REVIEW ARTICLE

Role of the National Control Laboratories in Ensuring the Quality, Safety and Efficacy of Blood Products in India

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ABSTRACT

National control laboratories (NCLs) are responsible for testing of the batches of drugs prior to their release on the market. NCLs play an important role in strengthening a country's regulatory systems. The National Institute of Biologicals is an NCL in India for the testing and coenzyme A (CoA) release of biologicals such as biotherapeutics, vaccines, and diagnostic medical devices. Every year, the National Institute of Biologicals tests and CoA releases thousands of batches of blood products following compendial specifications and schedule F, part XII-C (G) of Drugs and Cosmetics Rules 1945. This institute also participates in collaborative studies with the WHO for the establishment of international reference standards. In the last thirteen years (2010–2022), the blood products laboratory at this institute has evaluated 5159 batches of blood products, and 95 batches (1.84%) were declared as not of standard quality. As per CDSCO "the 'not of standard' quality products are categorized into three categories: A, B and C". These 95 batches include all three categories (A, B and C) of "not of standard" quality blood products.

Keywords: Blood products, High standard quality, National control laboratory.

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INTRODUCTION

India is the world's largest producer of generic drugs and meets 20% of global pharmaceutical demand in addition to its own needs. India exports pharmaceuticals to over 200 countries with the United States being the major importer. The India Economic Survey 2021 predicts that the domestic pharmaceutical industry will triple over the next decade. National pharmaceutical sales are expected to reach US$12-130 billion by 2030, up from US$42 billion in 2021.[1] Hence, in order to compete with the world, India must maintain the highest quality standards of its pharmaceuticals.

As per the world health organization (WHO), a drug must be tested on at least three parameters – quality, safety and efficacy – before it can be placed on the market.[2] The quality council of India was established as an independent and self-governing body with the mandate to ensure quality standards in all spheres of economic and social activity.[3] Henceforth, our country's goal should be to improve product quality, achieve high standards and transform from a technology importer to a technology exporter. The focus should be on the pharmaceutical industry.

This communication is anticipated to advise National Regulatory Authorities (NRAs), National Control Laboratories (NCLs), national healthcare policymakers, manufacturers of plasma-derived pharmaceuticals and relevant agencies on the fundamental aspects affecting the quality and safety of such products. India enacted the medicines and cosmetics Act 1940 to regulate the importation, manufacture, sale, and distribution of medicines and cosmetics in India.[4] The International Committee for Harmonization of Technical Requirements for Registration of medicinal products for human use (ICH) is an initiative to bring regulators and the pharmaceutical industry together on a common platform to address the scientific and technical aspects of the development and drug registration. The mission of ICH is to coordinate drug development in terms of safety, efficacy and quality to meet high global quality standards.[5]

Drug regulatory agencies should provide the pharmaceutical industry with timely and regular information on mandatory and non-mandatory drug regulatory and quality control requirements. India should gradually put in place strict laws and regulations in this area and more laboratories and

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organizations should be established to ensure the quality of medicines. Therefore, drugs without quality assurance will not be marketed. Governments should be responsible for ensuring the standard quality of medicines entering the market for human consumption. Strict regulations and controls will prevent the stagnation of substandard, misbrand, counterfeit and poor-quality medicines. In one study, the data for the period 2000 to 2013 was examined and inferred to expose the true picture of poor quality medicines in India. Stricter regulatory and legal measures are urgently needed to reduce counterfeit, adulterated, falsified or substandard medicines. India has also taken preventive measures at the national level to fight against substandard medicines to protect and promote human health.[6]

In India, under Sections 17, 17A and 17B of the Drugs and Cosmetics Act 1940, substandard medicines include mislabeled, counterfeit and adulterated medicines, respectively.[7] With the amendment of the D and C Act 2008, the Central drugs standard control organization (CDSCO), the "Drug Regulatory Authority of India", has classified Non-Standard Quality (NSQ) products into three categories (A, B and C), which helps to classify products during quality assessment.[8] Class A includes counterfeit and shoddy drugs; Class B includes far substandard drugs that fail disintegration or dissolution testing and oral drug active ingredient testing. For parenteral preparations lacking safety parameters, Category C is for products with minor defects in description, net content, discoloration, presence of granules, and labeling errors.[6]

Plasma Derived Drug Products (Blood Products)

Plasma-derived drugs are made from the plasma of humans. Plasma was obtained from whole blood donations or by apheresis.[9] Plasma is the source of several therapeutic drugs for the treatment and prevention of various injuries and life-threatening diseases commonly associated with protein deficiency disorders.[10-12] In recent years, protein purification using fractionation techniques has been used to obtain various human plasma proteins such as albumin, immunoglobulins, coagulation factors and fibrin sealants. The National Regulatory Authority (NRA) is responsible for regulating medicines derived from human plasma. In recent years, these products have presented complex and serious technical, scientific and regulatory challenges, which may pose barriers to ensuring the quality, safety and efficacy of these biologics.

