て調査・検討することである.

B. 研究方法

各国の狂犬病ワクチンの力価試験実施状況に係る調査:各国のヒト用不活化狂犬病ワクチンの力価試験法について文献的に調査した.

動物用狂犬病ワクチンで採用されている Immunocapture ELISA (IC-ELISA) 法に係る調査:現在我が国の動物用狂犬病ワクチンの力価試験法で採用されている ELISA 法の実施方法について文献的に調査した.

(倫理面への配慮)

本研究では、研究対象者に対する人権擁護上の配慮、不利益・危険性の排除や説明と同意を必要とする研究、実験動物を用いる研究等、倫理面への配慮が必要な研究は行わない。

C. 研究結果

世界保健機構による組織培養狂犬病ワクチンガイドライン: 世界保健機構(WHO)ではヒト用狂犬病ワクチンに対して NIH 法の実施を推奨している. また WHO では NIH 法の代替法としてこれまでには抗原測定法あるいは血清学的試験法の導入を各国と共に検討しているが, これら試験法は未だヒト用狂犬病ワクチンの力価試験法として推奨されていない.

米国における狂犬病ワクチン力価試験実施状況: 米国 FDA は狂犬病ワクチンの力価試験を自家試験において 2 回の NIH 法により得られる力価の平均値が >2.5 IU/mL となることを求めている.

ヨーロッパにおける狂犬病ワクチン力価試験実施状況: European Pharmacopoeia (Ph. Eur)は全てのロットにおいて NIH 法の実施を要求している. また Official Medicines Control Laboratories (OMCL)のロットリリースガイドラインでは全てのロットにおいて NIH 法と抗原量の測定を要求している. しかしながらフランスではフランスで製造される狂犬病ワクチンの品質の安定性を確認し, ELISA 法による試験品の抗原量のモニターを行い, 10 ロットにつき 1 回の割合で NIH 法を実施している.

動物用狂犬病ワクチンで採用されている Immunocapture ELISA (IC-ELISA) 法に係る調査: 我が国の動物用狂犬病ワクチンは, シードロットシステムにより製造されている. パスツール株由来固定毒西ヶ原株をハムスター肺由来細胞である HmLu 細胞に馴化した RC・HL 株を HmLu 細胞で培養・精製し, β－プロピオラクトンにより不活化したワクチンである. この狂犬病組織培養不活化ワクチンは国内の製造 5 社により製造され, 年間約 500 万頭分が供給されている. 我が国の動物用狂犬病ワクチンの国家検定における力価試験は, 有効抗原量を ELISA 法で測定し, 参照ワクチンの有効抗原量との相対力価で判定する方法が採用されている. 参照ワクチンの有効性は, 犬への接種による抗体応答, 従前のモルモットを用いた感染防御試験(モルモット)法および NIH 法等により評

価され，さらに直前の参照ワクチンロットの G 蛋白との相同性評価等により有効性を担保している．本 ELISA 試験法の確立により動物用狂犬病ワクチンの製造工程中に力価試験を実施することが可能となり，ワクチンの安定的な製造に貢献している．

D. 考察

今回の調査によりヒト用狂犬病ワクチンの力価試験においては NIH 法が,現在も WHO をはじめ各国において要求されており，ELISA 法を用いた抗原量の測定はワクチンの品質管理において参考データの域を出ていないことが示唆された．しかしながら我が国の動物用狂犬病ワクチンの力価試験においては，参照ワクチンの有効性を確認し，参照ワクチンと試験品の抗原量の相同性評価等により試験品の有効性を担保している．仮に同等の試験法をヒト用乾組狂犬ワクチンに導入すると，現行 35 日要している試験期間が少なくとも 14 日以内に短縮されることが期待される．しかしながら ELISA 法をヒト用乾組狂犬ワクチンに応用するためには新たにモノクローナル抗体の検討および探索が必要であるため，今後は動物用狂犬病ワクチンの検定法で用いられているモノクローナル抗体をはじめとした現行の Mab あるいは新規 MAb 抗体の作製を検討する必要が示唆された．また各国においては NIH 法を現在も狂犬病ワクチンの力価試験法として採用しているが，その実施者および実施頻度においては開きがあることが示唆された．しかしながらその詳細については不明な点も多い．また NIH 法の代替法についても WHO を中心に各国で検討されており，今後は現地調査も含めた各国機関との情報交換等を通して状況の把握に努めるとこが重要である．

