specific requirement regarding the educational qualifications of these persons. The permanent workers on the company's pay roll are only 25 whereas the maximum number of temporary workers goes upto 230 persons (October, 2011). This practice is totally unacceptable as carrying out pharmaceutical manufacturing operations through untrained and un-educated/semi-educated temporary workers can lead to very serious mishaps. The case of Batch No.J093 of Isotab 20 Tablets is one tragic example.*

- VI- The company does not have a proper canteen for the employees. It has a make shift arrangement with improper hygienic conditions.
- VII- Changing rooms for the workers do not meet cGMP (Current Good Manufacturing Practices) requirements.
- VIII- The manufacturing areas are in very poor condition. Majority of the installed machines are obsolete and old. The capacity of the machines is limited which cannot produce large quantities of products required by the company in a smooth and orderly manner.
- IX- HVAC Systems are practically non-existent in various production areas, which is a must according to the latest requirements laid down by the Health Authorities.
- X- Wooden doors, cabins, partitions, furniture and cabinets are in existence, use of wood is strictly prohibited by the Health Authorities, Aluminum partitions are also discouraged.
- XI- The factory has in-adequate microbiological testing facility.

CONCLUSION

- i) M/s. Efroze Chemical Industries is not overall cGMP (Current Good Manufacturing Practices) compliant. It has critical deficiencies as discussed in various portions of this report.
- ii) In view of this serious situation M/s. Efroze Chemical Industries is not fit to continue production of all products that it is currently licensed to manufacture without risking further unfortunate mishaps as in the case of contamination of Batch J093 of Isotab Tablets with Pyrimethamine resulting in more than 197 fatalities.
- iii) The company may be permitted to undertake limited production in the current premises under strict supervision for a limited period of time subject to strict adherence to cGMP requirements but curtailing the number of products being produced by a significant number that can be orderly produced in the current available facilities. Such permission may be given by the competent authority on the condition that the company will build a new cGMP (Current Good

Manufacturing Practices) compliant plant with proper machinery and equipment within a period of 18 to 24 months.

SYED SHAHID NASIR
Coopted Expert

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

**SCHEDULE
-5-**



THE NEWS
12 FEB 2012

**DEFECTIVE DRUGS INQUIRY TRIBUNAL
LAHORE HIGH COURT, LAHORE**

PUBLIC NOTICE

1. Vide Notification No. SO (JUDL-III) 9-84/2012 dated 30-01-2012, issued by Government of the Punjab, Hon'ble Mr. Justice Ijaz-ul-Ahsan, Judge, Lahore High Court, Lahore has been appointed as Defective Drugs Inquiry Tribunal to determine full facts of incidents of numerous deaths reportedly (prima facie) due to bone marrow suppression amongst patients registered with Punjab Institute of Cardiology and has also caused unrest among the people. Following are the terms of reference:
 - ▶ To ascertain the cause(s) of death(s) and ailment(s).
 - ▶ To determine if any such cause is related to the drug(s) administered and procured from the PIC (Punjab Institute of Cardiology)
 - ▶ If the drug reaction is established as the cause of death and/or ailment, to determine the source, manufacturing, processing, storage, dispensing and dosage of such drug(s).
 - ▶ To fix responsibility of lapses at each stage.
 - ▶ To make recommendation for averting such like incidents in future.
2. Through this notice general public is informed that the Tribunal will commence its inquiry proceedings at the Principal Seat of Lahore High Court, Lahore (Venue: Judges Library, New Wing, Lahore High Court, Lahore) on **14-02-2012 at 10:30 am**. Any person desirous of making submission before the Tribunal is required to register with the Registrar of the Tribunal and file written submissions alongwith relevant documents (if any) and copy of CNIC.
3. All the State functionaries including all concerned officers of the Federal and Provincial Governments are notified to render full assistance and cooperation to the Tribunal and its authorized officers in the performance of their functions.
4. The Registrar of the Tribunal is :

