ORDER SHEET
IN THE HIGH COURT OF SINDH, KARACHI

Suit No.2161 of 2016

Date	**Order with signature of Judge**

Present:
Mr. Justice Muhammad Ali Mazhar

Roche Pakistan Limited.....Plaintiff

Vs.

Pakistan & others.....Defendants

For hearing of CMA No.14255/2016.

Dates of hearing: 25.04, 05.05, 24.05, 07.06 & 22.06.2017.

Mr. Hyder Ali Khan, Advocate for the Plaintiff.

Mr. Faisal Siddiqi, Advocate for the Defendant No.4.

Mr. Salman Talibuddin, Additional Attorney General assisted by Ms.Alizeh Bashir Advocate.

Mr. Masood Hussain Khan, Assistant Attorney General.

Muhammad Ali Mazhar, J. By means of this suit for declaration and permanent injunction, the plaintiff has entreated for the declaration that decision of the defendant Nos.2 and 3 to register Reditux injection as a Similar Biotherapeutic Product is *ultra vires* the WHO Guidelines and the Drug Regulatory Authority of Pakistan Act, 2012; what's more the plaintiff has wished for the quashment of the decision of the defendant Nos.2 and 3 with permanent injunction prohibiting the defendant Nos.2 and 3 not to issue Letter of Registration nor permit the defendant No.4 to market and sell the aforesaid injection.

2. The epigrammatic facts put forward in the plaint are that the plaintiff is engaged in the import, marketing, sale and distribution of pharmaceutical products, diagnostic reagents, chemicals and equipment. At some point, the plaintiff applied to the competent authority for registration of its drug "Mabthera", which is trade name for Rituximab, a genetically engineered chemical chimeric monoclonal antibody approved by the United States' Food and Drugs Administration (FDA) for treatment of non-Hodgkin's lymphoma. However vide letter dated 28.02.2013 the brand name of the plaintiff's drug was changed from Mabthera to Ristova. The defendant No.2 was established pursuant to the provisions of Section 3 of the Drug Regulatory Authority of Pakistan Act, 2012 for effective coordination and enforcement of the Drugs Act, 1976 and to develop, issue, adopt and enforce standards and guidelines to ensure quality, efficacy and safety of therapeutic goods. The cause of distress to the plaintiff is the application moved by the defendant No.4 on 28.01.2011 for registration of its drugs Reditux Injection 500 mg/50mL and Reditux Injection 100mg/10mL (Reditux) which it claimed Similar Biotherapeutic Products of Rituximab (Mabthera/Ristova). Since the defendant No.4 claims Reditux to be a Similar Biotherapeutic Product of Rituximab so it is under obligation to strictly comply with the WHO Guidelines.

3. The learned counsel for the plaintiff argued that the clinical trials submitted by the defendant No.4 were retrospective whereas the defendant No.4 quoted Mabthera/Ristova as Reference Biotherapeutic Product without conducting any prospective studies. The application failed to accomplish the requirements of the

WHO Guidelines and DRAP Act therefore Reditux was not fit to be registered as a Similar Biotherapeutic Product. It was further contended that the DRAP Act especially describes Biological and lays out mechanisms for their licensing and registration. The obligation of fulfilling the requirement of the WHO Guidelines is to merely ensure the quality, efficacy and safety of Similar Biotherapeutic Products. No clinical trials for proving biosimilarity of Reditux have been conducted in accordance with WHO Guidelines. In this regard a recent study comparing the efficacy and safety of Mabthera and Reditux has been submitted by a number of pharmaceutical companies for registration of their so-called bio similar in various jurisdictions but the said study is a retrospective analysis and not in compliance with the prerequisites of the WHO Guidelines.

4. The learned counsel further argued that in the 256th meeting of the Registration Board held on 03.4.2016, the defendant No.4's case was deferred for expert opinion however, in 260th meeting convened on 29th June, 2016 the experts stated that the defendant No.4 submitted bio similarity studies and they recommended Reditux for registration.

5. It was further averred that the plaintiff wrote a letter to the Chairman of Registration Board with the request to revisit its approval as the defendant No.4 failed to provide head-to-head trials and quality, safety and efficacy data as per the WHO Guidelines nor provided full registration dossier but the plaintiff's efforts have been in vain. The learned counsel referred to the case of **M/s.Alfalah Medicos and another vs. Government of Punjab and others**, reported in **PLD 2017 Lahore 124** in which learned Lahore High Court laid down that WHO

Guidelines have statutory importance and unless their requirements are fully complied with, a Similar Biotherapeutic Product may not be licensed under the DRAP Act.

6. The learned counsel for the defendant No.4 argued that the only question involved in this case is whether the WHO Guidelines on evaluation of similar bio-therapeutic products are mandatory for registration of the defendant No.4's drug "Reditux" under the Drug Regulatory Authority of Pakistan Act, 2012, Drugs Act, 1976 and under the Rules and Regulations made under these Acts. The drug Reditux to be imported by the defendant No.4 has been granted registration letter which will only be issued after a further inspection of the facilities of Dr.Redy's Laboratories, India, by the Drug Regulatory Authority of Pakistan.

7. He further contended that the plaintiff has neither alleged nor questioned the defendant No.4's drug 'Reditux' for any patent violations, trademark or copyright nor any unfair competition involving the competition laws nor alleged that it is not safe. The three experts opinions certifying the defendant No.4's drug as safe and efficacious which is being sold in 15 countries including India, Russia, Ukraine etc. The bio-equivalence studies/trials have been conducted on the drug Reditux. The DRAP has taken nearly 06 years to register the defendant No.4's drug Reditux and the Registration Board granted the registration in its meeting held on 29.6.2016. The WHO Guidelines on evaluation of similar Bio-therapeutic products are not mandatory for registration because there is no express provision in any of the drug laws which states that the WHO Guidelines are mandatory for registration of biological drugs.

8. He further argued that Drug Regulatory Authority of Pakistan Act, 2012 has not repealed the Drugs Act, 1976. This Act creates a Central Authority known as the Drug Regulatory Authority of Pakistan whose function is to implement the Drugs Act, 1976, and the Rules made thereunder. The only provision of DRAP Act, 2012, which makes reference to registration of non-originator drugs is Schedule-I. The plaintiff ignored that the above provisions made reference of three provisions i.e Section 7(ix) of the Act, 2012, Schedule-I, Para 1 and Schedule-I, Para 6, if it is accepted that the above provisions are relevant then two principles of interpretation of statutes will prove that they are not applicable to the registration of drugs. Firstly, it is well settled that if there are special provisions dealing with a particular issue e.g. registration of drug like Section 7, Drugs Act, 1976 and the Drugs (Licensing, Registering and Advertising) Rules, 1976 then these provisions will prevail over general provisions contained in the statute. He further argued that the judgment rendered by the Lahore High Court in the case of **M/s.Alfalah Medicos and another vs. Government of Punjab and others** is distinguishable and has no binding force on this court primarily for the reason that in the said case registration of any drug was not involved but the case pertained to the tender process.

