24. The Network's products are disseminated with appropriate disclaimers, including that the content does not necessarily reflect the views or stated policy of the participating regulatory authorities, organizations, agencies and institutions (including WHO, acting as the Secretariat for the Network). A clarification of the nature of the proposals/recommendations put forward in such Network documents will be included along the following lines: "The name of the Network, including its Members and other participants may not be used for or in connection with commercial or promotional purposes".

G. Financing of, and fundraising for operation of the Network (including the WHO Secretariat support)

25. Members and Invited Experts are, in principle, responsible for meeting their own expenses in relation to the Network (including, but not limited to, travel and subsistence for the attendance of meetings). Subject to the availability of funds, the Members may decide to support the participation of other country organizations or agencies, individuals, and/or of Invited Experts.

26. The WHO Secretariat support and related day to day operations of the Network are financed by WHO. In addition, WHO may raise and accept funds from other sources to support the work of the Network, in accordance with WHO's established rules, regulations and administrative practices.

H. Miscellaneous

27. Amendments. These Terms of Reference may be modified in writing by consensus of all Members and with the endorsement of WHO.

***

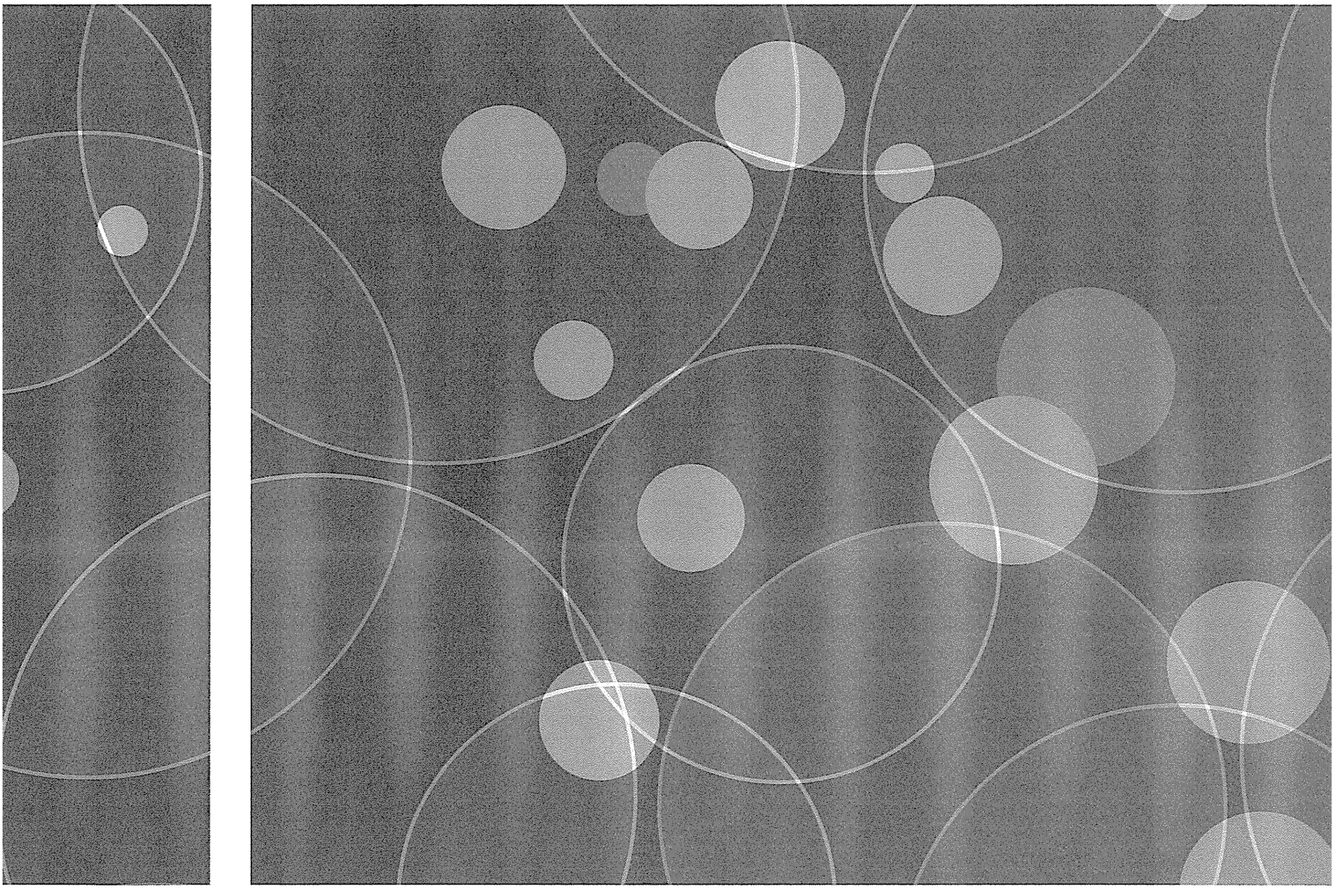
Annex

WHO Blood Regulators Network List of Members

The following agencies are Members of the BRN (in alphabetical order of countries):

Therapeutic Goods Administration (TGA), Australia
Health Canada, Canada
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), France
Paul-Ehrlich-Institut, Germany
Ministry of Health, Labour and Welfare (MHLW), Japan
Swissmedic, Switzerland
Food and Drug Administration (FDA), USA

ASSESSMENT CRITERIA FOR NATIONAL BLOOD REGULATORY SYSTEMS



World Health Organization

ASSESSMENT CRITERIA FOR
NATIONAL BLOOD REGULATORY SYSTEMS

World Health Organization

The assessment criteria for national blood regulatory systems were adopted by the WHO Expert Committee on Biological Standardization at its sixty-second meeting, held in Geneva from 17 to 21 October 2011. The document contains the collective views of the WHO Blood Regulators Network. It was developed in response to a request from WHO and the International Conference of Drug Regulatory Authorities for an assessment tool to assist capacity building of national regulatory authorities for the regulation of blood and blood products.