Quality control and assurance

Plasma-derived drugs are naturally complex, variable and unstable due to their biological properties. Therefore, quality control and assurance using reproducible chemical, physical and biological methods/techniques are necessary for safety, efficacy and quality for human consumption.[13] Due to the biological nature of the molecules, a high level of expertise is essential for the regulatory and lot release of these products for premarket approval.[14] Four main harmonized approaches must be implemented to ensure the efficacy, quality and safety of biological products:

- Good manufacturing practice (GMP): Strictly follow the GMP-WHO guidelines and prevent the cross-contamination in product manufacturing area.[15]
- Reference standard: International Reference Standards /National Reference Standards should be used for the quality standard analysis of the Biologicals.
- Product compliance: Standardization/validation of analytical methods needs to be done in the characterization of in-process and finished products.
- Good laboratory practices (GLP): Analytical/testing laboratories should comply ISO standard guidelines to ensure the high quality standards of the Biologicals.

National drugs regulatory authorities

The Central Drugs Standard Control Organization is an Indian regulatory authority headed by the Drugs Controller General of India (DCGI). NRAs have the responsibility to ensure that the pharmaceutical products available on the market for human use, whether manufactured or imported, are of high quality, effective, and safe. The Drugs and Cosmetics Act (DCA), 1940, is to regulate the import, manufacturing, sales, and distribution of drugs in India. Blood products are regulated within the legal definition of pharmaceutical products and fall under Schedule F, Part XII-C (G) of Drugs and Cosmetic Rules 1945 of the DCA. The pharmaceutical industry relies heavily on quality control assessments of pharmaceuticals and medical devices. Medical devices and drugs must be marketed as safe and therapeutically active formulations with precise, reliable and predictable performance. The production of new and improved drugs and diagnostic devices has accelerated in recent years. At the same time, quality control of the same is essential for safety and performance purposes, and accordingly, more demanding and sophisticated analytical methods are being developed for their evaluation to meet the requirements governing the pharmaceutical's quality control in accordance with the Indian Drugs and Cosmetics Act 1940.[4]

The National Institute of Biologicals (NIB) is the apex institute under the administration of the Ministry of Health and Family Welfare of the Indian government. It was established in 1992 as an organization under the Associations Registration Act 1860 to ensure quality control of various biological products likeprophylactic, blood reagents, blood products, sera, immuno-diagnostic kits, etc. indigenously produced and imported into India.(www.nib.gov.in). The National Institute of Biologicals is notified as a central drug laboratory (CDL) as well as a central medical device testing laboratory (CMDTL). The National Accreditation Board for Testing and Calibration Laboratories (NABL) has accredited NIB as per ISO/IEC 17025:2017 standard, and since 2010, NIB has retained its accreditation status without any break. This institute has performed the quality control evaluation of biopharmaceutical and medical device products to certify the product for standard quality or not of standard quality for batch release in the Indian market.

The Indian government should strengthen the National Control Laboratories (NCLs) and establish new NCLs in

the country for the quality assessment of medicines. These laboratories must be accredited for the quality control assessment of pharmaceutical products and must also carry out research and development activities in the field of development of analytical methods and reference standards for pharmaceutical and biopharmaceutical products.

Analytical methods and procedures are quality control tools for pharmaceutical products. NCLs should be developed using new advanced analytical methods, especially alternatives to animal testing. Newly developed methods should be validated, as validation of analytical methods is a key procedure to ensure that newly developed methods fulfill their purpose and produce reliable and accurate results.

Blood Products Evaluation for the Quality Control

NIB has designated a centralized samples receipt and report dispatch unit to receive samples from the Central drugs standard control organisation (CDSCO) and its Port offices, Zonal offices, State drug controller offices, State Medical Store Supplies (Rajasthan, Haryana, Jammu-Kashmir, Chhattisgarh, Telangana, etc.) and indigenous manufacturers for quality evaluation. Samples on form 18 and survey samples are directly submitted by Drug Inspectors. These samples are forwarded by the centralized samples receipt unit of the Institute for blood products laboratory.