SPL # 1942

Irfan Ahmad Saeed
Registrar, Defective Drugs Inquiry Tribunal

Telephone No. 042-99214213
Email: irfanahmadsaeed@yahoo.com

جنگ

12 FEB 2012

لاہور ہائی کورٹ، لاہور کا انکوائری ٹریبیونل برائے ناقص ادویات

اطلاع عام

1. حکومت پنجاب کے جاری کردہ نوٹیفکیشن نمبر SO(JUDL-III)9-84/2012 تاریخ 30-01-2012 کے مطابق جسٹس اعجاز الاحسن جج لاہور ہائی کورٹ کو ناقص ادویات کے تحقیقاتی ٹریبیونل کا سربراہ مقرر کیا گیا ہے تاکہ وہ مل کے مریمینوں کی سیدھا سولٹ اور لوگوں میں پھیلی ہوئی سبب چینی کی مکمل تحقیقات کروائی جاسکیں۔ حوالہ جات مندرجہ ذیل ہیں:
 - ◀ اموات و امراض کی وجوہات کی نشاندہی
 - ◀ کیا یہ وجوہات پنجاب انسٹیٹیوٹ آف کارڈیالوجی کے ادویات کے استعمال اور طریقہ کار سے متعلق ہیں؟
 - ◀ دوا کے ری ایکشن کے نتیجہ میں اگر موت واقع ہوئی یا بیماری بڑھی ہے تو اس کی وجہ کا تعین کہ وہ دوا کے ذریعہ، بیماری، سپلائی، سنسورج اور مقدار وغیرہ سے تو نہیں ہوئی؟
 - ◀ برسرِ کار پروکٹوریوں کی ذمہ داری کا تعین
 - ◀ مستقبل میں اس طرح کے سانحات سے بچنے کے لئے اقدامات
2. اس نوٹس کے ذریعہ عوام الناس کو مطلع کیا جاتا ہے کہ ٹریبیونل پرنسپل سیٹ لاہور ہائی کورٹ لاہور (بمقام ججز لاہوری نیوونگ لاہور ہائی کورٹ لاہور) سے 14-02-2012 صبح 10:30 بجے سے اپنی تحقیقات کا آغاز کرے گا۔ جو بھی شخص ٹریبیونل کے سامنے پیش ہونا چاہتا ہے اس سے درخواست ہے کہ وہ ٹریبیونل کے رجسٹرار کے پاس اپنی رجسٹریشن کروائے اور اپنے کمپیوٹرائزڈ شناختی کارڈ و متعلقہ دستاویزات (اگر کوئی ہیں تو) کے ساتھ اپنی تحریری درخواست دائر کرے۔
3. تمام حکومتی عہدیداران بشمول متعلقہ صوبائی و وفاقی افسران کو مطلع کیا جاتا ہے کہ وہ ٹریبیونل اور اس کے مجاز افسران کے ساتھ تحقیقات میں مکمل تعاون کریں۔
4. ٹریبیونل کے رجسٹرار حسب ذیل ہیں

SOJL # 1842

عرفان احمد سعید (رجسٹرار انکوائری ٹریبیونل برائے ناقص ادویات)