E. 結論

本研究においては乾組狂犬ワクチン力価試験を例にとり，現行の検定制度における試験法の代替法の導入による力価試験の合理化について検討した．その結果狂犬病ワクチンの力価試験においては抗原測定法あるいは血清学的試験法の導入等が各国において検討されていることが明らかとなった．しかしながら代替法の導入にはさらなる基礎研究が必要であり，早急な導入は難しいことが示唆された．したがって今後とも力価試験法の見直しを進めるための基礎研究および各国における情報収集が重要である．

F. 研究発表

1. 論文発表

特記事項なし

2. 学会発表

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G. 知的財産権の出願・登録状況

特記事項なし

厚生労働科学研究費補助金

医薬品・医療機器等レギュラトリーサイエンス総合研究事業

ワクチンの品質確保のための国家検定制度の抜本的改正に関する研究

分担研究報告書

血液製剤のサマリーロットプロトコール導入に向けた国際調査

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研究要旨：血液製剤の安全性確保に関しては薬事法により規定されており、「特定生物由来製品」に指定されており、医薬品の安全性を確保する為に製造販売業者に製造管理及び品質管理のための基準（GMP)や製造販売後安全管理の基準(GVP)の遵守を求めている。特定生物由来製品の場合、これらの基準が通常の医薬品より厳しく、さらに国立感染症研究所において検定を実施し、合格したもののみが市場への出荷を許可(ロットリリース)されている。ロットリリースは日本独自の制度ではなく、世界保健機関（WHO）などでもワクチンなどでその必要性が強調されている。そのガイドラインの中で、ワクチンにおいて規制当局によるロットリリースに際し、SLP を製造販売業者から提出させ、その内容が当該製品の承認事項に適合しているかを審査する事を必須としており、本邦においても 2011 年 7 月 4 日に薬事法施行規則の一部改正が発布され、国家検定に SLP 審査制度を導入する事が決められた。そこで、血液製剤に関し、SLP 導入に向けた調査を行い、その意義及び導入した場合の審査機関及び審査に関連する法令の準備について検討する事を研究目的とした。その結果、米国では CBER (Center for Biologics Evaluation and Research)が Lot Release を承認しており、Lot release protocol は CBER により審査・承認されていた。EU においては European Pharmacopoeia 内の Monograph で規定されており、検定試験も National Control Laboratory での実施が求められている。以上の事からも欧米諸国では SLP 審査が血液製剤のロットリリースに必須で有る事が明らかとなった。また、本邦も主要メンバーとして加盟している WHO 機関の Blood Regulators Network (BRN)に関しては規制当局の基準として SLP 審査の実施を求めており、今後、本邦においても SLP 審査の実施の意義及び導入した場合の審査機関及び審査に関連する法令の準備について検討する必要が有る。