The blood products laboratory (BPL) of the National Institute of Biologicals (NIB) is involved in carrying out quality control of the blood products according to monographs given in the Indian Pharmacopeia. All blood products, indigenously manufactured as well as imported, are evaluated in this laboratory. This laboratory has developed expertise and tested blood products such as human albumin, human, human normal immunoglobulin (IV, IM, SC), hepatitis B immunoglobulin (IV, IM, SC), plasma protein fraction, rabies immunoglobulin (IM), human tetanus immunoglobulin (IM), anti-D immunoglobulin (IV, IM), human coagulation factor VIII (plasma derivedand recombinant), human coagulation factor IX, human coagulation factor IX recombinant, fibrin sealant kit, anti-inhibitor coagulant complex, human prothrombin complex, human coagulation factor VIII (Recombinant PEGylated) and human coagulation factor IX (Recombinant PEGylated). BPL uses international standards from various sources, such as WHO, National Institute for Biological Standards and Control (NIBSC), and European Directorate for the Quality of Medicines & HealthCare (EDQM) to ensure the reliability of results. The test samples are tested as per the label claim of the product and following the respective compendial monograph. All methods are validated before applying for testing purposes. Internal quality checks and trend analysis are done to monitor the undesirable variability in test results.

Imports of Blood Products in India

To date, imported batches of blood products from 15 countries have been tested at the NIB. Each imported batch of blood products is tested for quality at the NIB before marketing approval by the regulatory authority. The certificate of analysis issued by NIB gives the details of the test parameters tested and their results. It also helps to eliminate the possibility of entering of sub-standard blood products entering the market.

In the last thirteen years (2010–2022), our laboratory at NIB has evaluated 5159 batches of blood products. Out of these 60 % of products imported from different countries like

Figure 1: Global distribution of the blood products evaluated at BPL, NIB, NOIDA.

Table 1: Major test parameters and test methodologies for quality control testing of blood products:

S. No.	*Test parameters*	*Methodology*
1.	Identification	Double immuno diffusion Immuno-electrophoresis Sodium dodecyl Sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) Immunoblotting Assay
2.	Purity	Size-exclusion chromatography (SEC)-HPLC Protein composition (Electrophoresis)
3.	Impurities	Antibody-A and Antibody-B Antibody-D Haem content prekelikirin assay
4.	Assay/Potency	Coagulation Specific potency assay Immunoglobulin G Total protein content by Kjeldahl method
5.	Transfusion transmitted viral markers	ELISA for detection of HIV 1and2 Ab ELISA for detection of HCV Ab ELISA for detection of HBsAg
6.	Safety	Sterility Animal based test for detection of pyrogens animal based test for abnormal toxicity Gel clot/ KCA method for bacterial endotoxin
7.	Physicochemical characteristic	pH Osmolality Solubility Physical Appearance/Description moisture content
8.	Other tests	Sodium content by atomic absorption spectroscopy Potassium content by atomic absorption spectroscopy Activated coagulation factors Anti-complementary activity (ACA) Heparin Thrombin

USA, European countries, China, South Korea, Canada, etc. and 40% are indigenous products, the global distribution of the imported products to India as shown in Figure 1.

The major test parameters and test methodologies used for quality control of various plasma derived productsas per Indianpharmacopoeia[16] are in Table 1.

Not of Standard Quality Product Batches

During the period of 2010–2022, 5159 batches of blood products were evaluated for quality and their certificates of analysis were issued. During this period, 95 batches of blood products were found 'not of standard quality (NSQ)' which constituted 1.84% of the total number of batches data shown in Figure 2. The reports of NSQ batches are sent to state as well as central drug authorities so that these must not enter to the Indian market. The regulation of imported blood products from different countries is compulsory. The purpose of quality control regulations for these products is not only to test the quality but also to improve the product's global standards.

The Government of India has started the "Make in India" mission to promote and accelerate indigenous manufacturing. But during period of last seven years only 40% of blood products are manufactured in India rest of these products (60%) are imported from other countries. Blood products are expensive and fall under the "critical" category. Presently, only the blood products laboratory at the National Institute of Biologicals, Noida is carrying out the quality evaluation of finished blood products in terms of 'standard quality' or 'not standard quality' for batch release in the Indian market for human use.

Monitoring of the Quality Control Performance of the Laboratory

Proficiency testing (PT) and external quality assurance scheme (EQAS) are the backbones of the quality management system in the quality testing laboratories. The Blood Products Laboratory is monitoring the quality control procedures through participation in various Proficiency Testing (PT) studies organized by the European Directorate for the Quality of Medicines and HealthCare (EDQM), France and by internal quality control checks (IQC).