ٹیلیفون نمبر: 042-99214213 | ای میل: irfanahmadsaeed@yahoo.com

نوائے وقت

12 FEB 2012

لاہور ہائی کورٹ لاہور کا انکوائری ٹریبونل برائے ناقص ادویات

اطلاع عام

1. حکومت پنجاب کے جاری کردہ نوٹیفکیشن نمبر SO(JUDL-III)9-84/2012 بتاریخ 30-01-2012 کے مطابق جسٹس اعجاز الحسن جج لاہور ہائی کورٹ کو ناقص ادویات کے تحقیقاتی فریوئل کا سربراہ مقرر کیا گیا ہے تاکہ دل کے مریضوں کی صحت و اموات اور لوگوں میں پھیلی ہوئی بے چینی کی مکمل تحقیقات کروائی جاسکیں۔ حوالہ جات مندرجہ ذیل ہیں:
 - ◀ اموات و امراض کی وجوہات کی نشاندہی
 - ◀ کیا یہ وجوہات پنجاب انسٹیٹیوٹ آف کارڈیالوجی کے ادویات کے استعمال اور طریقہ کار سے متعلقہ ہیں؟
 - ◀ دوا کے ری ایکشن کے نتیجہ میں اگر موت واقع ہوئی یا بیماری بڑھی ہے تو اس کی وجہ کا تعین کہ وہ دوا کے ذریعہ، بیماری، سپلائی، دستورِ علاج اور مقدار وغیرہ سے تو نہیں ہوئی؟
 - ◀ ہر سال پرکٹائیزوں کی ذمہ داری کا تعین
 - ◀ مستقبل میں اس طرح کے سانحات سے بچنے کے لئے تجاویز
2. اس نوٹس کے ذریعہ عوام الناس کو مطلع کیا جاتا ہے کہ فریوئل پر پہل سیٹ لاہور ہائی کورٹ لاہور (برقہام چور لاہور) نے نوٹس لاہور ہائی کورٹ لاہور سے 14-02-2012 صبح 10:30 بجے سے اپنی تحقیقات کا آغاز کرے گا۔ جو بھی شخص فریوئل کے سامنے پیش ہونا چاہتا ہے اس سے درخواست ہے کہ وہ فریوئل کے رجسٹرار کے پاس اپنی رجسٹریشن کروائے اور اپنے کمپیوٹر انڈسٹری کارڈ و مختلف دستاویزات (اگر کوئی ہیں تو) کے ساتھ اپنی تحریری درخواست دائر کرے۔
3. تمام حکومتی عہدیداران بشمول متعلقہ صوبائی و وفاقی افسران کو مطلع کیا جاتا ہے کہ وہ فریوئل اور اس کے مجاز افسران کے ساتھ تحقیقات میں مکمل تعاون کریں۔
4. فریوئل کے رجسٹرار حسب ذیل ہیں

574 # 1942

عرفان احمد سعید (رجسٹرار انکوائری ٹریبونل برائے ناقص ادویات)

ٹیلیفون نمبر: 042-99214213 | ای میل: irfanahmadsaeed@yahoo.com

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

SCHEDULE
-6-



LAHORE HIGH COURT, LAHORE.**ORDER**

The competent authority has been pleased to order to place the services of the following officers/officials already working in the Court of Hon'ble Mr. Justice Ijaz-ul-Ahsan, at the disposal of his lordship as Defective Drugs Inquiry Tribunal (DDIT), appointed vide Government of the Punjab, Home Department's notification No. SO(JUDL-III)9-84/2012, dated 30.01.2012:-

1.	Mr. Muhammad Tariq, Private Secretary	As Staff Officer
2.	Mr. Aamer Khalique Chishti, Private Secretary	As Private Secretary of the Tribunal
3.	Mr. Abadur Rehman, Additional Private Secretary	As Additional Private Secretary of the Tribunal
4.	Mr. Zia ur Rehman, Reader	As Custodian of Record
5.	Mr. Allah Wasaya, Naib Qasid	As Qasid to the Tribunal



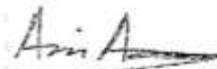
(SYED ALI AKBAR SHAH)
ADDITIONAL REGISTRAR (ESTT.)
FOR REGISTRAR

Endst.No. 2803 Gaz.S.V.B.

Dated Lahore the 08-02. 2012.

Copy forwarded for information and necessary action to:-

1. The Accountant General Punjab (Pay Roll-X), Lahore.
2. The Secretary, Government of the Punjab, Home Department, Lahore.
3. The Inspector General of Police, Punjab, Lahore.
4. Mr. Irfan Ahmad Saeed, D&SJ (Estt.), Lahore High Court, Lahore.
5. ✓ The Private Secretary to Hon'ble Mr. Justice Ijaz ul Ahsan, Lahore High Court, Lahore.
6. Officers concerned.
7. Office record.



ADDITIONAL REGISTRAR (ESTT.)

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

**SCHEDULE
-7-**



RESEARCH OFFICERS

SR. NO.	NAME	DESIGNATION
01	Mr.Muhammad Amir Munir	Research Officer, Research Centre, Lahore High Court, Lahore.
02	Mr. Nadir Hussain Shah Gilani.	Research Officer, Research Centre, Lahore High Court, Lahore.

