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Geneva, 17 to 21 October 2011**

**Assessment Criteria for
National Blood Regulatory Systems**

NOTE: This document has been prepared for the purpose of inviting comments on the proposals contained therein, and for the preparation of the materials to be considered by the Expert Committee on Biological Standardization at their next Meeting on 17-21 October 2011. **The text in its present form does not represent an agreed formulation of the Expert Committee. Comments proposing modifications to this text MUST be received by 1 October 2011** and should be addressed electronically to the attention of Dr Ana Padilla (e-mail address: padillaa@who.int) Blood Products and related Biologicals Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland.

The outcome of the deliberations of the Expert Committee will be published in the WHO website (www.who.int/bloodproducts). The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/KMS/WHP/09.1).

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Assessment Criteria for National Blood Regulatory Systems

This document contains the collective views of members of the WHO Blood Regulators Network (BRN)*. Its development responds to the request from WHO and the International Conference of Drug Regulatory Authorities (ICDRA) for an assessment tool to assist capacity building of national regulatory authorities for blood and blood products. Initial drafting of the tool began in 2008 taking into consideration pre-existing WHO evaluation templates for vaccines and medicinal products. Pilot self assessments were undertaken by Health Canada and Swissmedic in 2009-10 to support preparation of the assessment criteria. Modifications were introduced following this pilot phase and the consensus views of the members of the BRN are now presented. The document does not necessarily represent decisions or the stated policies of the participating regulatory authorities nor from any other parties.

Regulators will be encouraged to contribute with their self-assessments and comments to inform about the usefulness of the tool and help towards its finalization and discussion at the Meeting of the WHO Expert Committee on Biological Standardization, on 17 to 21 October 2011. It is expected the tool will help to identify gaps and main priorities on which capacity building programs may be developed to support introduction of blood products regulations at global level and to sustain development of the WHA Resolution 63.12 on availability, quality and safety of blood products.

***WHO Blood Regulators Network (BRN)**

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This document was agreed by the BRN on November 12, 2010

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Glossary and abbreviations

Associated medical devices

All devices involved in donor testing and manufacturing activities

Associated substances and materials

Include additive solutions such as anticoagulants and storage solutions. These materials are regulated as drugs in some jurisdictions

Blood component

Any therapeutic constituent of blood that is separated by physical or mechanical means (e.g. red cells, white cells, platelets, plasma). The term blood component is not intended to capture plasma derived products.

Blood establishment

Any structure, facility or body that performs any aspect of the following activities in relation to blood and blood components: collection, testing, processing, storage, packaging/labelling, release, and/or distribution.

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 and safety of blood products

Distributor

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

Essential function

A basic and general function of a regulatory system as a whole (such as a legal basis for its activities, enforcement power, independency of the regulator from the regulated parties etc), this function is fundamentally related to the systems ability to effectively ensure quality, safety and efficacy of blood products

Manufacturer of plasma derived products

Any facility that engages in processing or manufacturing of products derived from human plasma.

National Regulatory Authority (NRA)

WHO terminology for referring to national medicines regulatory authorities. NRA's should promulgate medicines regulations and enforce them.

Derived products

Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units (usually more than 12). Also called plasma derivatives or plasma-derived medicinal products

SOP

Standard Operating Procedure

Vigilance This term encompasses pharmacovigilance, hemovigilance and materiovigilance.

Assessment Criteria for National Blood Regulatory Systems

Introduction

As a pillar for the establishment of safe blood programs globally, WHO has advocated for the establishment and sustenance of strong National Regulatory Authorities (NRA's) both in developed and developing countries.

Ancillary to the existence of NRA's 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 as concerns activities related to regulation of blood products.

In its resolution WHA63.12, the World Health Assembly (WHA) recently 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, WHA urges 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

To achieve the aim of an international best practice national blood regulatory framework the WHO Blood Regulators Network (BRN) has identified a set of integrated general and specific regulatory functions applicable to the collection of source material through to the quality control of the final product, not only covering blood products but also associated substances and medical devices such as in vitro diagnostics (IVD's). It is recognised 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.

The document provides main criteria and indicators for each of these regulatory functions. It is felt that the criteria and indicators provide a framework which will identify areas for improvement to governments particularly in developing countries. A self assessment or external assessment process using these criteria could serve as a useful means to highlight strengths of NRA programs for regulation of blood products whilst 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 recognised 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 organised into those that are 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 blood regulatory system of international best practice.

Rating of main criteria and indicators: R= required; S= suggested

It is also recognised, that single required criteria may not formally be fulfilled even by regulators with proven effectiveness, whereas the underlying relevant safety issue is 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 comes into consideration.

