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EDITORIAL OPEN ACCESS

Regulatory systems for blood and blood components: What about effectiveness?

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Regulatory systems

Regulatory systems play a key role in assuring quality, safety, and efficacy of medical products, preventing unauthorized deviations and malpractices. Effective regulatory systems are an essential component of health systems including the integrated blood supply system, and contribute to desired public health outcomes, patient safety through elimination of avoidable harm, and innovation [1]. They consist of

1. a framework legislation anchoring the principles and essential or key elements;
2. flexible regulations spelling out the technical and quality details of the key elements;
3. a national regulatory authority (NRA) mandated by the law to oversee, inspect, license and document the observations.

In 1997 WHO began assessing regulatory systems using a set of indicators designed to evaluate the regulatory program for vaccines. Since then, a series of tools and revisions were introduced. In 2014 following the WHA Resolution 67.20 on *Regulatory system strengthening for medical products* [2], work began on the development of a unified tool for evaluation of medicines and vaccines regulatory programs following a mapping of existing tools in use within and external to WHO. This resulted in the Global Benchmarking Tool (GBT) [3] which represents the primary means by which to evaluate objectively regulatory systems, as mandated by the May 2014 WHA Resolution 67.20. The tool and benchmarking methodology enables the NRA to:

- identify strengths and areas for improvement;
- facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps;
- prioritize IDP interventions;
- monitor and evaluate progress and achievements.

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Since 2019 the GBT is eligible to benchmark the regulatory systems for medicines, vaccines, and blood products (GBT+Blood) including whole blood, blood component, and plasma derived medicinal products (PDMP) [4]. It should be noted that, considering different product streams (e.g., medicines and vaccines as compared to blood products), criteria included in the GBT remain the same with additional criteria specifically allocated for blood products acknowledging its particularities (e.g., hemovigilance).

The 2019 Global Benchmarking Tool (GBT+Blood) Revision VI+ version is the latest release for benchmarking of blood and blood products within national regulatory systems [4]. This GBT+Blood consists of ten (10) regulatory functions under the overarching framework of the national regulatory system (RS):

National regulatory systems (RS)

1. Registration and Marketing Authorization (MA)
2. Vigilance (VL)
3. Market Surveillance and Control (MC)
4. Licensing Establishments (LI)
5. Regulatory Inspection (RI)
6. Laboratory Testing (LT)
7. Clinical Trials Oversight (CT)
8. NRA Lot Release (LR)
9. Approval of blood and blood components, including plasma for fractionation (product and/or process approval) (AB)
10. Regulatory oversight of associated substances and medical devices including *in vitro* diagnostics (RM)

Tool and function number 10 on *Approval of blood and blood components, including plasma for fractionation (product and/or process approval) (AB)* represents the basic indicators or criteria, critical for granting a blood establishment a procurement license, irrespective of the country's state of development [5].

Approval refers to a procedure to determine the safety, efficacy, and quality of the blood and blood products, and the appropriateness of the "product

information" for the consumer. The objective of this regulatory function is to provide a system that ensures that only blood and blood products that have been duly authorized by the NRA are allowed to be manufactured, imported, distributed, sold, or supplied to end-users (hospital with prescribing clinicians and patients in need). The process of assessment for AB includes the review of quality, safety, and efficacy data submitted by the applicant. The same standards should be applied to imported and locally manufactured blood and blood components. There are 8 indicators and 25 sub-indicators for approval.

Mechanisms and procedures should be in place to monitor and ensure that all activities within the approval function for blood and blood components, including plasma for fractionation, are checked to reduce and prevent errors and to reasonably ensure that the processes are consistent and will provide assurance of quality products. Such approaches would lead to consistency in the performance of the approval regulatory function for blood and blood components, including plasma for fractionation, and to reliability of the regulatory approval process.

How about effectiveness?

WHO designed the GBT+Blood [4] to evaluate the overarching regulatory framework and the component regulatory functions (e.g., vigilance, clinical trial oversight) through a series of sub-indicators that may also be grouped and examined according to the cross-cutting categories or themes, for example, quality and risk management system. For each sub-indicator a fact sheet has been developed to guide the benchmarking NRA team and ensure consistency in the evaluation, documentation, and rating of the sub-indicator.