Judicial precedents cited by the
Counsel for the defendant No.4

(1) 1993 SCMR 1635 (Golden Oraphies (Pvt.) Ltd. and others vs. Director of Vigilance, Central Excise, Customs & Sales Tax and others). Interpretation of statute. Where a special provision had been made on a subject and there was also a general provision susceptible of covering the same field, presumption would be that the general provision is not intended to interfere with the operation of the special provision.

(2) 2000 SCMR 1305 (Maulana Nur-ul-Haq vs. Ibrahim Khalil). Interpretation of statutes. Mandatory or directory nature of a

statute. Where the consequence of failure to comply with the provision is not mentioned the provision is directory and where the consequence is expressly mentioned the provision is mandatory.

(3) PLD 1986 S.C. 14 (Ihsan-ur-Rehman vs. Mst. Najma Parveen). Precedent. Two different views expressed by separate High Courts. Such views although have persuasive value for each other but were not as such binding on each other.

(4) F. Hoffmann-La Roche Ltd. And Anr. vs Cipla Limited on 19 March, 2008) [Equivalent citations: 148 (2008) DLT 598, MIPR 2008 (2) 35]. The crucial aspect here is whether refusal of injunction would cause such irreparable hardship to the plaintiff as cannot be later compensated in mandatory terms……, this Court is of the opinion that as between the two competing public interests, that is, the public interest in granting an injunction to affirm a patent during the pendency of an infringement action, as opposed to the public interest in access for the people to a life saving drug, the balance has to be tilted in favor of the latter.

(5) Brawn Laboratories Ltd. vs Rhone Poulenc Rorer S.A. & Anr. (on 1 May, 1999) [Equivalent citations: 1999 IIIAD Delhi 849, 79 (1999) DLT 507, 1999 (49) DRJ 630]. Grant of injunction would not be in larger public interest as the same may result in denial of life saving drug to heart patients resulting in grave and irreparable loss, injury and consequences to patients.

(6) 2017 MLD 785 (Al-Tamash Medical Society vs. Dr. Anwar Ye Bin Ju & others). The phrase prima facie case in its plain language signifies a triable case where some substantial question is to be investigated or some serious questions are to be tried and this phrase 'prima facie' need not to be confused with 'prima facie title'.

9. The learned Additional Attorney General argued that pursuant to Section 7 of the DRAP Act, 2012 the DRAP is empowered to issue guidelines and monitor enforcement in respect of inter alia; the licensing of the manufacture of therapeutic goods, as well as the registration thereof; and the implementation of internationally recognized standards such as good laboratory practices, current good manufacturing practices, bioequivalence studies, clinical trials, bio similar evaluations and endorsement and systemic implementation of World Health Organization, International Conference on Harmonization and Food and Drug Administration guidelines. Clause 1(6) of Schedule I to the 2012 Act defines the term "Originator Biological Drugs" to mean those biological drugs that are licensed by national regulatory authorities

on the basis of full registration dossier. Similar Biotherapeutic Products are defined in Schedule I to mean biological drugs that are similar in terms of quality, safety and efficacy to licensed reference Biotherapeutic product. The parameters referred to in the said clause are "quality, safety and efficacy", which are measured against the profile of the originator Biological Drug.

10. It was further contended that the Guidelines on Evaluation of Similar Biotherapeutic Products adopted at the 60th meeting of the WHO Expert Committee on Biological Standardization (the WHO Guidelines), stipulates an obligation to provide all information to NRA as is required for the purpose of licensing on SBP, is that of the manufacturer of the SBP. No such obligation is imposed on the importer. The WHO Guidelines are intended only to be used as a basis for NRAs to establish their own regulatory frameworks, hence the WHO Guidelines are by their own terms, directory rather than mandatory in nature. While DRAP endeavors to implement the WHO Guidelines, which is a function that DRAP has the requisite authority to perform, there is no express obligation under the applicable law requiring it to ensure that the guidelines are implemented either at all or in their entirety.

11. He further argued that key considerations for the selection of RBPs with which to compare the proposed SBP, include that the RBP should inter alia (i) have been marketed for a considerable duration and (ii) have a volume of marked use. The Drug substance of the RBP and the proposed SBP should also be similar and the dosage from and route of administration of both drugs should be the same.

12. While referring to the Alfalah Medicos case, he argued that the learned Single Judge held that the principles set out in the WHO Guidelines serve as a benchmark for global acceptability of SBP and a step-wise approach is therefore, recommended, while this case is distinguishable on the facts and issues to be decided.

13. He further argued that in the 256th Meeting, the Registration Board considered the data provided by the defendant No.4 for the licensing Reditux. Amongst the factors considered by the experts, is the fact that compliance certificate for Reditux has been issued by both the Food and Drug Administration of the United State Department of Health and Human Services (USFDA) as well as the Medicines and Healthcare Products Regulatory Agency of the Department of Health of the United Kingdom (MHRA). The registration dossier supplied for the purpose has also been evaluated in detail and the experts have observed that Reditux is highly comparable to its RBP in terms of quality, efficacy and safety and they noted that the manufacturer of Reditux is certified by international regulatory agencies in various countries.

14. Much emphasis were made by the learned Additional Attorney General that DRAP will take certain additional steps in order to ensure the quality, safety and efficacy of a drug that is considered for registration as SBP which includes inspection of the laboratories of the manufacturer as well as of the method of transportation and facilities used for the purpose thereof. Upon arrival of the relevant product in Pakistan, DRAP carries out further testing to satisfy itself that the product that has been imported may be authorized for marketing in

Pakistan, i.e. that the quality, safety and efficacy of the product has not been compromised.