A. 研究目的

血液製剤の安全性は様々なステップで担保されている。ドナーからの採血の前に、医師の問診が有り、ドナーの体調や渡航歴から血液を介して感染する病原体へのリスクを軽減しており、また国の採血基準に適合した場合、採血を行い、数種の病原体の抗原・抗体検査、肝機能検査、不規則抗体検査を行い、さらに核酸増幅検査を実施し、いずれも適合とされた血液が原料血漿として血液製剤に用いられている。また製造に関わる安全性確保に関しては薬事法により規定されており、「特定生物由来製品」に指定されており、医薬品の安全性を確保する為に製造販売業者に製造管理及び品質管理のための基準（GMP)や製造販売後安全管理の基準(GVP)の遵守を求めている。特定生物由来製品の場合、これらの基準が通常の医薬品より厳しく、さらに国立感染症研究所において検定を実施し、合格したもののみが市場への出荷を許可(ロットリリース)されている。ロットリリースは日本独自の制度ではなく、世界保健機関（WHO）などでもワクチンなどでその必要性が強調されている。そのガイドラインの中で、ワクチンにおいて規制当局によるロットリリースに際し、SLP を製造販売業者から提出させ、その内容が当該製品の承認事項に適合しているかを審査する事を必須としており、むしろ現在のような検定試験（いわゆるダブルチェック）は必要に応じて実施することが推奨されている。そこで、本邦では2006-8年及び2009-11年度の２期にわけて組織された調査研究班がSLP審査制度を日本に導入する事の意義、導入した場合の審査機関及び審査に関連する法令の準備について厚生労働省の担当者を交えながら研究班で討議が重ねられ、2011年7月4日に薬事法施行規則の一部改正が発布され[1]、国家検定にSLP審査制度を導入する事が決められた。同改正により厚生労働大臣の指定する生物学的製剤について、製造販売業者は感染研が製品毎に定めた様式に従ってSLPを作成し、検定申請書に添付する事となった。

一方、血液製剤に関しては現状ではWHOによる規定は存在していなかった為、SLPの導入に関しては本改正では提案されなかった。そこで、血液製剤に関し、SLP導入に向けた調査を行い、その意義及び導入した場合の審査機関及び審査に関連する法令の準備について検討する事を研究目的とした。

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B. 研究方法

主に EU の血液製剤の製造基準である European Pharmacopoeia や WHO 関連書類及びBlood regulatory Networkの資料などを用い、欧米諸国を中心とする海外でのSLP 審査の動向を明らかにするとともにSLP 書式の翻訳を行い、本邦で実施する場

合の整合性、意義を検討する。

倫理面への配慮

本調査では個人情報に関連するような情報は調査対象としていないので特に配慮する必要は無い。

C. 研究結果

1. 海外における血液製剤の SLP 導入動向の調査

米国では CBER (Center for Biologics Evaluation and Research)が Lot Release を承認しており、Lot release protocol は CBER により審査・承認されている。CBER においては CBER Office of Compliance and Biologics Quality (OCBQ)か Division of Manufacturing and Product Quality (DMPQ) が審査を行っている。DMPQ は承認内容と違いが無い事を確認する。EU においては European Pharmacopoeia 内の Monograph で規定されており、検定試験も National Control Laboratory での実施が求められている。

また、Human Albumin については 2012 年の 12 月に Guideline が発表されており、Batch release の参考書式が決められている (添付資料１)。

以上の事からも欧米諸国ではSLP審査が血液製剤のロットリリースに必須で有る事が明らかとなった。

2. Blood Regulatory Network における必須条件としての SLP 審査

EU において Official Medicines Control Laboratories (OMCLs)が Official Control Authority Batch Release (OCABR)を行い、Lot Protocols の書式を決定しているが、より大きなフレームとして WHO の機関として Blood Regulators Network (BRN)が存在している。BRN は WHO の The Expert Committee on Biological Standardization (ECBS)は血液においても同様の組織の設立を求め、血液及び血液製剤の規制に関わる責任を有する規制当局及び試験機関のネットワークとして 2006 年に設立された。現在は、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]の７機関がメンバーとしてリストされており、日本は厚生労働省が担当機関となっている(添付資料２)。この中で、National Blood Regulatory Systems としての基準が規定されており、SLP 審査の実施が Requirement となっている。今後、国際協調の観点からも本邦でのSLP審査の実施が求められると考えられる。