The tool is intended to help Member States to identify gaps and priorities when developing capacity building programmes, and support the introduction of regulation of blood products. Establishment of such regulation was recommended in the 2010 World Health Assembly resolution (WHA63.12) on the availability, quality and safety of blood products.

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Authors and Acknowledgements

The drafting group was formed of Members of the WHO Blood Regulators Network (BRN) and the WHO Blood Products and Related Biologicals programme, Quality Assurance and Safety: Medicines, World Health Organization:

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Existing WHO evaluation templates for vaccines and medicinal products were consulted in developing this tool. The first consolidated draft was discussed at the Blood and Blood Products Workshop of the 14th International Conference of Drug Regulatory Authorities (ICDRA), Singapore, 2010, where it was supported for consideration by WHO Member States. Over 90 national regulatory agencies were represented in the Conference.

Through a global consultation process involving all WHO regions, regulators were encouraged to contribute their self-assessments and comments on the usefulness of the tool to help towards its finalization. Thanks are due to the WHO Regional Offices for their support in this process.

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Abbreviations

AE	adverse event
AR	adverse reaction
BRN	WHO Blood Regulators Network
ECBS	WHO Expert Committee on Biological Standardization
GCP	good clinical practice
GDP	good distribution practice
GMP	good manufacturing practice
ICDRA	International Conference of Drug Regulatory Authorities
NCL	national control laboratory
NRA	national regulatory authority
QMS	quality management system
SOP	standard operating procedure
SPC	summary of product characteristics

Glossary

The WHO Expert Committee on Biological Standardization adopted the following definitions for the purpose of this report.

Approval
A decision to authorize marketing of a drug by a national regulatory authority. The mechanism by which a regulatory authority ensures that there is compliance with regulatory requirements and standards that assure quality, safety and efficacy for all blood products and/or processes and establishments involved in collecting blood donations and/or manufacturing blood products. A regulatory approval is generally a precondition for marketing of a blood product.

Associated medical devices
All devices involved in donor testing and/or manufacturing activities.

Associated substances and materials
All substances or materials involved in manufacturing of blood products, including anticoagulants, additive solutions and storage solutions. These materials are regulated as drugs in some jurisdictions.