15. Heard the arguments. First of all I would like to focus on the Drugs Act, 1976 in which Section 4 is relevant to the regulation and prohibition of import of drugs, while Section 5 germane to regulation of manufacture of drugs, whereas Section 7 alluded to registration of drugs which postulates that the Federal Government shall cause all drugs to be registered in accordance with such conditions and procedure as may be prescribed. For the ease of reference, Section 7 of the Drugs Act 1976 is reproduced as under:-

> **"7. Registration of drugs: (1) The Federal Government shall cause all drugs to be registered in accordance with such conditions and procedure as may be prescribed and for that purpose set up a Registration Board, consisting of such number of persons, possessing such qualifications, as may be prescribed.**
>
> ***Explanation*: In this section, "drugs" means drugs which are in the finished form ready for use.**
>
> **(2) The members of the Registration Board shall exercise such powers, including the powers of an Inspector, as may be prescribed.**
>
> **(3) The Registration Board shall, [with the approval of the Federal Government and, by notification in the official gazette,] make regulations to regulate the conduct of its business.**
>
> **(4) Any member of the Registration Board may, at any time, by writing under his hand addressed to the Federal Government, resign his office or shall vacate his office if the Federal Government, being of opinion that in the public interest it is necessary so to do, so directs.**
>
> **(5) Subject to sub-section (4), the members of the Registration Board shall hold office for the prescribed period.**
>
> **(6) The Federal Government shall, by notification in the official Gazette, fix the date after which no drug which is not registered shall be allowed to be exported, imported, manufactured, stored, distributed or sold.**
>
> **(7) A person applying for the registration of a drug shall furnish such information in respect of the drug as may be prescribed, including information relating to its efficacy, safety and quality, or as may be required by the Registration Board for the purpose of the evaluation of the drug.**
>
> **(8) Single-ingredient drugs shall be registered generally by their generic names while compound drugs shall be registered generally by their proprietary names.**
>
> ***Explanation:* In this sub-section,--**

(a) "single-ingredient drugs" means drugs containing one active ingredient;

(b) "compound drugs" means drugs containing more than one active ingredient.

(9) The registration of a drug shall be subject to such conditions, as may be prescribed.

(10) Where the Registration Board registers a drug, it shall inform the person applying for its registration and the Provincial Governments of its having done so and of the conditions subject to which it has been registered.

(11) If the Registration Board, on the basis of information received or an inquiry conducted by it, is of opinion that:-

(a) the registration of a drug was procured by fraud or misrepresentation; or

(b) the circumstances in which a drug was registered no longer exist; or

(c) there has been a violation of the conditions subject to which a drug was registered; or

(d) it is necessary in the public interest so to do;

the Registration Board may, after affording to the person on whose application the drug was registered an opportunity of showing cause against the action proposed to be taken, cancel or suspend the registration or specify any further conditions to which the registration shall be subject and inform such person and the Provincial Governments accordingly.

(12) The Provincial Governments shall take all such steps as may be necessary to ensure compliance with the conditions subject to which a drug is registered and to prevent the manufacture or sale of a drug:-.

(a) which has not been registered; or

(b) the registration of which has been cancelled or stands suspended."

16. However Rule 29 of the Drugs (Licensing, Registering & Advertising) Rules, 1976 is somewhat relevant which elucidates that the Registration Board may, if it considers necessary in case of a new drug molecule, cause the application for registration and the information and material supplied to it under Rule 26 to be evaluated by a Committee on Drugs Evaluation, whereas Rule 26 makes reference of an application for registration of a drug for the local manufacture of a drug substance having the same active ingredient or salt thereof, therapeutic use, dosage form and route of administration that has already been approved by the Registration Board and has not been withdrawn from the sale for the reasons of safety or

effectiveness. In sub-rule (2) of Rule 29 the Registration Board may before issuing a certificate of registration cause the premises in which the manufacture is proposed to be conducted to be inspected by itself or by its sub-committee or by a panel of Inspectors or experts appointed by it for the purpose. In sub-rule 6 it is further provided that Registration Board shall, before registering a new drug or molecule for which the research work has been conducted in other countries and its efficacy, safety and quality has been established therein, requires the investigation on such pharmaceutical, pharmacological and other aspects, to be conducted and clinical trials to be made as are necessary to establish its quality and where applicable, the biological availability, and its safety and efficacy to be established under local conditions. However, it is provided under the same sub-rule that for the special circumstances to be recorded in writing, the Registration Board may register a drug and require such investigations and clinical trial to be conducted after its registration.

17. By virtue of the Drug Regulatory Authority of Pakistan Act, 2012, the Drug Regulatory Authority of Pakistan (DRAP) was established to provide for effective coordination and enforcement of the Drugs Act, 1976 and to bring harmony in inter-provincial trade and commerce of therapeutic goods. The provincial assemblies of Khyber Pakhtunkhwa, Punjab and Sindh have passed resolution under Article 144 of the Constitution of the Islamic Republic of Pakistan to the effect that Majlis-e-Shoora (Parliament) may by law regulate the issue. In this Act “Biological” means biological drugs as defined in Schedule-I, while “Pharmaceutical dossier” means a set of documents, as specified in Schedule-I whereas

"Therapeutic goods" includes drugs or alternative medicine or medical devices or biological or other related products as may be notified by the Authority. Under Section 3 the Authority has been established and its composition is provided under Section 4, whereas under Section 7 certain powers and functions have been conferred upon the authority. For the ease of reference, relevant provision of Section 7 of DRAP Act, 2012 and the Schedule-I relied upon by the plaintiff's counsel is reproduced as under:-

"7. Powers and functions of the Authority.- The powers and functions of the Authority shall be to:-

(a) .....

(c) issue guidelines and monitor the enforcement of,-

(i) .....

.....

(ix) implementation of internationally recognized standards such as good laboratory practices, current good manufacturing practices, good distribution practices, cold chain management, bioequivalence studies, stability studies, anti-spurious codes, clinical trials, biosimilar evaluations, and endorsement and systematic implementation of World Health Organization, International Conference on Harmonizations and Food and Drug Administration guidelines etc.;

"SCHEDULE-I
[see section 2 (v, xii, xviii, xix, & xxviii)]

1. BIOLOGICALS includes:-

(1) Biological drugs produced by biological systems and which require standardization by biological assays according to the relevant and updated recommendations of the World Health Organization published in Technical Report Series and Biological Standardization Report and includes,-

(a) blood products including Plasma, Albumin, Clotting Factors, Factors VIII, IX, Mixed Clotting Factors Tractions, Fibrinogens, Immunoglobulins;

(b) immunological products including Antisera, Antitoxins, specific Immunoglobulins;

(c) in vivo diagnostics including Tuberculins, Lepronin, Histoplasmin, Coccidioidin, Allergens, Allergens Extracts, Antibodies conjugated with isotopes for imaging studies;

(d) antigens, cytokines/antibodies/cells injected to elicit a biological response;

(e) vaccines, including:--

(i) bacterial vaccines including live, killed whole cell, protein sub-unit, polysacchride or glyco-conjugate, toxin derivatives, and rDNA biotechnology developed;

(ii) viral vaccines including live, inactivated, sub-unit, rDNA, conjugated;

(iii) polyvalent combinations of vaccines containing combination of vaccines defined in e (i) and d(ii).