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

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Section A

| 1.0 Essential function: National regulatory system | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 1.1. A comprehensive legal (statutory) basis for establishment of a regulatory system applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics, exists. | 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 its adaptations take into consideration the developing state of the art. | |
| | | R | 1.1.3. Regulations have been established and are available, and they are intelligible to those that need to comply with/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: <ul style="list-style-type: none"> 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. | |

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| | | S | 1.1.7. The development of regulations includes opportunity for input by all interested parties. | |
| 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 and 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. | |
| | | S | 1.2.3. The activities of the various authorities involved are coordinated by an administrative mechanism. | |

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| 2.0 Essential function: National regulatory authority | | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Rating | Comments |
| | Main criteria | indicator | | |
| 2.1. Independence of the regulatory authority in decision making | R | R | 2.1.1. Clear division of roles and responsibilities between NRA and blood establishments/manufacturers/distributors (industry), reflecting independence of the regulatory system is implemented | |
| | | 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 manufacturer's or license holder's representatives. | |
| | | R | 2.1.5. Code of conduct for regulatory staff exists. | |
| | | S | 2.1.6. Written procedures for meetings with sponsors exist. | |
| 2.2. NRA has established an institutional development plan. | S | S | 2.2.1. NRA has an institutional development plan, which is implemented and updated. | |
| | | S | 2.2.2. Development plan includes: vision, strategic objectives, timeline/deadline for target/implementation, indicators, functions/duties of NRA, ongoing staff training plan, resources needed, information/communication strategy, human resource development plan. | |

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| | | S | 2.2.3. Performance indicators established and used for monitoring attainment of objectives. | |
| 2.3. Adequate resources to carry out its functions properly and to enforce regulatory functions exist. | R | R | 2.3.1. Adequate number of trained staff and budgetary provisions exist for all essential functions. | |
| | | R | 2.3.2. All staff has appropriate qualifications to conduct regulatory activities and is provided with timely, relevant and regularly updated training. | |
| | | R | 2.3.3. Mechanisms are in place to ensure that those performing regulatory functions have sufficient and current expertise in specialized areas. | |
| | | R | 2.3.4. Policies and procedures exist for recruitment and selection of external experts and the management of expert advisory committees, including potential conflict of interest. | |
| | | R | 2.3.5. An agreement between the NRA and external experts defining roles and responsibilities is established and signed by both parties. | |
| | | S | 2.3.6. The sources of funding of the responsible authorities to perform its regulatory functions are defined. | |
| | | S | 2.3.7. Written criteria for selection and recruitment of regulatory staff are defined. | |
| 2.4. A Quality management system (QMS) is in place. | S | S | 2.4.1. The NRA has implemented a QMS for all its core functions as specified below. | |
| | | S | 2.4.2. Budgetary provisions are made for implementation/ maintenance of the QMS. | |
| | | S | 2.4.3. A qualified quality manager has been designated as responsible for the implementation of the QMS. | |

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| | | 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 and evidence that corrective and preventive actions are taken as a result of monitoring/audits exist. | |
| 2.5. Transparency and accountability is 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. Opportunity for interaction between NRA and stakeholders is given. | |

| 3.0 Core function: Licensing/registration of blood establishments | | | | |
|------------------------------------------------------------------------------------------------------------------------|---------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <i>Applicable to blood and blood components</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | Indicator | | |
| 3.1. Legislative authority to require registration/licensing of blood establishments and for enforcement power exists. | R | R | 3.1.1. Legislation/regulation requires that 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 authority to take regulatory action (e.g. revoke, suspend the licence) if the establishment does not comply with regulatory requirements. | |
| 3.2. Licensing/registration system is established and operational for blood establishments. | R | R | 3.2.1. License/registration applications are assessed by the NRA based on written guidelines | |
| | | R | 3.2.2. A list of all licensed/registered blood establishments is maintained and made available where needed. | |
| | | S | 3.2.3. Guidelines for applicants on the content, the format, the requirements and the procedures to follow in order to submit an application for an establishment license or required registration are available. | |
| | | S | 3.2.4. Facility documentation (e.g. site master file, qualification of responsible person) is submitted as part of license/registration | |

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| | | S | application and is assessed to demonstrate that facility is suitable for the activities to be performed (e.g. blood collection, donor screening, testing, storage, etc). | |
| | | S | 3.2.5. Renewal period for establishment license/registration is defined. | |
| | | | 3.2.6. Decentralized or delegated activities to other agencies/authorities follow the standards, guidelines and procedures as agreed by the central regulatory authority and a reporting mechanism is established between the responsible authorities. | |
| 3.3. Significant changes to an establishment license/registration are submitted and assessed by the NRA prior to implementation. | R | R | 3.3.1. Changes are assessed based on type of change. | |
| | | S | 3.3.2. Written guidelines for applicants with definition of types and scopes of changes and documentation required are available. | |
| 3.4. Compliance with principles of Good Manufacturing Practice (GMP) is assessed as part of establishment licensing / registration process. | R | R | 3.4.1. Compliance with applicable principles of GMP is a condition for maintaining an establishment license/registration and for approval of significant changes. | |
| | | R | 3.4.2. National GMP and GDP principles are published and are consistent with/based on recognized standards for 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) agreement with other NRA's for exchange of inspection reports/certificates, or | |