Blood component[1]
A constituent of blood (erythrocytes, leukocytes, platelets, cryoprecipitate and plasma) that can be prepared by various separation methods and under such conditions can be used either directly for therapeutic purposes or for further processing or manufacturing.

Blood establishment
Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components when intended for transfusion or further industrial manufacturing.

Blood product
Any therapeutic substance derived from human blood, including whole blood, blood components and plasma-derived medicinal products.

Core function
A specific function through which the regulatory system assures quality, safety and efficacy of blood products.

Distributor
Any facility that engages in distribution, including storage, importation or exportation of blood products, which may include wholesalers.

Essential element
A basic characteristic of a regulatory system as a whole (such as a legal basis for its activities, enforcement power, independence of the regulator from the regulated parties etc.), which is fundamentally related to the system's ability to effectively ensure quality, safety and efficacy of blood products.

Good clinical practice (GCP)
A standard for the design, conduct, performance, monitoring, auditing, recording, analysing and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

1 Stem cells may or may not be included in the scope of the regulatory activity of the competent authority for blood and blood products. Similar criteria for safety, quality and efficacy should be met as for blood and blood components.

Good distribution practice (GDP)
The part of quality assurance that ensures the quality of a pharmaceutical product is maintained by means of adequate control of all activities which occur throughout the distribution process.

Good manufacturing practice (GMP)
All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations.

Legislation
A legal instrument of government that defines laws which govern a particular subject matter, e.g. regulation of quality, safety and efficacy of medicines. Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms (see also Regulations).

Licensing
Authorization by the national regulatory authority for the manufacture, importation, exportation, or distribution of medical products.

Manufacturer
Any natural or legal person (structure, facility or body) with responsibility for any aspect of the following activities in relation to blood products: collection, testing, processing, storage, packaging, labelling, release, and/or distribution.

National regulatory authority (NRA)
National regulatory authorities (also called national medicines regulatory authorities) are legally-established bodies that promulgate medicines regulations and enforce them.

Plasma-derived medicinal product
Any therapeutic product derived from human plasma and produced by an industrial-scale manufacturing process that pools multiple units. Also called plasma derivatives or plasma-derived products.

Quality management system (QMS)
A management system that directs and controls an organization with respect to quality, and that ensures that steps, processes, procedures and policies related to quality activities are being followed.

Registration
A procedure under which information regarding the identification, location(s) and scope of activities of all parties involved in manufacturing or supplying a medicinal product and associated medical devices and substances is submitted to the regulatory authority in order to comply with administrative requirements before starting, continuing or amending relevant activities.

Regulations
Legislative instruments of government that provide more prescriptive information regarding compliance with relevant legislation. Regulations are specifically designed to provide the legal framework and details necessary to achieve the administrative and technical goals of legislation.

Standard operating procedure (SOP)
Defines a prescriptive document that outlines how an activity is carried out.

Sponsor
An individual, company, institution or organization that takes responsibility for the initiation, management and/or financing of a drug submission or clinical trial.

Vigilance
A mechanism of oversight involving an organized system for gathering safety information. This term encompasses pharmacovigilance, haemovigilance and materiovigilance.

Introduction

Blood transfusion is an indispensable, potentially life-saving medical intervention, and blood products such as clotting factors and some immunoglobulins are designated by WHO as essential medicines. However, the inherent risks of blood and the complexity of providing adequate, timely and equitable access to safe blood products require an organized national or regional blood regulatory system. Within that system, a competent blood products regulatory authority assures that appropriate standards are met for production of blood products and monitoring of blood safety. Consequently, as a pillar for the establishment of safe blood programmes globally, WHO has advocated for the establishment and sustenance of strong national regulatory authorities (NRAs) both in developed and developing countries.

In 2010, in resolution WHA63.12, the World Health Assembly expressed its concern about the unequal access globally to blood products, particularly plasma-derived products, leaving many patients without needed transfusions and many of those with severe congenital and acquired disorders without adequate plasma-derived treatments. In this resolution, the World Health Assembly urged Member States "to take all the necessary steps to update their national regulations on donor assessment and deferral, the collection, testing, processing, storage, transportation and use of blood products, and operation of regulatory authorities in order to ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards."