(f) toxins and venoms including snake venoms, scorpion venoms etc;

(g) immunostimulants of biological origin including BCG vaccine for immunotherapy;

(h) biotechnology products which are primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology or other processes involving site specific genetic manipulation techniques.

(i) human interferons, natural hormones, recombinant antibodies, monoclonal antibodies and derivatives gene therapy products;

(2) "Biological Drugs (Finished form)", are Biological Drugs that are defined in sub-section (1) above and are manufactured, packed by the manufacturer under his responsibility of quality assurance and is further released by the National Control Authority or the National Control Laboratory of the country of origin under the World Health Organization's Lot Release system of evaluation.

(3) "Biological Drugs (Ready-to-fill form)", are Biological Drugs that are defined in sub-section (1) above but are manufactured at one site in the form of a "Ready-to-fill Bulk" but are transferred to another site for final filling, labeling, packaging and quality control of the finished form. No further formulation or dilution of the Ready-to-fill bulk is allowed in this case of manufacture. The final product is released by the Pakistan's National Control Laboratory for Biologicals under the World Health Organization's Lot Release system of evaluation.

(4) "Biological Drugs (Concentrated form)", are Biological Drugs that are defined in sub-section (1) above that are manufactured at one site but are stored in the form of Concentrated-Bulk of the active ingredient at controlled temperatures. Such Concentrated-Bulk may be transferred to any other site under temperature controlled conditions for further dilution, stabilization, filling and packaging. The diluted and stabilized bulk requires its own set of quality control test and the final finished form of such Biological Drugs under go another set of complete quality control tests. The final product is released by the Pakistan's National Control Laboratory for Biologicals under the World Health Organization's Lot Release system of evaluation.

(5) "Biological Drugs (Naked vials)", are Biologicals Drugs that are defined in sub-section (1) above that are manufactured and filled at one site but the final containers are neither labeled nor packed in cartons. These drugs are imported in unlabeled vials and are labeled and packed in carton locally. In such cases at least an identity test is required to confirm the positive identification of the required antigen. The final product is released by the Pakistan's National Control Laboratory for Biologicals under the World Health Organization's Lot Release system of evaluation.

(6) Originator Biological Drugs means a biological drug which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data:

(a) reference biotherapeutic product (RBP) means an originator biological drug product that was licensed on the basis of a full registration dossier. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards;

(b) biosimilar biological drugs mean Similar Biotherapeutic Product (SBP) which is similar in terms of quality, safety and

efficacy to an already licensed reference biotherapeutic product;

(c) similarity means absence of a relevant difference in the parameter of interest.

(7) No human biological drug is allowed sale and use until a "Lot Release Certificate" from the Federal Government Analyst of the National Control Laboratory for Biologicals, Islamabad has been obtained.

(8) Pharmaceutical dossier includes a set of documents submitted by a Person for the registration of a therapeutic good, containing complete information about:

(a) muster formula;

(b) all ingredients both active pharmaceutical ingredients and inactive excipients added with their safety profile data;

(c) complete manufacturing procedure of the drug, biological or medical device;

(d) quality control steps and procedures at each level of raw material selection, in-process testing, finished drug testing, and stability testing;

(e) clinical trial data and published reports about the safety and efficacy of the drug;

(f) complete details of manufacturing plant and equipment, quality control laboratories and equipment;

(g) ware-houses capacities and facilities; details of human resources available and the latest cGMP report shall also be part of this document set;

(h) any other information required by the registration board for establishing the safety, efficacy, bioavailability, bioequivalence, or biosimilarity of the drug.

2.....
....."

18. The superstructure of the plaintiff's lawsuit is progressed on the plea that in the wake of DRAP Act, 2012 promulgation, a number of powers and functions of the Authority have been laid down under Section 7 which embraces and encompasses the implementation of internationally recognized standards such as good laboratory practices, current good manufacturing practices, good distribution practices, cold chain management, bioequivalence studies, stability studies, anti-spurious codes, clinical trial, biosimilar evaluations, and endorsement and systematic implementation of World Health Organization, International Conference on Harmonization and Food and Drug Administration guidelines etc. The learned counsel for the plaintiff accentuated that the Registration Board without

complying with the stipulations of bioequivalence studies and bio-similar evaluations accorded registration to defendant No.4's injection Reditux as similar biotherapeutic drug.

19. The WHO Expert Committee on biological standardization issued guidelines on evaluations on similar biotherapeutic products (SBPs). The instructions expresses that biotherapeutic drugs have a successful record in treating many life threatening and chronic disease. However, their cost has been high thereby limiting their access to patients, particularly in developing countries, these products rely in part for their licensing on prior information regarding safety and efficacy obtained with the originator products. The clinical experience and established safety profile of the originator products should contribute to the development of similar biotherapeutic products (SBPs) as a part of its mandate for sharing global quality, safety and efficacy of biotherapeutic products. The WHO has imparted globally accepted norms and standards for the evaluation of these products. The guidelines further communicates and emanates that standard of evidence supporting the decision to license (SBPs) be sufficient to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public health. The elaboration of the data requirements and consideration for licensing of these products facilitates development of Worldwide access to biotherapeutics of assured quality, safety and efficacy at more affordable prices. The perseverance and impelling cause of guidelines is to make available globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety and efficacy that have

been licensed based on full licensing dossier. A reference biotherapeutic product is used as the comparator for head-to-head comparability studies. The key principles for the licensing of SBPs further expound that the basis for licensing a product as a SBP depends on its demonstrated similarity to a suitable RBP in quality, non-clinical and clinical parameters and the decision to license should be based on evaluation of whole data package for each of these parameters and if relevant differences are found the product do not qualify as SBP and a more extensive non-clinical and clinical data set will be required to support the application of licensure.

20. Compliant with clause (v) of Section 2 of Drug Regulatory Authority of Pakistan Act, 2012 "biological" means biological drugs as defined in Schedule-I (supra). In line with this Schedule biological drug requires standardization by biological assays according to the relevant and updated recommendations of the World Health Organization published in Technical Report Series and Biological Standard Report, whereas "Originator Biological Drugs" connotes a biological drug which has been licensed by the national regulatory authorities on the basis of full registration dossier and "Pharmaceutical dossier" assimilates a set of documents submitted by a person for the registration of a therapeutic good, containing complete information with regard to manufacturing procedure of the drug biological or medical device. The same Schedule also differentiates and distinguishes the Biological Drugs in 04 configurations and dispositions for instance "Biological drug (Finished form)", these Biological Drugs are manufactured and packed by the manufacturer under his responsibility of quality assurance; "Biological Drugs

(Ready-to-fill form)", are manufactured at one site in the form of a "Ready-to-fill Bulk" but are transferred to another site for final filling, labeling, packaging and quality control, "Biological Drugs (Concentrated form)" are manufactured at one site but stored in the form of concentrated bulk of the active ingredient that may be transferred to another site under temperature control conditions and "Biological Drugs (Naked vials)" are manufactured and fill at one site but the final containers are neither labeled nor packed in cartons locally.