The GBT+Blood also incorporates the concept of "maturity level" or ML (adapted from ISO 9004), allowing regulatory authorities and WHO to assess the overall "maturity" or completeness of the regulatory system on a scale of 1 (existence of some elements of regulatory system) to 4 (operating at advanced level of performance and continuous improvement).

To facilitate the benchmarking, the tool is supported by a computerized platform including the calculation of maturity levels. This opens the door to artificial intelligence through big data and deep learning both at country and global level.

Why this editorial?

Looking at the scopes of a random selection of international Transfusion Medicine scientific journals I found the following:

- The scope of this journal (*IJBTI*) is supposed to cover all aspects of transfusion medicine including blood transfusion, immunohematology, immunogenetics, histocompatibility, tissue transplantation and hematopoietic, cellular, and gene therapies, related molecular biology and biotechnology and medico-legal aspects.[1]
- The *Journal of Blood Transfusion* publishes on all topics related to Transfusion Medicine, e.g., transfusion clinical practice, immunohematology, blood component collection and production, transfusion-transmissible diseases, immunogenetics, histocompatibility, transplantation, hemostasis, medical-legal correlations, biotechnology, and connected molecular biology.
- *Transfusion Medicine* publishes articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohematology, immunogenetics, histocompatibility, medico-legal applications, and related molecular biology and biotechnology.
- *Vox Sanguinis* reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies.
- *TRANSFUSION* reports on the latest technical advances, discusses opposing viewpoints regarding controversial issues, and presents key conference proceedings. In addition to blood banking and transfusion medicine topics, it presents submissions concerning patient blood management, tissue transplantation and hematopoietic, cellular, and gene therapies.
- The *Global Journal of Transfusion Medicine* intends to cover technical, ethical, clinical, administrative, and legal issues pertaining to the field of Transfusion Medicine and allied branches inclusive of voluntary blood donor motivation, immunohematology, transfusion transmissible infections, human leukocyte antigen (HLA) immunobiology, transplant immunology, therapeutic aphaeresis, regenerative medicine and cell therapy, besides bone marrow and solid organ transplantation, cryobiology, and molecular biology.

This interesting, though limited review of journal scopes, learns that in general the scientific attention and attraction is in the technical core business field, with only one journal listing the broader "administrative and legal issues" fundament to the institutions and sustainable operational practices of Transfusion Medicine. Administrative issues include governance and stewardship, legal issues pertain to the legislative and regulatory systems [6–8].

Now that WHO has included the procurement of blood and blood products in the GBT system as an important tool to support countries in achieving Universal Health Coverage (UHC) [9] by 2030, the changing tide urges us

[1]Medico-legal aspects relate to, e.g., informed consent, liability, personal injury, and consumer rights protection.

to include these fundamental issues in the scope of the journal and encourage the readership to study, learn, understand, implement, document, and publish on the importance and impact of appropriate regulatory systems on the effectiveness and quality of the blood supply and clinical consumption as integral elements of the healthcare system [10].

ABBREVIATIONS

AB	Approval of Blood and Blood Components including Plasma for Fractionation (Product and/or Process Approval)
CT	Clinical Trials Oversight
GBT	Global Benchmarking Tool
HLA	human leukocyte antigen
IDP	Institutional Development Plan
ISO	International Standardization Organization
LI	Licensing Establishments
LR	NRA Lot Release
LT	Laboratory Testing
MA	Marketing Authorization
MC	Market Surveillance and Control
ML	Maturity Level
NRA	National Regulatory Authority
PDMP	Plasma Derived Medicinal Product
RI	Regulatory Inspection
RM	Regulatory Oversight of Associated Substances and Medical Devices including *in vitro* Diagnostics
RS	Regulatory System
TM	Transfusion Medicine
UHC	Universal Health Coverage
VL	Vigilance
WHA	World Health Assembly
WHO	World Health Organization

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Author Contributions

Cees Th. Smit Sibinga – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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