I.T. ASSISTANCE

SR. NO.	NAME	DESIGNATION
01	Mr.Naseem Abbas Bhatti	IT Staff, Information Technology Section, Lahore High Court, Lahore.
02	Hafiz Muhammad Ishaq	IT Staff, Information Technology Section, Lahore High Court, Lahore.

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

SCHEDULE

-8-



STATEMENT OF EXPENSES

To

PS to Hon'ble Mr. Justice Ijaz ul Ahsan,
Lahore High Court,
LAHORE.

Subject:

DETAIL OF EXPENSES.

Air ticket expenses for Karachi

1 st visit	=	Rs.128,000/-
2 nd visit	=	Rs.73,311/-

Total (i)	=	Rs.201,311/-
------------------	---	---------------------

Hotel stay for 3 nights with meal. (for Miss Trudi Hilton)		Rs.38,000/-
---	--	-------------

Car rental service	=	Rs.10,000/-
--------------------	---	-------------

Conference hall charges	=	Rs.12,000/-
-------------------------	---	-------------

Total (ii)	=	Rs. 60,000/-
-------------------	---	---------------------

Total (iii) Stationary expenses		Rs.20,000/-
---------------------------------	--	-------------

GRAND TOTAL (i+ii+iii)	=	Rs. 281,311/-
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Kindly place before the hon'ble Judge.

(EJAZ FARRUKH)

Senior Law Officer/Liaison Officer DDIT

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

APPENDICES



APPENDICES

APPENDICES	TITLE	PAGES
APPENDIX-1	Complete order sheets of the Tribunal.	5213-5310
APPENDIX-2	Report filed by I.O. in urdu version.	5311-5340
APPENDIX-3	Report dated 27-04-2012 filed by investigation team regarding FIR No.47/12 u/s 302/322, 420/468, 471/468 PPC read with u/s 23/27 Drugs Act, Police Station Shahdman, LAHORE.	5341-5345
APPENDIX-4	<i>Reports regarding visit of Efroze Chemical Industries Karachi dated 30.04.2012 and 05.05.2012 filed by Mr.Abdul Razzaq Cheema, SSP Investigation, Lahore.</i>	5346-5364
APPENDIX-5	<i>Report dated 30.04.2012 filed by Mr.Dastgir Ahmad Bhatti, Chief Drug Inspector on behalf of D.G. Health regarding withdrawal of drugs/medicines from the market manufactured by Efroze Chemical Industries.</i>	5365-5370
APPENDIX-6	<i>Report dated 30.04.2012 filed by Mr.Arif Nadeem, Secretary Health, Government of Punjab regarding withdrawal of drugs/medicines from the market manufactured by Efroze Chemical Industries.</i>	5371-5375
APPENDIX-7	<i>Press Clippings.</i>	5376-5754
APPENDIX-8	<i>Miscellaneous documents, CD's, Books, Medicines, Presentation etc.</i>	5755-5850

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

EXHIBITS/MARKS



LIST OF WITNESSES (EXHIBITS/MARKS)

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
I.W.1	Prof. Dr. Muhammad Azhar.	Ex.IW-1	IW-1/1 to IW-1/9	1-63	01
		Addl. Written Statement.	IW-1/10 to IW-1/26		
IW-2	Dr. Muhammad Jehanzeb Khan. Ex-Secretary Health.	Ex.IW-2	IW-2/1 to IW-2/14	64-284	
			IW-2/15 to IW-2/20		
IW-3	Mr. Muhammad Shahid Khan, Home Secretary	Ex.IW-3	IW-3/1 to IW-3/13	285-353	
IW-4	Syed Khalid Saeed Bukhari, Advisor Medicines WHO		IW-4/1 to IW-4/35	354-481	
IW-5	Mr. Michael Deats, Technical Officer Medicine WHO	Ex.IW-5/1 to Ex.IW-5/4		482-501	
IW-6	Mr. Mohamed Ahmad Bin Shahna			502-504	02
IW-7.	Ms. Trudi Hilton, Chief Pharmacist, IHP, NHS			505-518	
IW-8	Dr. Muhammad Javed, MS PIC	Ex.IW-8	IW-8/1 to IW-8/50	519-594	
IW-9	Mr. Ameer Muhammad, Store Keeper. PIC	Ex.IW-9	IW-9/1	595-607	
IW-10	Mr. Abid Niamat, Pharmacist/Store Incharge PIC	Ex.IW-10	IW-10/1	608-726	
			IW-10/2 to IW-10/86		