21. In the written statement filed by the defendant Nos.1 to 3, it is avowed that the DRAP is nascent organization established in 2012 and is continuously improving as per internationally accepted standards/procedures for registration of biological goods. After promulgation of the Act, biological evaluation, research department has been enacted as one of the divisions of the Authority. It is further contended that in view of complex molecular structure of biological and to ensure the quality, safety and efficacy, the registered biological drugs including the imported and locally manufactured, after the release by the manufacturer is further subject to release by the National Control Laboratory of Biological of Drug Regulatory Authority of Pakistan for sale in Pakistan. The said laboratory is working as per the lot release system of World Health Organization and such condition is also provided in clause 7 of the Schedule-I under which no human biological drug is allowed to sell until a lot releasing certificate from the Federal Government analyst of the National Control Laboratory for Biologicals, Islamabad is obtained. They also highlighted that in the month of November, 2012 the Drugs Act was promulgated, consequently a Division of Biological

Evaluation and Research was enacted as separate division for biological drugs defined in Schedule-I of the said Act. Hefty accentuation engendered in the same written statement that the Schedule does not specify to establish the WHO guidelines on evaluation of Biosimilar Drugs, however, it specifies the standardize biological drugs by biological assays as per recommendation of WHO published in technical report.

22. The case profile and résumé put on view that the defendant No.4 had submitted application for registration of Reditux injection on 02.02.2011. The application was tabled in the 48th meeting of experts committee of biological drugs on 10.10.2012 when the product was recommended subject to the latest GMP inspection report by NRA. However the Registration Board again dwelled on and ruminated the application in its 254th meeting and get hold of the following decision :-

> "Decision: Registration Board deferred the case for completion of applications, remaining fee, CoPP status, information regarding availability in country of origin and deliberations regarding requirement for bio-similarity of products."

23. Nevertheless, in 256th meeting of Registration Board convened in February, 2016 the registration case was taken up however the Registration Board deferred it again for expert opinion. Two separate tables referring to the minutes of meeting with brand name and drug composition in relation to the Case No.12 of the defendant No.4 for consideration and weighing up their application for registration of Reditux injection are reproduced as under:-

S.No.	Name of Importer & Manufacturer	Brand name/ Drug Composition	Dy.No & Date of application/Fee status/Pack size/ demanded price	Document details (CoPP) Me too status Remarks	Decision of RB
1.	Macter International (Pvt) Limited, Karachi Dr.Reddy's Laboratories Ltd., Ranga Reddy District, Hyderabad, India.	Reditux TM Injection 100mg Each 10ml vial contains:- Rituximab (r-DNA origin)..... 100mg (Antineoplastic Monoclonal Antibody). (For Human Use) Original Notarized and Legalized GMP certificate no. 259/M3B/2014 issued by Drug Control Administration, Andra Pradesh, Date of Issue 13/02/2014 and valid up to 18/12/2015. COPP no.2821/M3B/2014 for finished drug of strength 100mg issued by Drug Control Administration, Govt. of Andhra Pradesh. Original notarized and legalized. Valid up to 18/12/2015. Indications: Non Hodgkin Lymphoma Antineoplastic Monoclonal Antibody	Date of application 2.02.2011 Fee deposited 15000 (02-2-2011) + 85000 (09-10-2011) Total 100000 Balance fee Nil Structural similarity of subject biological product is available in provided DMF by manufacturer. Protein sequence is compared with WHO sequence.	The reference product is Ristova by Roche. The case was recommended in 48th ECBD + Biosimilarity +PICS Copies of COPP provided, valid up to 18-12-2015. Bioequivalence and efficacy Clinical trials data is submitted Safety Studies Four years post marketing surveillance data of 818 patients. Animal toxicity studies are available in provided DMF by manufacturer	Deferred for expert opinion of following a. Brig (Retd), Muzamil Hasan Najmi, foundation Medical College, Rawalpindi b.Brig.Amir Ikram, AFIP, Rawalpindi. c. Dr.Masud-ur-Rehman DDG, DRAP, Islamabad.
2.	Macter International (Pvt) Limited, Karachi. Dr.Reddy's Laboratories Ltd. Ranga Reddy District, Hyderabad, India	Reditux TM Injection 500mg Each 50ml vial contains:- Rituximab (r-DNA origin)..... 500mg (Antineoplastic Monoclonal Antibody) (For Human Use) COPP no. 2381/M3B/2014 Issued by Drug Control Administration, Govt. of Andhra Pradesh. Date of Issue 22/03/2014. Valid up to 18/12/2015. Original notarized and Legalized. Indications: Non Hodgkin Lymphoma Antineoplastic Monoclonal Antibody	Date of application 02.02.2011 Fee deposited 15000+85000 Balance fee Nil <u>Animal toxicity studies</u> are available in provided DMF by Manufacturer	The reference product is Ristova by Roche. The case was Recommended in 48th ECBD + Biosimilarity + PICS Copies of COPP Provided, Valid up to 18-12-2015 Bioequivalence and efficacy Clinical trials Data is Submitted safety studies: Four years Post marketing Surveillance Data of 818 Patients.	Deferred for expert opinion of following a. Brig (Retd), Muzamil Hasan Najmi, foundation Medical College, Rawalpindi b.Brig.Amir Ikram, AFIP, Rawalpindi. c. Dr.Masud-ur-Rehman DDG, DRAP, Islamabad.

24. In the 260th meeting of the Registration Board summoned in the month of June, 2016, the expert opinion was well-thought-out with an astute and sharp-sighted approach by the Board and in view of the opinion rendered by the experts on the quality, quantity and efficacy and biosimilarity, the product was approved for registration. In line with the documents submitted by the defendant No.4 to DRAP, the "Reditux" is registered in India since April, 2007. It is also registered for import in various countries such as Russia, Iran, Ukraine, Sri Lanka, Peru, Gabon, Jamika, Myanmar, Nepal, Venezuela and Vietnam. The defendant No.4 also submitted comparative study with regard to the efficacy and safety of Rituximab (Mabhtera) which is biosimilar to Reditux. Retrospective study was also carried out to compare the efficacy, safety and toxicity with Mabhtera with Reditux in the patient with defuse large B-cell lymphoma. The experts insisted that Reditux is as efficient as Mabhtera in terms of response rates, progression free survival and overall survival with comparable toxicity and there is no significant differences in the toxicity, tumor response rates, progressive free survival and overall survival and two available brands. The manuscript of experts report is as follows:-

"In the minutes for 260th Meeting Registration Board held on 28-29th June, 2016 it was decided as under:-

<u>Expert Opinions</u>

By Brig. (Retd) Prof. Muzamil Hasan Najmi, on products (Biological) of M/s. Macter International, Karachi.