Purpose and application of the document

The purpose of this document is to provide a tool to assist capacity building of national regulatory authorities (NRAs) for the regulation of blood and blood products. Ancillary to the existence of NRAs to regulate activities assuring the provision of safe blood products, there is currently a need to develop criteria defining best practices or attributes of national blood regulatory systems globally for activities related to regulation of blood products. This document provides a description of elements and functions which may support the creation of an appropriate blood regulatory system where none exists so far, and which may also be used as a tool to assess strengths and gaps of established systems. For both developed and developing countries, an assessment tool that reflects international best practices in blood regulation could serve to highlight strengths of the NRA while identifying gaps or areas for future development. In addition, adoption of global criteria by NRAs could promote international convergence of regulations, which can have a beneficial impact on global safety and availability of blood products.

To promote these objectives, this document identifies the essential elements and core regulatory functions that should be present in an effective NRA to assure the quality, safety and efficacy of blood and blood products, as well as associated substances and medical devices including in vitro diagnostics. Additionally, this document provides major criteria, indicators and associated ratings for the essential elements and core functions that are intended to help NRAs assess their performance in the regulation of blood and blood products and prioritize efforts to address any gaps that are identified.

Understanding and use of the document

To achieve the aim of an international best practice national blood regulatory framework, a set of integrated general and specific regulatory functions have been identified that are applicable to all aspects of blood product regulation, from the collection of source material through to the quality control of the final product, and covering not only blood products but also associated substances and medical devices, including in vitro diagnostics. Section A of this document identifies essential elements that are necessary to establish the legal basis, authority and general characteristics of the NRA. Section B identifies specific core functions of the NRA that are necessary for comprehensive oversight of blood products, related substances and medical devices. It is recognized that the functions may be interdependent and that in some countries the specific functions captured in this document may not be within the scope of one national blood regulatory authority but may be captured by other national authorities or other acceptable mechanisms to achieve compliance to the assessment criteria. Some regulatory functions may be applicable regardless of the intended use of the blood (e.g. for transfusion purposes or for further manufacturing use). However, regulatory structures should be designed in such a way as to avoid fragmentation and uncoordinated delegation.

This document provides the main criteria and indicators for each essential element and core function. The criteria and indicators provide a framework that will identify areas for improvement to governments, particularly in developing countries. A self-assessment or external assessment process using these criteria could also serve as a useful means to highlight strengths of NRA programmes for regulation of blood products while identifying gaps or areas for future development. National authorities are encouraged to use the assessment criteria as a roadmap towards evolving a best practice blood regulatory system.

It is recognized that many national blood regulatory systems will not be able to meet all the criteria and indicators listed in this document. The criteria and indicators are therefore organized into those considered as being required (R) and thus necessary in order to be effective as a blood regulator, and those that are considered as being desirable or suggested (S) to achieve a blood regulatory system of international best practice.

It is also recognized that single required criteria may not formally be fulfilled even by regulators with proven effectiveness, but that underlying relevant safety issues can be met by other means. This offers the opportunity to compare different ways of ensuring safety of blood products and points out areas where refinement of the assessment criteria may need to be considered.

With experiences gained, future versions of these assessment criteria are expected to better accommodate effective alternatives, or may suggest the need for additional guidance, such as for prioritization of efforts.

Section A. Essential elements

1. National regulatory system

Applicable to blood, blood components, plasma-derived medicinal products, associated substances, and medical devices including in vitro diagnostics