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| | | | <p>b) list of reference countries/agencies whose certificates and decisions are accepted exist, or</p> <p>c) site inspections are carried out abroad</p> | | |
| 3.5. | Quality Management System requirements for all functions performed by blood establishments are established. | R | R | 3.5.1. The essential components for a QMS are covered and include: Change control system, document control and record retention system, emergency contingency plan, proficiency testing program, quality control program, internal audit system, written specifications for all critical supplies, equipment, services, validation of computer systems, deviation management system, process control, process improvement, training program and complaint handling. | |
| 3.6. | Assessment of compliance with standards regarding donor selection criteria and testing of donations is part of establishment licensing/registration process (Alternatively this requirement can also be met under section "Approval of blood and blood components (Product and/or Process approval)". | R | <p>R</p> <p>R</p> | <p>3.6.1. Compliance with applicable standards is a condition for maintaining an establishment license.</p> <p>3.6.2. National standards are published and are consistent with/based on recognized standards for blood and blood components.</p> <p>3.6.3. Inspections are carried out for checking compliance with these standards.</p> | |

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| 4.0 Core function: Licensing/registration of manufacturers and distributors of plasma derived products | | | | |
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| <i>Applicable to plasma derived products</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | Indicator | | |
| 4.1. Legislative authority to require registration/licensing of manufacturers and distributors of plasma derived products and for enforcement power exists. | R | R | 4.1.1. Legislation/regulation requires that manufacturers and distributors of plasma derived products that intend to manufacture, distribute, import or export plasma derived products must be registered/licensed by the designated NRA. | |
| | | R | 4.1.2. The NRA has authority to take regulatory action (e.g. revoke, suspend the licence) if the company does not comply with regulatory requirements. | |
| 4.2. Licensing/registration system is established and operational for manufacturers and distributors of plasma derived products. | R | R | 4.2.1. License/registration applications are assessed by the NRA based on written guidelines. | |
| | | R | 4.2.2. A list of all licensed/registered manufacturers and distributors is maintained and made available where needed. | |
| | | S | 4.2.3. Guidelines for applicants on the content, the format, the requirements (depending on the activities) and the procedures to follow in order to submit an application of an establishment license or required registration are available. | |
| | | S | 4.2.4. Facility documentation (e.g. site master file, key personnel, qualification of responsible person) is submitted as part of license/registration application and is assessed | |

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| | | S | to demonstrate that the facility is suitable for the activities to be performed. | |
| | | S | 4.2.5. Renewal period for establishment license/registration is defined. | |
| | | S | 4.2.6. Decentralized or delegated activities to other agencies/authorities follow the standards, guidelines and procedures as agreed by the central regulatory authority and a reporting mechanism is established between the responsible authorities. | |
| 4.3. Significant changes to an establishment license/registration are submitted and assessed by the NRA prior to implementation. | R | R | 4.3.1. Changes are assessed based on type of change. | |
| | | S | 4.3.2. Written guidelines for applicants with definition of types and scopes of changes and documentation required are available. | |
| 4.4. Compliance with principles of GMP and GDP is assessed as part of establishment licensing/registration process. | R | R | 4.4.1. Compliance with applicable principles of GMP and GDP is a condition for maintaining an establishment license/registration and for approval of significant changes. | |
| | | R | 4.4.2. National GMP and GDP standards are published and are consistent with/based on recognized standards for manufacturing and distribution of plasma derived products. | |
| | | R | 4.4.3. Periodic inspections according to GMP and GDP principles are carried out for supervision of manufacturers and distributors of plasma derived products. For inspections carried out abroad <ul style="list-style-type: none"> a. agreement with other NRA's for exchange of inspection reports/certificates, or | |

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| | | | <ul style="list-style-type: none"> b. list of reference countries/agencies whose certificates and decisions are accepted exist, or c. Site inspections are carried out abroad. | |
| 4.5. | Quality Management System requirements for all functions performed by manufacturers and distributors are established. | R | R | 4.5.1. The essential components for a QMS are covered and include: Change control system, document control and record retention system, emergency contingency plan, quality control program, internal audit system, written specifications for all critical supplies, equipment, services, validation of computer systems, deviation management system, process control, process improvement, training program and complaint handling. |