Rituximab is a chimeric monoclonal antibody produced by recombinant DNA technique. It reacts with the CD20 protein present on the surface of B lymphocytes which are thus destroyed. Reduction in the number of B lymphocytes results in decreased antibody production by these cells.

The drug is approved for treatment of certain leukemias and lymphomas including non-Hodgkin's lymphoma. It is also used in some of the autoimmune diseases. It is a disease modifying drug for rheumatoid arthritis, particularly refractory to other treatments.

The drug can cause several adverse effects which include severe reaction after administration as infusion, cardiotoxicity, lung toxicity, tumor lysis syndrome and reactivation of viral infections including hepatitis B. However, keeping in view the nature of diseases in which it is used, the benefit/risk ratio is favourable.

M/s.Macter International, Karachi has applied for registration of the brand of Rituximab which is of Indian origin. The manufacturer, Dr.Reddy's Lab has provided details of manufacturing method and biosimilarity studies of their product, Reditux TM Injection 100 and 500 mg. The Company has obtained cGMP compliance certificates from USFDA and MHRA of UK. Having reviewed the data provided, I am of the opinion that both strengths of Reditux TM injection may be approved so that a cost effective alternative brand of this drug may become available for the patients.

2. Expert Opinion by Dr.Masud ur Rehman, DDG, DRAP on biological product of M/s.Macter International, Karachi.

Introduction:

Rituximab a long chain monoclonal antibody is produced by recombinant DNA technique. Having site of action on CD20 protein present on the surface of B lymphocytes. It binds there and destroys B Lymphocytes cancerous cell. Reduction in the number of B lymphocytes results in decreased antibody production by these cells. The drug is approved for treatment of leukemias, lymphomas including non-Hodgkin's lymphoma. It is also used in some of the autoimmune diseases. It is a disease modifying drug for rheumatoid arthritis, particularly refractory to other treatments.

Evaluation of Dossier:

Product dossier carries scientific data of structural characterization & comparability with innovator product (Mabthera/Rituxan) in peptide mapping, intact protein mass, UV circular dichorism, Disulphide bonding pattern by LC-MS. There is comparability/similarity of structure in high order structure by fluorescence spectroscopy, thermal stability by scanning calorimetric method, glycosialation analysis by Reagent Array Analysis (RAAM), Charge insomers by IEF, SDS PAGE, SEC HPLC. Potency is determined by CDC & ADCC. Specific binding of FCyR1, FCyRIIa, FCyRIIB, FCyRIIIa and FCyRn regions by ELISA, SPR & FACS has also been done.

Pharmacokinetic studies:

Pharmacokinetic and extensive animal toxicology studies data is provided. Clinical efficacy trial on Non Hodgkin Lymphoma (NHL) of stage II, III and IV patients has shown overall response of 93.8%. Toxicity data is also provided which is in acceptable range. Four years post marketing safety data of 808 patients is also submitted.

Manufacturers Profile:

Manufacturer of Rituximab is Dr.Reddy's Laboratories, India. Its a GMP certified manufacturer by many international regulatory agencies such as Brazil, Peru, QP EU, GCC and Iran. The Company has also obtained cGMP compliance certificates from USFDA and MHRA of UK.

Recommendations:

M/s.Macter International, Karachi has applied for registration of the generic brand of Rituximab. Reditux generic biosimilar injection may be approved so that a cost-effective alternative brand of this drug may become available for the patients. Based on aforementioned evaluated specifications by M/s.Macter International, Karachi, the product registration is recommended.

3. Reply of Brig. Amir Ikram, AFIP, Rawalpindi
Thanks for referring the case of Reditux TM Injection 100mg and 500mg strength. Comments are as below:-

1. Product Safety: The provided literature shows that the preparations are safe. Trials have been conducted in the country of

origin with satisfactory outcome. The manufacturer is following GMPs.

2.Efficacy: The clinical trials conducted in the country of origin indicate that the preparations are efficacious, however further evaluation if requisite may be done.

3.The provided material indicates that the preparations are comparable to published literature for innovator rituximab. The preparations are required and if probably not incorrect not much of preparations are easily available within the country. Its transportation under requisite parameters specially temperature has to be guaranteed by the company at all levels.

The three experts have recommended the products for registration. The case is submitted is before the board for consideration as per import policy.

Decision: Registration Board considered the expert opinions and approved the registration of Reditux Injection 500mg manufactured by Dr.Reddy's Laboratories Ltd. Ranga Reddy District, Hyderabad, India as per Import Policy for Finished Drugs and valid legalized CoPP." [Emphasis applied].

25. The plane reading deduced and reckoned a number of finer points concluded and verified by the experts after an astute analytical assessment, survey and scrutiny of entire data which can be summed up as under:-

i. **The manufacturer, Dr.Reddy's Lab has provided details of manufacturing method and biosimilarity studies of their product, Reditux TM Injection 100 and 500 mg.**

ii. **The Company has obtained cGMP compliance certificates from USFDA and MHRA of UK.**

iii. **Both strengths of Reditux TM injection may be approved so that a cost effective alternative brand of this drug may become available for the patients.**

iv. **Product dossier carries scientific data of structural characterization & comparability with innovator product (Mabthera/Rituxan) in peptide mapping, intact protein mass, UV circular dichorism, Disulphide bonding pattern by LC-MS.**

v. **There is comparability/similarity of structure in high order structure by fluorescence spectroscopy, thermal stability by scanning calorimetric method, glycosialation analysis by Reagent Array Analysis (RAAM), Charge insomers by IEF, SDS PAGE, SEC HPLC. Potency is determined by CDC & ADCC.**

vi. **Specific binding of FCyR1, FCyRIIa, FCyRIIB, FCyRIIIa and FCyRn regions by ELISA, SPR & FACS has also been done.**

vii. **Pharmacokinetic and extensive animal toxicology studies data is provided. Clinical efficacy trial on Non Hodgkin Lymphoma (NHL) of stage II, III and IV patients has shown overall response of 93.8%.**

viii. **Toxicity data is also provided which is in acceptable range. Four years post marketing safety data of 808 patients is also submitted.**

ix. **Manufacturer Dr.Reddy's Laboratories, India is a GMP certified manufacturer by many international regulatory agencies such as Brazil, Peru, QP EU, GCC and Iran. The Company has also obtained cGMP compliance certificates from USFDA and MHRA of UK.**

x. **Reditux generic biosimilar injection may be approved so that a cost-effective alternative brand of this drug may become available for the patients.**

xi. The provided literature shows that the preparations are safe.

xii. Trials have been conducted in the country of origin with satisfactory outcome.

xiii. The clinical trials conducted in the country of origin indicate that the preparations are efficacious, however further evaluation if requisite may be done.

xiv. The provided material indicates that the preparations are comparable to published literature for innovator rituximab.