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-11	Dr. Syed Ali Hassan Ex.DMS.PIC	Ex.IW-11	IW-11/1 to IW-11/11	727-756	03
IW-12	Dr. Muhammad Jaafar Saleem, M.S. PIC	Ex.IW-12	IW-12/1 to IW-12/18	757-800	
IW-13	Mr. Muhammad Yousaf, Pharmacist PIC	Ex.IW-13	IW-13/1 to IW-13/47	801-866	
IW-14	Mr. Tariq Rehman, Proprietor Omar Trading Company	Ex.IW-14	IW-14/1 to IW-14/17	867-1144	04
IW-15	Mr. Muhammad Musharraf Rehman, Partner Omar Trading Company	Ex.IW-15	IW-15/1 to IW-15/129	1145-1293	
IW-16.	Amjad Iqbal, Employee Omar Trading Company	Exh.IW-16		1294-1300	
IW-17	Dr. Obaid Ali, Federal Government Analyst	Ex.IW-17	IW-17/1 to IW-17/26	1301-1356	05
IW-18	Dr. Shahid Hussain Pachuo, Deputy Directory General (E&M) Karachi	Ex.IW-18	IW-18/1 to	1357-1604	
IW-19	Dr. Saif ur Rehman Khattak, Federal Inspector of Drugs. DRA, Karachi	Ex.IW-19	IW-19/1 to IW-11	1605-1627	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-20	Mr. Dawood Muhammad Bareach, Spl. Secretary Health, GOP	Ex.IW-20	IW-20/1 to IW-20/21	1628-1716	06
IW-21	Mr. Zulfiqar Ali, Ex-Store Keeper PIC	Ex.IW-21		1717-1725	
IW-22	Mr. Abdus Salam Mufti, Ex-Director Drug Testing Laboratory	Ex.IW-22	IW22/1 to IW22/15	1726-1916	
IW-23	Mr. Moazzam Ali Khan, Ex. Chief Drugs Inspectors	Ex.IW-23	IW-23/1 to IW23/11	1917-1945	
IW-24	Mr. M.Saeed Iqbal, Drug Inspector, Data Ganj Bakhsh Town	Ex.IW024	IW-24/1 to IW-24/33	1946-2096	
IW-25	Dr. Faisal Masud, Chief Executive Services Hospital	Ex.IW-25	IW-25/1 to IW-24/4	2097-2126	
IW-26	Professor Muniza Qayyum, Professor Of Pharmacology FJM. College	Ex.IW-26	IW26/1	2127-2131	
IW-27	Professor Nosheen Yousaf, Professor of Pathology, AIMC	Ex.IW-27	IW-27/1 to IW 27/30	2132-2193	
IW-28	Dr. Farzana Chaudhry, Chairman Pharmacy Department, University of Veterinary Sciences	Ex.IW-28	Nil	2194-2200	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-29	Mr. Rauf Khalid, Former Drug Controller.	IW-29	IW-29/1 to IW-29/15	2201-2350	07
IW-30	Professor Dr. Bashir Ahmad, Professor of Pharmacology, University of the Punjab	Ex.IW-30`	IW-30/1 to IW-30/3	2351-2373	
IW-31	Mr. Zulfiqar Cheema, DIG, Police Elite Force, Lahore	Ex.IW-31	IW-31/1 to IW-31/7	2374-2487	
IW-32	Dr. Ayaz Ali Khan, Director (Pharmacy) Office of Director General Health	Ex.IW-32	IW-32/1 to IW-32/9	2488-2590	
IW-33	Dr. Tariq Javed Khan, Professor of Pharmaceutical Chemistry, University of Punjab	Ex.IW-33		2591-2599	08
IW-34	Professor Farkhanda Kokab, Professor of Epidemiology, Institute of Public Health, Lahore	Ex.IW-34	IW-34/1 to IW-34/	2600-3275	
IW-35	Dr. Muhammad Ashraf Tahir, Director General Punjab Forensic Science Agency	Ex.IW-35	IW-35/1 to IW-35/	3276-3562	
IW-36	Dr. Mubashar Attiq Azhar, Former Chief Chemical Examiner, Government of Punjab	Ex.IW-36	IW-36/1 to IW-36/4	3563-3580	
IW-37	Dr. Abbas Ali Khan, Officiating Chemical Examiner.	Ex.IW-37	IW-37/1 to IW-37/7 IW-37/8 to IW37/20	3581-3662	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-38	Dr. Khalid Hussain, Assistant Professor, College of Pharmacy, University of Punjab	Ex.IW-38	IW-38/1 and IW-38/2	3662-3675	09
IW-39	Dr. Hamid Latif, Professor of Chemistry, University of Punjab	Ex.IW-39	IW-39/1 to IW-39/11	3676-3705	
IW-40	Dr. Nasir Iqbal, Associate Professor of Histopathology, Forensic Histopathologist Government of Punjab	Ex.IW-40	IW-40/1 to IW-40/7	3706-3720	