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| 5.0 Core function: Approval of blood and blood components (Product and/or process approval) | | | | |
|-----------------------------------------------------------------------------------------------------------------------|---------------|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <i>Applicable to blood and blood components</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 5.1. Legal provisions for a system to ensure quality, safety and efficacy of blood and blood components exist. | R | R | 5.1.1 A marketing approval system is required including for any imported products. | |
| | | R | 5.1.2 NRA has authority to issue a marketing approval, to suspend it and to withdraw it if the product is considered unsafe or does not comply with regulatory requirements. | |
| 5.2. A system for ensuring quality, safety and efficacy of blood and blood components is established and operational. | R | R | 5.2.1. Specifications related to quality, safety and efficacy of blood and blood components are defined and under direct or indirect supervision of NRA. | |
| | | R | 5.2.2. The critical standards for product manufacturing are legally binding including donor selection, laboratory testing, component preparation, storage, issuance, tracking, tracing and record keeping. | |
| | | S | 5.2.3. Procedures to recognise exceptions are clearly defined (e.g. if collected by a medical practitioner for a specific therapeutic purpose). | |
| | | S | 5.2.4. Requirements and standards are based on internationally recognized standards. | |
| 5.3. Donor selection and deferral criteria are established as appropriate to the intended use of the component. | R | R | 5.3.1. Donor selection and deferral criteria (temporary and permanent deferrals) take into account the health of the donor and the safety/suitability of the donation. | |

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| | | R | 5.3.2. Mechanisms for regularly reviewing and updating the criteria are in place and take into consideration the development of issues that might have a negative impact on the quality and safety of blood and blood components, e.g. epidemiological situation or emerging diseases. | |
| 5.4. Transmissible disease testing requirements are established as appropriate to the intended use of the component. | R | R | 5.4.1. Mechanisms for regularly reviewing (e.g. by qualified experts in epidemiology) and updating the testing requirements are in place. | |
| | | R | 5.4.2. Epidemiological data regarding the prevalence and incidence of infectious disease markers in blood donors is available and regularly updated. | |
| 5.5. Labelling requirements are established. | R | R | 5.5.1. Each blood component has a unique and clear identifier and is fully traceable. | |
| | | R | 5.5.2. Amendments to the label are submitted to the NRA and assessed prior to implementation. | |
| | | S | 5.5.3. Requirements are based on internationally recognized standards | |
| 5.6. Approval system for blood and blood components is operational. | R | R | 5.6.1. Assessment includes relevant aspects of quality, safety and where applicable efficacy of blood and blood components. | |
| | | S | 5.6.2. Guidelines for applicants on the content, the format and the procedures to follow in order to submit an application for approval exist. | |
| | | S | 5.6.3. Written guidelines for assessment of applications are implemented. | |
| | | S | 5.6.4. Appeal procedures are in place. | |
| | | S | 5.6.5. An assessment report is prepared and used as a reference for decision. | |

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| <p>5.7. Requirement exists for manufacturing changes to be submitted and assessed by the regulatory authority.</p> | <p>S</p> | <p>S</p> | <p>5.7.1. Written guidelines for applicants with definition of types and scopes of changes and documentation required are available.</p> | |
| | | <p>S</p> | <p>5.7.2. Written guidelines for assessment based on type of change (e.g. significant, notifiable, administrative) exist.</p> | |
| <p>5.8. Appropriate assessment expertise is available.</p> | <p>R</p> | <p>R</p> | <p>5.8.1. Access to experts with relevant qualifications and experience (internal and/or external) for assessment of blood and blood components (preclinical, clinical, and quality data) is assured.</p> | |
| | | <p>S</p> | <p>5.8.2. Written procedures for selection, management, and use of external experts are in place.</p> | |

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| 6.0 Core function: Approval of plasma derived products | | | | |
|----------------------------------------------------------------------------------------------------------------------|---------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <i>Applicable to plasma derived products</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 6.1. Legal provision for an approval system to ensure quality, safety and efficacy of plasma derived products exist. | R | R R | 6.1.1. Approval is required for plasma derived products, also for imported products. 6.1.2. NRA has authority to approve plasma derived products, to suspend an approval and to withdraw it if the product is considered unsafe or does not comply with regulatory requirements. | |
| 6.2. An approval system for plasma derived products is established and operational. | R | R R S S S S | 6.2.1. There is a requirement for the applicant to include a list of all the blood establishments that collected the plasma used in the product. 6.2.2. Selection, deferral and transmissible disease testing requirements for plasma donors are established (see Indicators 5.3.1, 5.4 and 5.5). 6.2.3. Guidelines for applicants on the content, the format and the procedures to follow in order to submit an application for market authorization are available. 6.2.4. Appeal procedures are in place. 6.2.5. The national control laboratory is involved in assessment as appropriate. 6.2.6. Written procedures for selection, management, and use of external experts are available. | |