26. The learned counsel for the plaintiff referred to the case of **M/s.Alfalah Medicos** (supra). Basically, in this case the petitioner challenged the decision of Grievance Committee dismissing the representation of petitioner No.2. The procurement of Interferon was sought in connection with the prevention and control of Hepatitis Control Program initiated by Government of Punjab. Clause 12 of the bidding documents required Bio equivalence/Bio similarity. The prequalification application of Getz Pharma was rejected for not meeting the criteria mentioned in clauses 10 and 11 of the bidding documents. The prime question is enumerated in paragraph 9 of the judgment as to whether the terms contained in the bidding documents requiring Bio equivalence/Bio similarity of the drugs violated the federal standards and stifled free competition. The court held that Unipeg was not declared bio-similar drug by the DRAP whereas Unipeg took the plea that it is registered since 2010. The DRAP gave two years' for carrying out bio-similarity studies as such the petitioner still has time available for complying with clause Nos.10 and 11 of the bidding documents. The survey of this judgment makes unequivocally clear that the primary dispute was in relation to the terms and conditions of tender documents, however, learned Judge also made very lucid and eloquent discussion on the subject of bio-similarity and bio-equivalence that the regulatory authorities all over the world have outlined the requirements to demonstrate

bio-similarity of drugs and bio-similar manufacturers need to generate data from Lab testing and non-clinical testing to show that bio-similarity.

27. While referring to 60th meeting of the WHO Experts Committee learned Additional Attorney General made much emphasis that the procedure of biological standardization stipulate the obligation to provide all information required for the purposes of licensing as SBP by manufacturers but no such obligation is imposed on the importer. Whereas on experts report the Additional Attorney General focused that compliance certificate for Reditux has been issued by Food and Drug Administration of the United State Department of Health and Human Services (USFDA) as well as medicines and healthcare product regulatory agency of United Kingdom. The registration dossier has also been evaluated by the experts and they have observed that Reditux is duly comparable to its RBP in terms of quality, efficacy and safety. He also assured that DRAP will take certain additional steps in order to ensure quality, safety and efficacy and in this regard, the laboratory inspection of manufacturer will also be carried out.

28. Though Section 7 of the Drugs Act, 1976 pertains to registration of Drugs but there is no provision for the implementation of international recognized standards including bio-equivalence and bio-similar evaluations for systemic implementation of WHO guidelines, however, this stipulation is complementary to the powers and functions of Drug Regulatory Authority of Pakistan established under Section 3 of the DRAP Act, 2012. Under Section 32 of the DRAP Act it is clearly enumerated that the provisions of this Act shall be in addition to and not in derogation of the provisions made

in the Drugs Act, 1976, whereas sub-section (2) enunciates and articulates that in case of inconsistency between the provisions of this Act and any other law for the time being in force, the provisions of this Act shall prevail. It is not the case that the defendant No.4's applied for the license to manufacture Reditux injection in Pakistan but they have applied for the registration to sell and market this product on import. This has not been controverted and negated by the plaintiff that the same injection/vaccine is being sold in other countries. The perusal of experts committee report divulges and depicts that all relevant aspects were considered and all experts gave unanimous findings in favour of registration. The lawsuit does not germane or associate to any claim or controversy vis-à-vis copyrights, trademark or patent but the breadth and extensiveness of challenge confines to the alleged failure to accomplish and achieve bio-similar/bio-equivalence studies entailed under the WHO guidelines. The plaintiff has not raised any allegation of bias or favoritism nor challenged the experts report to bear out that the experts have committed errors or slipups and or they failed to scrutinize and examine the relevant data provided to them nor the plaintiff has alleged anything with regard to quality, safety and efficacy of the product in issue. On the contrary the experts report unequivocally and unambiguously pinpoint all correlated factors and characteristics which resulted unanimous decision to recommend the product for registration.

29. The Common Technical Documents, Rituximab (r-DNA-origin) issued by Dr.Reddy's Biologics Development Centre is on record. The clinical study report includes biopharmaceutics studies, studies

pertinent to pharmacokinetics using human biomaterials, human pharmacodynamics studies, efficacy & safety, post-marketing experience, report forms & individual patient listings. An excerpt from Indian Journal of Medical and Pediatric Oncology, Oct-Dec 2013, Vol. 34, Issue 4 showing "Comparison of the efficacy and safety of Rituximab (Mabthera™) and its biosimilar (Reditux™) in diffuse large B-cell lymphoma patients treated with chemo-immunotherapy which reads as under:-

"Background: Rituximab (Mabthera™) have been in use in India since 2000. A biosimilar molecule of rituximab (Reditux™) was approved in India in 2007. This retrospective audit was done to compare the efficacy and safety of Mabthera™ with Reditux™. Materials and Methods: We reviewed the charts of 223 adult diffuse large B-cell lymphoma patients who had received cyclophosphamide, doxorubicin, vincristine and prednislone with rituximab chemotherapy. Tumor recurrence, survival and toxicities experienced during chemotherapy were obtained from the patient charts. The survival analysis was restricted to patients who received at least 4 cycles of the same brand. Results: Of the 223 patients evaluated, 101 received Mabthera™, 72 received Reditux™. There were no differences in the infusional reaction rates, grades 3 and 4 neutropenia and oral mucositis between the two brands. Complete-remission (CR) rates were similar with Mabthera™ and Reditux™ (75% and 82%, respectively; *P* = 0.294). The progression free survival (PFS) rate at 5 years were 72% in Mabthera™ and 81% in Reditux™ (*P* = 0.382). The overall survival (OS) at 5 years comparable in the two groups (66% in Mabthera™ and 76% in Reditux™ : *P* = 0.264). Conclusion: We observed no significant differences in the toxicity, tumor response rates, PFS and OS between the two available brands of rituximab.