IW-41	Mr. Sultan Ghani, Consultant/Pharmacist DRA, Government of Pakistan	Ex.IW-41	Nil	3721-3727	
IW-42	Dr. Abdul Latif Sheikh, Director Pharmacy, Agha Khan University Hospital Karachi	Ex.IW-42	IW-42/1 to IW-42/3	3728-3781	
IW-43	Dr. Tahir Aziz Mughal, Senior Manager Pharmacy, Shaukat Khanum Hospital, Lahore	Ex.IW-43	Nil	3782-3813	
IW-44	Sh. Muhammad Shafiq, Advocate.	Ex.IW-44 and Ex.IW-44/A	IW-44/1 to IW-44/14	3814-3836	
IW-45	Muhammad Humayun Khan Shaheed, 537-A Peoples Colony Faisalabad	Ex.IW-45	IW-45/1 to IW-45/4	3837-3858	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-46	Dr. Salman Kazmi, Joint Secretary, PMA.	Ex.IW-46	IW-46/1 to IW-46/2	3859-3957	10
IW-47	Mr. Furqan Khurshid Hashmi, Assistant Professor (Pharmacy Practice) General Secretary Pharmacist Association	Ex.IW-47	IW-47 to IW-47/5	3958-3992	
IW-48	Mr. Mehmood Ahmad, H.No.E/354, St.No.5 Husnain Abad, Lahore Cantt.	Ex.IW-48 and Ex.IW-48A	IW-48/1 to IW-48/13	3993-4013	
IW-49	Mr. Najam Saeed, Chairman Chief Minister Inspection Team	Ex.IW-49.	IW-49/1 to IW-49/24	4014-4106	
IW-50	Dr. Zahid Pervaiz, Former D.G. Health Presently working as M.S. Mayo Hospital Lahore.	Ex.IW-50	Nil	4107-4115	
IW-51	Dr. Muhammad Tahir Azam, Chief Executive Mega Pharmaceuticals Ltd.	Ex.IW-51	IW-51/1 to IW-51/57	4116-4261	
IW-52	Ms. Majida Mujahid, Federal Inspector of Drugs	Ex.IW-52	IW-52/1 to IW-52/3	4262-4282	
IW-53	Sh. Akhtar Hussain, Deputy Director General, Cabinet Division Islamabad	Ex.IW-53	IW-53/1 to IW-53/8	4283-4358	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-54	Mr. Shakeel Ahmad Khan, General Manager (Plant) Efroze Chemical Industries Karachi	Ex.IW-54	IW-54/1 to 54/6	4359-4601	11
IW-55	Mr. Khurram Munaf, Director Technical Efroze Chemical Industries Karachi	Ex.IW-55	IW-55/1 to 55/35	4601-4801	
IW-56	Mr. Fayyaz Ahmad, Senior Quality Control Officer, Efroze Chemical Industries Karachi	Ex.IW-56	Nil	4802-4809	
IW-57	Mr. Attique ur Rehman, Quality Control Manager, Efroze Chemical Industries Karachi	Ex.IW-57	Nil	4810-4821	
IW-58	Mr. Imtiaz Ahmad, Quality Control Manager, Efroze Chemical Industries Karachi	Ex.IW-58	IW-58/1	4822-4828	
IW-59	Mr. Altaf Ahmad Qureshi, Production Manager, Efroze Chemical Industries, Karachi	Ex.IW-59	Nil	4829-4839	
IW-60	Syed Tabish Nomani, Production Executive Efroze Chemical Industries Karachi	Ex.IW-60	Nil	4840-4848	
IW-61	Mr. Amjad Javed Lodhi, Production Executive, Efroze Chemical Industries, Karachi	Ex.IW-61	Nil	4849-4854	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-62	Mr. Kashif Abdullah, Deputy Production Manager, Efroze Chemical Industries Karachi	Ex.IW-62	Nil	4855-4861	12
IW-63	Mr. Iftikhar Ahmad Shah, Store Officer, Efroze Chemical Industries Karachi	Ex.IW-63	Nil	4862-4878	
IW-64	Mr. Waqas Hussain Shah, Supply Chain Executive, Efroze Chemical Industries Karachi	Ex.IW-64	Nil	4879-4885	
IW-65	Dr. Nisar Ahmad Cheema, D.G. Health	Ex.IW-65	IW-65/1 to 65./7	4886-4981	
IW-66	Mr. Shoaib Ansari, Helper Efroze Chemical Industries Karachi	Ex.IW-66	Nil	4982-4986	
IW-67	Syed Razi Haider Kazmi, Helper Efroze Chemical Industries Karachi	Ex.IW-67	Nil	4987-4994	
IW-68	Mr. Muhammad Rizwan, Helper, Efroze Chemical Industries Karachi	Ex.IW-68	Nil	4995-5001	
IW-69	Mr. Muhammad Saleem, Security Incharge Efroze Chemical Industries Karachi	Ex.IW-69	Nil	5002-5006	