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| <p>6.3. Assessment of applications for market authorization is implemented.</p> | <p>R</p> | <p>R</p> <p>R</p> <p>S</p> <p>S</p> <p>S</p> | <p>6.3.1. Assessment of quality, safety, and efficacy of plasma derived products, including assessment of effectiveness of measures used by manufacturer to inactivate/remove viruses is performed.</p> <p>6.3.2. Procedures to recognise exceptions are clearly defined.</p> <p>6.3.3. Assessment reports are prepared and used as reference for decision.</p> <p>6.3.4. Written criteria exist for recognition of other NRA's reports/decisions (if applicable).</p> <p>6.3.5. Written guidelines for assessment of applications are available.</p> | |
| <p>6.4. There is a requirement for changes to be submitted and assessed by the regulatory authority prior to implementation.</p> | <p>R</p> | <p>R</p> <p>S</p> <p>S</p> | <p>6.4.1. Changes are assessed based on type of change.</p> <p>6.4.2. Written guidelines for applicants with definition of types and scopes of changes and documentation required are available.</p> <p>6.4.3. Written guidelines for assessment based on type of changes are available.</p> | |
| <p>6.5. Appropriate assessment expertise exists.</p> | <p>R</p> | <p>R</p> | <p>6.5.1. Access to experts (internal and/or external) for assessment of plasma derived products (preclinical, clinical, and quality data) - list staff and/or experts with relevant qualifications and experience.</p> | |
| <p>6.6. Clear and comprehensive information on authorized plasma derived products is available.</p> | <p>R</p> | <p>R</p> <p>R</p> | <p>6.6.1. The product information made available is approved.</p> <p>6.6.2. Summary of Product Characteristics (SPC) or equivalent information is available for all plasma derived products.</p> | |

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| | | S | 6.6.3. SPC-like information that is regularly updated is publicly available. | |
| 6.7. List of authorized products exists. | S | R | 6.7.1. Listing of authorized products is made available where needed. | |
| | | S | 6.7.2. Listing of authorized products is publicly available. | |

DRAFT FOR CONSULTATION

| 7.0 Core function: Regulatory oversight of associated substances and medical devices including in vitro diagnostics | | | | | |
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| <i>Applicable to associated substances and medical devices including in vitro diagnostics</i> | | | | | |
| | | Rating | | Indicators related to the main criteria | Comments |
| | | Main criteria | indicator | | |
| 7.1 | Legal provisions exist for regulatory oversight of the relevant associated substances and medical devices. | R | R | 7.1.1 Premarket review and approval is required for IVD/screening test kits used for donor selection and testing of blood and blood components for therapeutic use and/or for further manufacturing of plasma derived products (e.g. tests for donor haemoglobin, tests for infectious disease markers). | |
| | | | R | 7.1.2 Premarket review and approval is required for medical devices involved in the manufacture of blood components (e.g. apheresis machines). | |
| | | | R | 7.1.3 Premarket review and approval is required for associated substances, (e.g. anticoagulants, additive solutions). | |
| | | | R | 7.1.4 NRA has the enforcement power to investigate and act against marketed products and involved companies that do not comply with the requirements. | |
| 7.2 | Systems for premarket review and approval of associated substances and relevant medical devices are established and operational. | R | R | 7.2.1 Premarket review includes assessment of quality, safety and effectiveness. | |
| | | | S | 7.2.2 Guidelines for applicants on content (data requirements), format, and procedures for submitting an application exist. | |
| | | | S | 7.2.3 Written guidelines for product assessments exist. | |

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| | | S | 7.2.4 If decentralized, roles and responsibilities of the bodies involved are defined and there is a mechanism for information exchange between control authority and NRA. | |
| 7.3 Appropriate assessment expertise is available. | R | R | 7.3.1 Access to experts with relevant qualifications and experience (internal and/or external) for assessment of blood and blood components (preclinical, clinical, and quality data) is established. | |
| | | S | 7.3.2. Written procedures for selection, management, and use of external experts are in place. | |

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| 8.0 Core function: Access to a laboratory independent of manufacturers | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 8.1. Access of the NRA to a National Control Laboratory (NCL) independent of the manufacturer(s) is established. | R | R | 8.1.1. Policy and operational agreements are in place for use of any external control laboratories. | |
| | | R | 8.1.2. Adequate testing plans, testing procedures and related documentation are available. | |
| | | R | 8.1.3. Responsibilities for testing in the pre licensing and post licensure period are clearly defined. | |
| | | S | 8.1.4. NCL is involved in definition of specifications and analytical methods during assessment of marketing authorizations. | |
| 8.2. Appropriate organization and financial support from management ensure the implementation of adequate testing programmes (including documentation) using appropriate equipment and qualified and experienced staff. | R | R | 8.2.1. Written testing procedures and related documentation are in place. | |
| | | R | 8.2.2. Retest policy is established. | |
| | | R | 8.2.3. A strategy for introduction and validation of new/improved tests exists. | |
| | | R | 8.2.4. Reporting and issuance to the NRA of all critical results including out of specifications handling is implemented. | |
| | | S | 8.2.5. Document control is established. | |
| | | S | 8.2.6. SOPs, test procedures, sample handling, data management is organised. | |