Key words: ***Anti-CD20, biosimilar, lymphoid neoplasms, monoclonal antibody, observational study, survival outcomes.***

B-cell non-Hodgkin's lymphoma in 1997. Food and Drug Administration approval for Mabthera™ was received in June, 1998. Mabthera™ was marketed in India in early 2000 and is being used as the standard of care for DLBCL as well as low grade lymphomas.[4] However, cost of Mabthera™ is a limiting factor for its use.

A similar biologic medicinal product, commonly referred to as biosimilar, is a copy version of an approved original biologic medicine.[5] There have been frequent concerns raised about biosimilars in the medical fraternity. Since the implementation of a biosimilar approval pathway in 2005, several biosimilars have been developed.[6]

A biosimilar molecule (Reditux™) was developed by Dr.Reddy's Laboratories, Hyderabad, India and was licensed for clinical use in India, in 2007.[7,8] Thereafter, most of the oncologists in India are using the biosimilar, Reditux™ for the treatment of DLBCL in patients who were unable to afford the Mabthera™."

30. It is a matter of record that the Drugs Act, 1976 repealed the Drugs Act, 1940 and DRAP Act was

promulgated in the year 2012 under which the Drug Regulatory Authority of Pakistan was established in terms of Section 3 with certain powers and functions to be exercised by the Authority. It has not been pleaded that before DRAP Act, 2012 there was no mechanism and procedure for licensing or manufacturing of the drugs or its registration, but equally viable procedure was already laid down. This cannot be presumed or assumed that all previous registrations and licenses issued prior to WHO guidelines were erroneous or without lawful authority but at that time also requisite formalities with regard to quality, safety and efficacy were required to be comprehended as expedient and pragmatic under the law. Under Section 7 of the DRAP Act, it is the responsibility of the authority to monitor the enforcement of laws specified in Schedule VI and if we look into Schedule VI the relevant laws means Drugs Act, 1976. Though Schedule I of the DRAP Act, 2012 concentrated and resolute on biological. In unison, certain prohibitions have been laid down on import, manufacture and sale of therapeutic goods in the Schedule II. Nothing has been pointed out by the plaintiff that the registration of the drug in question is prohibited under any clause of Schedule II.

31. The learned counsel for the defendant No.4 referred to the judicial precedents in which the superior courts expounded different rules and exposition of law. In case of **Golden Oraphies (Pvt.) Ltd.** (supra), a well settled principle of law has been elucidated that where a special provision had been made on a subject the general provision is not intended to interfere with the operation of the special provision. In case of **Maulana Nur-ul-Haq** (supra) the court held where the consequence of failure to

comply with the provision is not mentioned the provision is directory and not mandatory. In the case of **Ihsan-ur-Rehman** (supra), the court held that two different views of High Courts are not binding on each other. Whereas in the case of **F. Hoffmann-La Roche Ltd.** (supra) the court considered two competing public interests, that is, the public interest in granting an injunction to affirm a patent as opposed to the public interest in access for the people to a lifesaving drug and held that the balance has to be tilted in favor of the latter. In the case of **Brawn Laboratories Ltd.** (supra) the court held that grant of injunction would not be in larger public interest as the same may result in denial of life saving drugs. While in the case of **Al-Tamash Medical Society** (supra) authored by me I have discussed the conditions to grant the injunction and its refusal in detail.

32. The learned counsel for the defendant No.4 referred to an order dated 12.10.2015, passed in C.P.No.D-758 of 2013 against the plaintiff and NAB Reference No.24/2016 in which the Managing Director of the plaintiff's company was shown as accused No.3. Since the above litigation have not much nexus or proximity with the controversy immersed and engrossed in this case, therefore I would not prefer to comment on it.

33. The question of public admittance at large to life saving drugs presupposes vast magnitude. The inimical effect on such access due to grant of injunction will cause disadvantages manifold to the larger public interest. It is an admitted verity that same injection is even now being vended in several other countries and in Pakistan it will be marketed on import and not through a license to manufacture so in all fairness this is not the intention of legislature that for each import and on each

moment in time, separate exercise should be carried out by DRAP to match bioequivalence or biosimilarity under WHO guidelines rather the research reports and the dossier submitted by the originator may serve the purpose which have already been considered by the experts in the present set of circumstances. The responsibility of issuing license to manufacture and or registration of drugs is entrusted and devolved on the DRAP. While according license or registration to any drug, this is their inherent and intrinsic responsibility to ensure the best satisfaction with conscientiousness and trustworthiness and if something is found wrong then naturally DRAP is required to act in furtherance of correction and rectification. The Experts have recommended that Reditux generic biosimilar injection may be approved so that a cost-effective alternate brand of drug may become available for the patients; the provided literature shows that the preparations are safe; trials have been conducted in the country of origin with satisfactory outcome; the clinical trials conducted in the country of origin indicate that the preparations are efficacious and the provided material indicates that the preparations are comparable to published literature for innovator rituximab. The chronology translates and deciphers that in the instant case, after due satisfaction and vetting of experts report the DRAP decided to accord registration.

34. In my solicitous outlook and analysis, the plaintiff has failed to demonstrate any prima facie case nor any balance of convenience or irreparable loss in case injunction is refused. In the case of Al-Tamash Medical Society vs. Dr. Anwar Ye Bin Ju & others, (supra) authored by me, it was held that an injunction is an

equitable relief based on well-known equitable principles. Since the relief is wholly equitable in nature, the party invoking the jurisdiction has to show that he himself was not at fault. The phrase prima facie case in its plain language signifies a triable case where some substantial question is to be investigated or some serious questions are to be tried and this phrase 'prima facie' need not to be confused with 'prima facie title'. Before granting injunction the court is bound to consider probability of the plaintiff succeeding in the suit. All presumptions and ambiguities are taken against the party seeking to obtain temporary injunction. The balance of convenience and inconvenience being in favour of the defendant i.e. greater damage would arise to the defendant by granting the injunction in the event of its turning out afterwards to have been wrongly granted, than to the plaintiff from withholding it, in the event of the legal right proving to be in his favour, the injunction may not be granted. A party seeks the aid of the court by way of injunction must as a rule satisfy the court that the interference is necessary to protect from the species of injury which the court calls irreparable before the legal right can be established on trial. In the technical sense with the question of granting or withholding preventive equitable aid, an injury is set to be irreparable either because no legal remedy furnishes full compensation or adequate redress or owing to the inherent ineffectiveness of such legal remedy.

35. In the wake of above discussion, the injunction application (C.M.A No.14255/2016) is dismissed.

Karachi:-
Dated. 12.10.2017 **Judge**