SR. NO.	NAME	NUMBER OF EXHIBITS	NUMBER OF MARKS	PAGES	DETAIL OF VOLUMES
IW-70	Mr. Abdullah Feroz, Managing Director Efroze Chemical Industries Karachi	Ex.IW-70	IW-70/1	5007-5011	
IW-71	Mr. Nadir Khan Feroz, Deputy Managing Director, Efroze Chemical Industries Karachi	Ex.IW-71	IW-71/1 to 71/7	5012-5034	
IW-72	Dr.Javaid Akram, Principal, Allama Iqbal Medical College, Lahore.	Ex.IW-72	IW-72/1 to 72/5	5035-5142	
Schedules 1-8		Notifications, Reports of WHO and Coopted Expert, statement of expenses		5143-5211	13
Appendices 1		Complete Order Sheets of defective drugs inquiry tribunal		5212-5310	14
Appendices 2-8		Different reports, press clippings and Miscellaneous docs, CDs, books, medicines and presentations etc.		5311-5850	15

REPORT OF THE DEFECTIVE DRUGS INQUIRY TRIBUNAL



2011 - 2012

SNAPS
GALLERY



VISIT OF DTL











VISIT OF PIC









ation
STRATION

1 of 1

Preview



www.pic.com.pk

HOME

PATIENT MEDICAL RECORD FACE SHEET

13/04/2012 10:59 AM Emergency

Patie

Medical Record No.	2012 - 030458		
Patient Name	MUHAMMAD SHAFIQ		
S/O, D/O:	KHUAD BUKSH		
W/O:			
Address:	CHAK NO PHATOWALA TEH SHAKHAR		
City:	NAROWAL	Date:	0300-2190071
Age:	45 years	Sex:	MALE
		Marital Status:	MARRIED
NI Card No.		Religion:	MUSLIM
Purchase Fee : Rs. 1/-	Category		
Socio-economic Status of Patient / Guardian			
Self	<input type="checkbox"/>	Dependent	<input type="checkbox"/>

Local intranet

Done

PATIENT MEDICAL R...