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| 8.3. An externally accredited quality management system is in place in the laboratory. | S | S S | 8.3.1. Quality Policy and Quality Manual exist. 8.3.2. Qualified quality manager is designated and a quality management system is in operation. | |
| 8.4. Equipment documentation is in place. | R | R R S S | 8.4.1. Calibration and maintenance schedules are available. 8.4.2. Validation protocols are available. 8.4.3. Commissioning records (i.e. installation and qualification) is available. 8.4.4. Operation manuals and logs exist. | |
| 8.5. Human resource management is implemented. | R | R S S | 8.5.1. Qualified and experienced staff in accordance with defined competencies is available. 8.5.2. Staff training plan is developed and implemented. 8.5.3. Impact of staff training is monitored. | |
| 8.6. An audit and review system exists. | S | S S S | 8.6.1. Comprehensive internal audit and review systems are in place. 8.6.2. Documentation of actions taken as a result of audit is available. 8.6.3. The lab is audited by external organizations. | |
| 8.7. Validation policy for introduction of tests is implemented. | R | R R | 8.7.1. Validation programme for non-compendial tests is available. 8.7.2. Procedures for transfers of validated methods (e.g. Manufacturer) exist. | |
| 8.8. A general safety programme exists. | R | R R | 8.8.1. Lists of hazardous substances are available. 8.8.2. Responsible staff is designated. | |

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| | | S | 8.8.3. Full safety programme exists. | |
| 8.9. Policy for use of reference standards and reagents exists. | R | R | 8.9.1. Access to a catalogue (list, specifications and sources) and regular supply system for standards and reference materials is implemented. | |
| | | R | 8.9.2. Appropriate use of reference materials is ensured. | |
| | | R | 8.9.3. Use of reagents of assured quality (e.g. grades) is ensured. | |
| | | S | 8.9.4. System is in place to establish and qualify national reference standards in IUs. | |
| 8.10. Data trends are monitored and analysed. | R | R | 8.10.1. Results of reference materials are monitored. | |
| | | R | 8.10.2. Results are compared with those of manufacturer. | |
| | | S | 8.10.3. Laboratory results are monitored. | |
| 8.11. Participation in international proficiency schemes and collaborative studies is organised. | S | S | 8.11.1. Regular participation (date of last participation, scope, product(s), coordinating institution) is organised. | |
| 8.12. Regulatory outcome of testing is analysed and used as decision basis. | R | R | 8.12.1. Compliance with authorized specifications is checked. | |
| | | R | 8.12.2. Results are compared with those of manufacturer. | |
| | | R | 8.12.3. Corrective action is initiated in case of non compliance. | |

| 9.0 Core function: Control of clinical trials | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 9.1. Applicable legal provision for the regulation of biomedical research in human subjects exists. | R | R | 9.1.1. An authorization system for clinical trials is required. | |
| | | R | 9.1.2. Scope and requirements for regulation of clinical trials are defined. | |
| | | R | 9.1.3. NRA has the enforcement power for the authorization, suspension and withdrawal of clinical trials. | |
| | | R | 9.1.4. Legal provisions assure an ethical oversight over clinical trials. | |
| | | R | 9.1.5. Compliance with principles of Good Clinical Practice (GCP) is mandatory. | |
| 9.2. A system for authorization of clinical trials is operational. | R | R | 9.2.1. A system is established for clinical trial assessment and authorization. | |
| | | R | 9.2.2. Inspection system established to verify compliance with principles of GCP | |
| | | R | 9.2.3. Expertise is available from within or outside NRA. | |
| | | S | 9.2.4. Written guidelines for assessment of clinical trials and changes are implemented. | |

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| | | S | 9.2.5. Written guidelines and forms on the data requirements, the format, and procedures for submitting a clinical trial application are available to sponsors. | |
| | | S | 9.2.6. Provision for scientific advice (eg preclinical and clinical) on design of clinical trials or issues related to submission of appropriate data is in place. | |
| | | S | 9.2.7. There are written guidelines for GCP. | |
| 9.3. Data requirements for clinical trial applications are defined. | R | R | 9.3.1. Production and quality of clinical candidate material (eg product characterization, lab specimens) is included. | |
| | | R | 9.3.2. Provision for pre-clinical data exists. | |
| | | R | 9.3.3. Assessment of clinical trial protocol with respect to patient safety and informed consent is performed. | |
| 9.4. Assurance of ethical oversight exists. | R | R | 9.4.1. A system of independent ethical review and approval in accordance with principles of GCP exists. | |
| | | S | 9.4.2. Ethics committees (e.g. Institutional Review Board) are formally defined including composition. | |
| | | S | 9.4.3. Ethics Committee includes members external to the concerned institution. | |
| | | S | 9.4.4. Roles and duties of Ethics committees to oversee clinical trials are outlined. | |

| 10.0 Core function: System for lot release of plasma derived products | | | | |
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| <i>Applicable to plasma derived products and donor screening tests</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 10.1 Legal provisions for an official lot release certification are in place. | R | R | 10.1.1.NRA has authority to issue lot release certificates and enforcement power to suspend or revoke lot release. | |
| | | R | 10.1.2.NRA has legal authority to perform lot release and/or acceptance policy/criteria of lot release performed by another NRA (e.g. lot release certificate from the country of origin). | |
| | | S | 10.1.3.Written criteria for exemption from lot release exist. | |
| 10.2 Lot release system is established and operational. | R | R | 10.2.1 Lot release protocols and procedures are established and/or acceptance of lot release performed by another NRA is in place. | |
| | | R | 10.2.2 Lot release is based at a minimum on review of summary lot specific data. | |
| | | R | 10.2.3 Qualified staff (ie staff with relevant qualifications, training and experience) to perform lot release is available. | |
| | | R | 10.2.4 Testing policy and test protocols including acceptance criteria are defined. | |
| | | R | 10.2.5 Records on lot release are maintained. | |
| | | R | 10.2.6 Procedures for communication with the product manufacturer are defined. | |