Internal Quality Control: The laboratory monitors quality procedures from time to time by Internal Quality Control check on a quarterly basis (data not shown). In this method trend analysis of results of international reference standard or secondary reference standard of in-house control is done. For a successful IQC, there should not be any significant shift in the trend.

PT: Our laboratory is regularly participates in the following proficiency testing schemes which was organized by EDQM, France.

- PTS 146 - Potency Assay in human coagulation factor VIII
- PTS 164 - Fibrinogen and thrombin potency assay in fibrin sealant kit (FSK)
- PTS 201 – Protein composition in immunoglobulin
- PTS 202 – Molecular size distribution in immunoglobulin

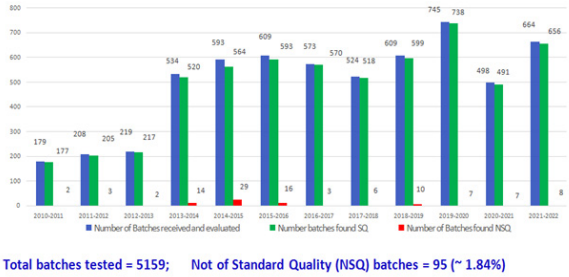

Figure 2: Quality evaluation of various blood products at NIB.

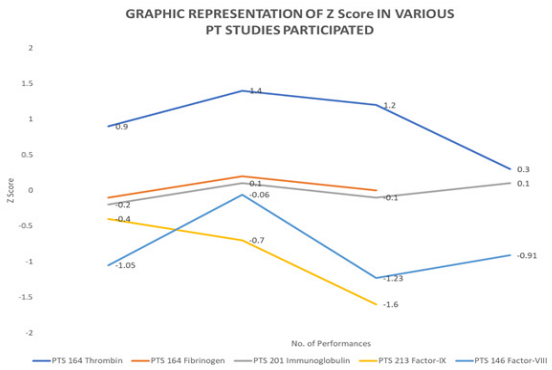

Figure3: Graphic representation of Z scorereceived by laboratory for PT studies

- PTS 213 – Potency assay in human coagulation factor IX
- PTS224 - Determination of total protein in Immunoglobulins
- PTS234 - Determination of molecular size distribution in human albumin

Since, the start of participation, the performance of the laboratory has continuously been satisfactory in all schemes. The graphic representation of Z score received for some PT schemes (where applicable) is shown in Figure 2.

Participation in Inter Laboratory Collaborative Studies for the Development of International and National Standards

Our laboratory has participated in collaborative studies organized by NIBSC, UK for the establishment of 3rd WHO international standards for Thrombin and 3rd WHO international standards for rabies immunoglobulin.

The laboratory has been part of the collaborative study for the establishment of the first national human insulin reference standard, which was organized by the National Institute of Biologicals, Noida and it was released by Indian Pharmacopoeia commission as Indian Pharmacopoeia Reference Standard (IPRS).

CONCLUSION

The NIB Blood Products Laboratory assessed 5159 lots of blood products for quality standards. These groups include groups of imported and domestically produced blood products for the period 2010–2022. Of these 60% of products imported from different countries of the world, only 40% of the products

are local products. During the QC evaluation of the product, the laboratory found 95 lots of products (i.e., 1.84%) did not meet quality standards, and the remainder met quality standards. If a substandard product is marketed and used by users for the treatment of patients, it can lead to serious health problems and the patient may even die. Therefore, quality standards and guarantees for these blood medicines are absolutely necessary, without exception. There is also a need to ensure that a single drug enters the market without the assurance of quality standards to ensure the high quality, efficacy and safety parameters of the drugs in the market.

The government of India can also initiate a standard pharmaceutical quality assurance awareness policy/system by affixing a "Passed QC" mark on every primary package of drug/drug before it enters the market. NRAs should establish appropriate national/secondary standard reference materials and perform calibration against international reference standards to improve harmonization. It may be available to Indian manufacturers and National Control Laboratories (NCL).

Post-marketing Surveillance

Countries should establish national-level policies/systems for post-marketing surveillance of biological products in phase 4 (Drugs and Cosmetics Act) clinical trials. Clinicians, healthcare professionals and healthcare professionals should be strongly encouraged to report unexpected adverse events that occur in patients after taking these plasma-derived medicinal products to the NRA (CDSCO) and the manufacturer.

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