D. 考察

本研究の結果、ワクチン同様、血液製剤

に関してもサマリーロットプロトコールの審査の実施が必要であると考えられる。特に、日本は既に Blood Regulatory Network の主要７ケ国のメンバーとなっており、また国際的にはこれらの検査機関を含め、SLP 審査を実施している事が必要条件となっている。本邦での血液製剤における SLP 審査実施について、その意義及び導入した場合の審査機関及び審査に関連する法令の準備について詳細に検討する必要が有ると考えられる

E. 結論

本研究の結果、ワクチン同様、血液製剤に関してもサマリーロットプロトコールの審査の実施が必要であると考えられる。

F. 研究発表

1. 論文発表

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2. Kazuya Takizawa*, Tatsuo Nakashima*, Takuo Mizukami*, Madoka Kuramitsu,Daiji Endoh, Shigeto Kawauchi, Kohsuke Sasaki, Haruka Momose, Yoshiharu Kiba, Tetsuya Mizutani, Rika A. Furuta, Kazunari Yamaguchi and Isao Hamaguchi. Degenerate PCR strategy with DNA microarray for detection of multiple and various subtypes of virus in the blood screening. ***Transfusion*** in press

2. 学会発表

特になし

G. 知的財産権の出願・登録状況

1. 特許取得

特になし

2. 実用新案登録

特になし

3. その他

特になし

EU Official Control Authority Batch Release

Human Blood Derived Medicinal Products

Guideline for Human Albumin

This version in force from 01/01/2012
Replacing version in force from 01/01/2008

European Commission
European Directorate for the Quality of Medicines & HealthCare
COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Document title	Official Control Authority Batch Release of Human Albumin
Legislative basis	Council Directive 2001/83/EC formerly 89/381/EEC, amended by Directive 2004/27/EC
Date of entry into force of present version	1 January 2012
Adoption of present version	May 2011
Original entry into force	October 1999
Revision status	Update to section 4 as revised in PA/PH/OMCL (10) 111 DEF and to harmonise with the model template
Previous titles and other references	Inventory Of Provisions Relating To Medicinal Products Derived From Human Blood Or Plasma; Established in 1994 By The Ad Hoc Biotechnology/Pharmacy Working Party And Updated March 1995; III/3009/93 Final Formerly finalised under PA/PH/OMCL (97) 50, DEF, editorial changes and changes to section 4 in 2001 approved as PA/PH/OMCL (2001) 13, DEF, editorial changes to update with reference to EC legislation 2001/83/EC finalised under PA/PH/OMCL (2002) 70, DEF, revision to update legislation, section 3 and use of PMF finalised under PA/PH/OMCL (2004) 111, DEF. Revised to accommodate use of plasma pool certificates, finalised under PA/PH/OMCL (05) 68 DEF. Revised to adapt to changes in Ph. Eur. monograph requirements under PA/PH/OMCL (07) 56 DEF
Custodian organisation	The present document was elaborated by the EDQM in the OMCL network and finalised under PA/PH/OMCL (11) 106 DEF

OFFICIAL CONTROL AUTHORITY BATCH RELEASE OF HUMAN ALBUMIN

1 Introduction

Control Authority Batch Release of medicinal products derived from human blood and plasma is performed within the framework of Article 114 Paragraph 2 of Directive 2001/83/EC and Article 1, paragraph 78 of the amending Directive 2004/27/EC and following the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

Requirements are given in the general monograph 'Human plasma for fractionation (0853)' of the European Pharmacopoeia (Ph. Eur.) and in the relevant product specific monographs. All general and specific Ph. Eur. monographs relevant to these products apply.

The Ph. Eur. monograph 0255 Albumin solution, human is relevant for this product.

2 Sampling and tests to be performed by the Control Laboratory

The following samples should be supplied to the Official Medicines Control Laboratory performing batch release:

At least 5 samples of 1.5 ml each of each manufacturing plasma pool involved in the production of this batch.

If the plasma pools have already been tested by a Control Authority, the submission of a copy of the certificate of approval is sufficient.

Plasma pool samples should stored at –20 °C and shipped on dry ice.

and

An appropriate number of finished product, not less than 3.