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| | | S | 10.2.7 Written procedures and guidelines (including templates of certificates), check list, and / or SOP's developed and used to review summary lot protocol, are implemented for lot release process. | |
| | | S | 10.2.8 Testing procedures are externally accredited. | |
| 10.3 | Quality management system for official lot release is implemented. | R | <p>R</p> <p>S</p> <p>S</p> | <p>10.3.1. Official laboratory complies with Section "Access to a laboratory independent of manufacturers".</p> <p>10.3.2. Appropriate data collection and analysis (e.g. Lot to lot consistency, trend analysis) is implemented.</p> <p>10.3.3. Continual review and scientific dialogue with the manufacturers and product review experts on issues of quality test results exist.</p> |
| 10.4 | Access to product related documentation to guide particular areas of scrutiny in lot release is possible. | R | R | <p>10.4.1. Approved relevant marketing authorisation and its update are available.</p> <p>10.4.2. Access to complaints and adverse event reports is possible.</p> <p>10.4.3. Full access to the manufacturer's batch record is possible.</p> <p>10.4.4. Access to inspection reports is possible.</p> |

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| 11.0 Core function: Regulatory inspections and enforcement activities | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 11.1. Legal provision exists to inspect premises where regulated activities are performed in order to assess and enforce compliance with the applicable laws, regulations and standards. | R | R | 11.1.1.Mandate for inspections by NRA and enforcement of compliance with principles of GMP and GDP and other standards exists. | |
| | | R | 11.1.2.Applicable standards and practices are defined in legal provisions. | |
| | | R | 11.1.3.NRA has authority to take enforcement action against the accountable companies or persons that are not in compliance. | |
| | | R | 11.1.4.NRA has authority to sample products, manufacturing materials and records if necessary. | |
| | | R | 11.1.5.NRA has authority for product recalls. | |
| | | R | 11.1.6.Conflict of interest & confidentiality provisions exist. | |
| 11.2. Inspection and enforcement systems are established and operational. | R | R | 11.2.1.Established policy and program exist for conducting inspections of all regulated activities. | |
| | | R | 11.2.2.Inspection plan with adequate human and financial resources for conducting inspections at appropriate intervals exists. | |
| | | R | 11.2.3.The NRA maintains files of each inspection, the inspection report, and final decisions taken. | |

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| | | R | 11.2.4. There is an established process for appropriate regulatory action to address inspectional findings (e.g. recall of products, amended licenses). | |
| 11.3. Appropriate expertise/qualifications of inspectors is available. | R | R | 11.3.1. Inspectors have the appropriate expertise to conduct inspections of blood establishments, manufacturers and distributors of plasma derived products. | |
| | | S | 11.3.2. Training of inspectors includes specific aspects related to the activities of relevant establishments. | |
| | | S | 11.3.3. Use of a team approach is possible in order to include specialised knowledge and expertise in specific products where needed. | |
| 11.4. A Quality Management System, consistent with international principles for pharmaceutical and related inspectorates is implemented. | R | R | 11.4.1. Written procedures exist for conducting inspections (inspection manual) and following-up of deficiencies/violations. | |
| | | S | 11.4.2. Established procedure (eg periodic internal and external audits) to monitor inspection process exists. | |
| | | S | 11.4.3. Monitoring of timelines and indicated actions is implemented. | |
| 11.5. A recall system exists with mechanisms to ensure the proper disposition of blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics. | R | R | 11.5.1. Policy and procedures for a recall system including product disposition exist. | |
| | | R | 11.5.2. Recall system is based on defined action and documented communication to the appropriate level of the distribution system. | |
| | | R | 11.5.3. A feedback-mechanism exists to confirm that appropriate action (including destruction when necessary) has been taken at all appropriate levels. | |
| | | R | 11.5.4 Full Lot traceability is in place. | |

| 12.0 Core function: Vigilance systems | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 12.1. Legal provisions for a national vigilance system exist. | R | R | 12.1.1. Authority exists to specify reporting of adverse events (AE) and adverse reactions (AR) within the national vigilance systems. | |
| | | R | 12.1.2. NRA has a legal mandate and enforcement power for mandatory reporting elements of the national vigilance system. | |
| | | R | 12.1.3. Authority for the NRA to require the marketing authorization holder to perform a specific study of safety and/or effectiveness in the post-marketing period. | |
| 12.2. National vigilance systems for the monitoring and management of AE and AR are established and operational. | R | R | 12.2.1. Roles and responsibilities of the key parties, the NRA, surveillance staff involved in (AE) and AR monitoring and management activities are clearly defined and documented. | |
| | | R | 12.2.2. Guidelines exist and are published and accessible (i.e. distributed or available when needed) to all staff involved in AE and AR surveillance. | |
| | | S | 12.2.3. Guidelines include the following: <ol style="list-style-type: none"> a. Objectives of the system; b. List of AE and AR to be reported; c. Case definition for all AE and AR to be reported; | |