Patient Registration

**FIRST VISIT TO
KARACHI**







Raw Material Requisition

Date: 21/08/2011
 Product: Isorbide 20mg. Tablet
 Batch No: J-893
 Batch Size: 480000 tablets / 58.00 kg.

Code No.	G. C. No.	Name of Item	Quantity	Weight by	Checked
P-001/10		Isorbide-5-Mononitrate 70/30 Division (2% Overage)	11.858 kg.	28/8	28/8
P-001/11		Pregelatinized Starch	28.800 kg.	28/8	28/8
P-001/12		Avicel PH-102	28.800 kg.	28/8	28/8
P-001/13		Talcum Powder	1.600 kg.	28/8	28/8
P-001/14		Magnesium Stearate	0.571 kg.	28/8	28/8
P-001/15		Aerosil 200	0.571 kg.	28/8	28/8







RAW MATERIAL (PASSED)

PRODUCT: PVP K-30
 Q.C. NO.: R-0164/11-12 M.R.N. NO.: 11919
 LOT NO.: YK001S110722A1P RETEST DUE DATE: 10-09-2013
 QUANTITY: 40 x 25 Kg ANALYST: Ms. Safia Noor
 ORIGIN: China
 POTENCY: ---
 RELEASE DATE: 11-09-2011

Q.A. MANAGER

Functional Polymer Industry Committee
 Shanghai Yuhing Chemtech Co., Ltd.

MARK
EFROZE
KARACHI

Address: Room 209, Building 1, No. 88, Darwin Road, Zhangjiang Hi-Tech Park Pudong New District, Shanghai, China
 TEL: +86-21-51332620 Fax: +86-21-51332646 http://www.yuhingchem.com



全国功能高分子行业委员会
 上海宇昂化工科技发展有限公司

China Functional Polymer Industry Committee
 Shanghai Yuhing Chemtech Co., Ltd.

Polyvinyl Pyrrolidone (PVP K30) USP28

BATCH NO.: YK001S110722A1P

G.W.: 28.0KGS

MFT. DATE: JULY. 22, 2011

N.W.: 25.0KGS

EXP. DATE: JULY. 22, 2014

EFROZE

QAD: FRM-0006 / 2008 / v:4.00
 EFROZE CHEMICAL INDUSTRIES (PVT.) LTD.
 QUALITY ASSURANCE DEPARTMENT

RAW MATERIAL (PASSED)

PRODUCT: PVP K-30
 Q.C. NO.: R-0164/11-12 M.R.N. NO.: 11919
 LOT NO.: YK001S110722A1P RETEST DUE DATE: 10-09-2013
 QUANTITY: 40 x 25 Kg ANALYST: Ms. Safia Noor
 ORIGIN: China

Room 209, Building 1, No. 88, Darwin Road, Zhangjiang Hi-Tech Park Pudong New District, Shanghai, China
 TEL: +86-21-51332620 Fax: +86-21-51332646 http://www.yuhingchem.com



**SECOND VISIT
TO KARACHI**



Mefnac Ds tablet	J-392	20-9-11	05
"	J-393	"	05
Trisil tablet	J-873	"	01
"	J-874	20-9-11	01
Tramapant tablet	J-032	20-9-11	02
Mefnac Ds tablet	J-394	21-9-11	05
"	J-395	"	05
Trisil tablet	J-875	21-9-11	01
Klacid dry suspo	J-094	"	02
Isotas 20mg tablet	J-093	"	03
Parasam tablet	J-109	22-9-11	05
Maladar tablet	J-032	"	02
Trisil tablet	J-876	"	01

* On 7-9-11 No activity b/c batch still not dry

September 2011

Liam tablet	J-375	5-9-11	01
"	J-376	"	01
Parasam tablet	J-105	"	02
Trisil tablet	J-854	"	05
Liam tablet	J-377	6-9-11	01
Parasam tablet	J-106	"	02
Trisil tablet	J-855	"	05
Trisil tablet	J-856	"	05

PROFORMA-000271950V-1.00	
Etroze	
CLEANED EQUIPMENT	
EQUIPMENT	Cone blower
LAST PRODUCT	Tramapant Tablet
BATCH NO.	J-046
DATE CLEANED	23-04-12
CHECKED BY	WTH