The Control Laboratory should perform the following tests:

On the manufacturing plasma pools for all batches of albumin:

- For virological markers anti-HIV-1 and 2, HBsAg, and HCV RNA as determined by NAT

On manufacturing plasma pools used for batches of albumin that will be used to prepare human anti-D immunoglobulin:

- Determination of B19 virus by NAT

On the finished product:

- Appearance
- distribution of molecular size
- Pre-kallikrein activator

3 Protocol submission

The protocol submitted by the manufacturer should reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product. A **MODEL** protocol is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monograph(s) of the Ph Eur for products of this type. The manufacturer should omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph Eur monograph(s) (if available) for a particular product should be given in the protocol submitted**.

Results of the tests are required (passed or failed is not sufficient, initial results and, where applicable, results of retests should be given). Sufficient detail should be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed should also be included. Results of qualification tests on reference materials should be given for each new in-house reference material.

3.1 Summary information on the batch of finished product

Trade name: .....

International non-proprietary name (INN)/Ph Eur name/ common name of product (whichever is appropriate): .....

Batch number(s): .....

Finished product (final lot): .....

Final bulk: .....

Type of container: .....

Total number of containers in this batch: .....

Date of expiry: .....

Date of start of period of validity: .....

Storage temperature: .....

Marketing Authorisation number issued by (Member State/EU): .....

Name and address of manufacturer: .....

Name and address of Marketing Authorisation Holder if different: .....

3.2 Production information

Site of manufacture: .....

Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

Viral inactivation
Batch No . . . . has been subjected to a viral inactivation treatment by the following process: (give details such as solvent, detergent, concentrations, temperature, time, dry heat, pasteurisation, etc. as appropriate), according to the method described in the Marketing Authorisation (M.A.).

3.2.1 Starting materials

Plasma Master File Certificate(s) (if applicable)
Reference(s) and date(s) of plasma master file certificate(s) covering the pools listed:

List of plasma pools used to produce this finished product:

Code number	Date of manufacture	Reference of OCABR certificate of approval	Volume

Copy of OCABR certificate(s) of approval for plasma pools to be included:

3.2.2 Intermediate product

Human albumin paste (Fraction V): .....
Manufacturer: .....
Identification number: .....
Amount: .....
Date of manufacture: .....
Storage temperature, storage time and approved storage period (as laid down in the Marketing Authorisation, see summary of information scheme 3.2): .....

Tests on intermediate (e.g.:haem, PKA, pyrogens, ethanol, aluminium: results and specification) Lot numbers of plasma pool used in the production (details of this lot should be specified as under 3.2.1).

3.2.3 Blending of final bulk

3.2.3.1 Composition of final bulk

Date of blending, identification code of ingredients: bulk albumin, preservatives, other components.
Final bulk container: identification code and quantity.

3.2.3.2 Control tests on final bulk

As specified in the Marketing Authorisation.

3.3 Finished product

3.3.1 Identification of the batch finished product

Date and reference of manufacture: .....

Date of filling: .....

Type of container: .....

Number of containers after inspection: .....

Filling volume: .....

Date of start of period of validity: .....

Expiry date: .....

3.3.2 Composition of finished product

Composition of 1 L of solution (1 L solution contains . . .)

3.3.3 Control tests on finished product

Depending on the Marketing Authorisation and the Ph. Eur. monographs, a certificate of analysis should include the following:

Characterisation of product
e.g. appearance, fill volume, identity, pH, total protein, protein composition, distribution of molecular size, . . .

Safety tests on product
e.g. sterility, pyrogens, endotoxin content, prekallikrein activator, . . .

other tests as specified
e.g. Haem content, stabilisers, Aluminium, Potassium, Sodium, stability, osmolality. . .

4 Certification

Certification by qualified person taking the overall responsibility for production and control:

I herewith certify that _____(name of the product) batch N°_____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition the OMCL performing OCABR has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU administrative procedure for OCABR.