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| | | <p>S</p> <p>S</p> | <p>d. Information on how to report AE and AR for all blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics (i.e. who should report, how, where and when reports should be sent);</p> <p>e. Process for analyzing data and providing feedback to relevant staff and key parties;</p> <p>f. Process for investigating and responding to serious AE and AR (including who should be in charge of the investigation);</p> <p>g. Process for informing patients, parents, community and country (where relevant) of findings of investigation and relevant actions.</p> <p>12.2.4.A standardized reporting form with comprehensive information to monitor AE and AR exists.</p> <p>12.2.5.System for providing periodic feedback on AE and AR, including summary and specific investigation reports from the national to all levels (including health facility level) is established.</p> | |
| <p>12.3. Guidance on AE and AR monitoring and management is provided to appropriate staff</p> | <p>S</p> | <p>S</p> | <p>12.3.1.Guidelines and templates on AE and AR reporting and monitoring are provided to appropriate staff dealing with AE and AR.</p> | |
| <p>12.4. There is demonstrated capacity to detect, investigate and take action regarding significant AE and AR.</p> | <p>R</p> | <p>R</p> <p>R</p> | <p>12.4.1.NRA regularly informed of data relevant to quality and safety of blood products including:</p> <ul style="list-style-type: none"> a. blood transfusion safety; b. transmissible disease surveillance data; c. device failures. <p>12.4.2.Manufacturers are required to inform NRA of any new safety issues or marketing/regulatory decisions taken in other countries.</p> | |

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| | | R | 12.4.3. Procedures for initiating corrective/regulatory action (e.g. recall) are available. | |
| | | R | 12.4.4. There is documented capacity to investigate AE's and AR's, e.g. <ul style="list-style-type: none"> a. routine reporting of AE and AR according to established guidelines and /or standard operating procedures; b. clear understanding and adequate training among key parties of respective roles and responsibilities; c. access to resources (personnel, laboratory) for conducting comprehensive investigations. | |
| | | R | 12.4.5. Case investigations are timely and complete, e.g.: <ul style="list-style-type: none"> a. timelines for prompt investigation and preliminary reporting related to serious adverse reactions are established; b. investigation thorough and findings clearly described. | |
| | | S | 12.4.6. Demonstrated reporting system (active or passive, sentinel or countrywide/statewide) with satisfactory sensitivity. E.g. <ul style="list-style-type: none"> a. number of reports annually/last 12 months; b. reporting rate; c. breakdown of reports by types of AE, age group, districts etc. | |

| 13. Core function: Ensuring traceability and record keeping by manufacturers for all regulated products | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 13.1. NRA ensures that standards for traceability and record keeping are in place for all aspects of manufacturing and distribution. | R | R | 13.1.1. Requirement for manufacturers to implement methods and maintain records that enable traceability exists: <ul style="list-style-type: none"> a. for manufacturers of blood products traceability from donor to recipient and vice versa; b. ensure integrity of records of manufacturing and complete records of distribution. | |
| | | R | 13.1.2 Procedures for record keeping and retention period defined by NRA are available. | |

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| 14.0 Core function: International cooperation | | | | |
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| <i>Applicable to blood, blood components, plasma derived products and associated substances and medical devices including in vitro diagnostics</i> | | | | |
| Main criteria related to the function | Rating | | Indicators related to the main criteria | Comments |
| | Main criteria | indicator | | |
| 14.1. National policy to facilitate international cooperation and harmonization is implemented. | S | S | 14.1.1. National policy/strategy on international interactions exists, e.g. information sharing on product approvals, safety data and policy initiatives. | |
| | | S | 14.1.2. Agreements exist between the NRA and other international organizations and regulatory authorities. | |
| | | S | 14.1.3. NRA participates in harmonization initiatives/forums. | |
| 14.2. Sharing/exchange of risk information with international organizations and other regulatory authorities is implemented. | R | R | 14.2.1. Ability is shown to participate in international risk management efforts when needed. | |
| | | S | 14.2.2. Ability exists to engage in international risk assessment when needed, e.g. access to epidemiological data, expertise in risk assessment. | |
| | | S | 14.2.3. Capacity or expertise to access epidemiological data and formally assess risks is available. | |
| | | S | 14.2.4. Documented procedures for timely sharing of risk information internationally exist. | |
| | | S | 14.2.5. Records are kept of risk information that has been exchanged. | |