Main criteria related to the element	Rating*		Indicators related to the main criteria	
	Main criteria	Indicator		
1.1. A comprehensive legal (statutory) basis exists for establishment of a regulatory system applicable to blood, blood components, plasma-derived products, associated substances, and medical devices including in vitro diagnostics.	R	R	1.1.1.	Provisions for the main regulatory functions can be identified and are up to date.
		R	1.1.2.	The regulations or their adaptations take into consideration developments in the field of blood and related technologies.
		R	1.1.3.	Regulations have been established and are available; they are intelligible to those that need to comply with or enforce them, and the ways of communication used are adequate.
		R	1.1.4.	Legislation exists that defines therapeutic products for human use to be regulated, and establishes standards of quality, safety and efficacy for: a. blood, blood components and plasma-derived products; b. associated substances and medical devices including in vitro diagnostics.
		R	1.1.5.	Legislation exists that provides a legal basis for the responsible NRA to perform the essential functions.
		R	1.1.6.	Legislation enables the appropriate institutions to issue regulations.
		S	1.1.7.	The development of regulations includes the opportunity for public consultation.
1.2. The legislation assigns the enforcement of regulations regarding the products covered in 1.1 to one or more responsible regulatory authorities.	R	R	1.2.1.	The competent authorities involved in the regulatory system for blood, blood components, plasma-derived products, associated substances, and medical devices including in vitro diagnostics are clearly identified and can be named for each of the regulatory functions.
		R	1.2.2.	The responsibilities, functions and the organization of each of these authorities are clearly defined, in particular as regards the scope of the regulation (regulatory functions) they have under their control.
		R	1.2.3.	The activities of the various authorities involved are coordinated and supervised by an administrative mechanism.

* R=required; S=suggested

2. National regulatory authority

Applicable to blood, blood components, plasma-derived medicinal products, associated substances, and medical devices including in vitro diagnostics

Main criteria related to the element	Rating*		Indicators related to the main criteria
	Main criteria	Indicator	
2.1. There is independence of the regulatory authority in decision-making.	R	R	2.1.1. A clear division of roles and responsibilities is implemented between the NRA, blood establishments, manufacturers and distributors, reflecting independence of the regulatory system.
		R	2.1.2. Accountabilities for decision-making are clear.
		R	2.1.3. Internal policy on potential conflicts of interest for staff exists.
		R	2.1.4. NRA management and assessment activities (including use of expert committees) never include representatives from manufacturers or licence holders.
		R	2.1.5. A code of conduct for regulatory staff exists.
		S	2.1.6. Written procedures for meetings with manufacturers, distributors and other sponsors exist.
2.2. The NRA has established an institutional development plan.	S	S	2.2.1. The NRA has an institutional development plan, which is implemented and updated.
		S	2.2.2. The development plan includes: vision; strategic objectives; timeline and deadline for target implementation; indicators; functions and/or duties of the NRA; ongoing staff training plan; resources needed; information and/or communication strategy; and a human resource development plan.
		S	2.2.3. Performance indicators are established and used for monitoring attainment of objectives.

2. National regulatory authority

Applicable to blood, blood components, plasma-derived medicinal products, associated substances, and medical devices including in vitro diagnostics

Main criteria related to the element	Rating*		Indicators related to the main criteria
	Main criteria	Indicator	
2.3. The NRA has adequate resources to carry out its functions properly and to enforce regulatory functions.	R	R	2.3.1. An adequate number of trained staff and budgetary provisions exist for all essential functions.
		R	2.3.2. All staff members have appropriate qualifications to conduct regulatory activities and are provided with timely, relevant and regularly updated training.
		R	2.3.3. Tasks and responsibilities of staff members are well defined.
		R	2.3.4. Mechanisms are in place to ensure that those performing regulatory functions have sufficient and current expertise in specialized areas.
		R	2.3.5. Policies and procedures exist for recruitment and selection of external experts and the management of expert advisory committees, including potential conflict of interest.
		R	2.3.6. An agreement between the NRA and external experts defining roles and responsibilities is established.
		S	2.3.7. The sources of funding of the responsible authorities performing regulatory functions are defined.
		S	2.3.8. Written criteria for selection and recruitment of regulatory staff are defined.

2. National regulatory authority

Applicable to blood, blood components, plasma-derived medicinal products, associated substances, and medical devices including in vitro diagnostics

Main criteria related to the element	Rating*		Indicators related to the main criteria
	Main criteria	Indicator	
2.4. A quality management system (QMS) is in place.	S	S	2.4.1. A QMS is implemented by the NRA for all its core functions as specified below.
		S	2.4.2. Budgetary provisions are made for implementation and maintenance of the QMS.
		S	2.4.3. A qualified quality manager is designated as responsible for the implementation of the QMS.
		S	2.4.4. The documentation needed to establish, implement and maintain the QMS is defined (quality manual, SOPs, etc.).
		S	2.4.5. The QMS is based on recognized international standards.
		S	2.4.6. The QMS is certified or accredited by external bodies.
		S	2.4.7. An internal and external audit and review system exists as well as evidence that corrective and preventive actions are taken as a result of monitoring and/or audits.
2.5. Transparency and accountability are ensured.	R	R	2.5.1. Legally-specified, confidential and trade secret information is available for internal use and decision-making. However, all other information is publicly available and kept up to date.
		R	2.5.2. Listing of authorized products and companies is made available where needed.
		R	2.5.3. Information on sanctions, recalls and public health warnings is publicly available.
		S	2.5.4. Information on decisions is available and easily accessible to the public and includes negative decisions in selected cases (may vary depending on national regulation).
		S	2.5.5. An opportunity for interaction between the NRA and stakeholders is given.

* R=required; S=suggested

3. Licensing and/or registration of blood establishments

Applicable to blood and blood components including plasma for fractionation

Main criteria related to the function	Rating*		Indicators related to the main criteria	
	Main criteria	Indicator		
3.1. Legislative authority exists to require registration and/or licensing of blood establishments, and for enforcement power.	R	R	3.1.1.	Legislation and/or regulation exist that require a blood establishment that intends to collect, test, process, store, manufacture, distribute, import or export blood and blood components to be authorized, accredited, registered or licensed by the designated NRA.
		R	3.1.2.	The NRA has the authority to take regulatory action (e.g. revoke, suspend the licence) if the establishment does not comply with regulatory requirements.
3.2. A licensing and/or registration system is established and operational for blood establishments.	R	R	3.2.1.	Activities that are decentralized or delegated to other agencies or authorities follow the standards, guidelines and procedures as agreed by the central regulatory authority, and a reporting mechanism is established between the responsible authorities.
		R	3.2.2.	Required registration and/or licence applications are assessed by the NRA based on written guidelines.
		R	3.2.3.	A list of all licensed and/or registered blood establishments is maintained and made available where needed.
		R	3.2.4.	Advice for applicants is available on the content, format, requirements and procedures to follow in order to submit a required registration and/or application for an establishment licence.
		S	3.2.5.	Facility documentation (e.g. site master file, qualification of a responsible person) is submitted as part of a required registration and/or application for an establishment licence and is assessed to demonstrate that the facility is suitable for the activities to be performed (e.g. blood collection, donor screening, testing, storage, etc.).
		S	3.2.6.	Renewal periods for an establishment licence and/or registration are defined and consistent with mechanisms of surveillance.

3. Licensing and/or registration of blood establishments

Applicable to blood and blood components including plasma for fractionation

Main criteria related to the function	Rating*		Indicators related to the main criteria
	Main criteria	Indicator	
3.3. Significant changes to an establishment licence and/or registration are submitted and assessed by the NRA prior to implementation.	R	R	3.3.1. Changes are assessed based on the type of change.
		S	3.3.2. Written guidelines for applicants are available that define the types and scopes of changes and documentation required.
3.4. Compliance with the principles of good manufacturing practice (GMP) is assessed as part of the establishment licensing and/or registration process.	R	R	3.4.1. Compliance with applicable principles of GMP is a condition for maintaining an establishment licence and/or registration and for approval of significant changes.
		R	3.4.2. National GMP and good distribution practice (GDP) principles are published and are consistent with or based on recognized standards for the manufacturing and distribution of blood and blood components.
		R	3.4.3. Periodic inspections according to GMP and GDP principles are carried out for supervision of blood establishments. For inspections carried out abroad: a. there is an agreement with other NRA's for exchange of inspection reports and/or certificates; or b. a list of reference countries and/or agencies whose certificates and decisions are accepted exist; or c. site inspections are carried out abroad.
3.5. QMS requirements are established for all functions performed by blood establishments.	R	R	3.5.1. The essential components for a QMS are covered.