Name: _____

Function: _____

Date: _____

Signature:_____

添付資料２

World Health Organization

WHO Blood Regulators Network

Terms of Reference

Revised 2011

Background

1. The regulations and standards to be applied in the area of blood and blood products rely on a highly technical foundation and scientific expertise. Notwithstanding differences in the needs and challenges faced by regulatory authorities in responding to their own national and regional requirements, there is a continuous need to improve cooperation among the leading regulatory agencies in light of the globalization of the marketplace and an increasingly mobile global population which heightens the vulnerability of nations to communicable disease threats.

2. A network of leading regulatory authorities provides an effective and flexible forum for enabling a rapid dialogue and fostering development of international consensus on effective regulatory approaches. Such a group should provide a high level of competence to enhance the evaluation of, and regulatory approaches to, complex issues in the area of blood, blood products and associated drugs and medical devices including *in vitro* diagnostics (IVDs).

3. The need for the World Health Organization ("WHO") to establish a global network of regulatory authorities in the blood field was recognized by the WHO Expert Committee on Biological Standardization ("ECBS") during its 55th meeting in Geneva, Switzerland in November 2004. The ECBS recommended that WHO promote cooperation of experienced regulatory authorities and unanimously agreed that a "peer regulators group" should be established on a priority basis as a cooperative action of experienced regulators. The ECBS further recommended that WHO invite countries that have expressed an interest to join the network.

4. Accordingly, the WHO Blood Regulators Network was established as a group of leading regulatory authorities in the blood and blood products field. In general, each of these authorities has a well established, demonstrated institutional capacity and national/regional legal standing to address the delineated objectives of the Network.

A. Objectives

5. Consistent with the recommendations of the ECBS, the WHO Blood Regulators Network (hereinafter "the Network") addresses issues related to advancing technical expertise in the

areas of blood, blood products and associated drugs and medical devices including *in vitro* diagnostics (IVDs). Its objectives are: (a) to identify issues; (b) to share expertise and information; (c) to promote convergence of regulatory policy and (d) to propose solutions to specific issues, especially emerging public health challenges.

6. The Network is focused on the following areas with a particular emphasis on reacting quickly and flexibly to critical situations:

(a) scientific assessment of current and emerging threats to the safety and availability of blood and blood products;

(b) scientific assessment of the impact (i.e., potential benefits and drawbacks) of new technologies in the field of blood and blood products;

(c) exploration of opportunities among regulatory authorities to cooperatively address emerging public health challenges; and

d) exploration of opportunities for regulatory collaboration/harmonization, particularly in response to emerging public health challenges (such as, for example, actions to prevent transmission of emerging agents in blood products or tools for removing these agents).

B. Functions of the Network

7. The Network has the following functions for the purpose of furthering its objectives:

(a) establish a fast and effective mechanism for communication among the Members, and with scientific or other regulatory bodies;

(b) communicate its considerations and recommendations to the ECBS, through the WHO Secretariat, with the aim to advance the work of the ECBS and strengthen its recommendations; and

(c) support WHO in enhancing and assisting regulatory authorities worldwide, as well as the regional networks of regulatory authorities which are to be further developed in all WHO regions.

C. Members

8. The Network consists of a small group of Regulatory Authorities (also referred to as "Members") that have responsibility, in their respective countries, for the regulation of blood, blood products and associated drugs and medical devices including IVDs and the necessary expertise and well established, demonstrated institutional capacity to address emerging public health challenges. A list of the Network Members, which is found as a separate annex, is regularly updated by the WHO Secretariat and is also made available on the WHO Blood Regulators Network website.

9. Each Member shall designate a Representative to participate in the Network. The Representatives themselves have expertise, and have ongoing access to colleagues with expertise, in the areas of regulation, standard setting, licensing, batch release, and pharmacovigilance of blood and blood products, including relevant epidemiology. Every Representative shall act as a contact person, and shall be responsible for communication within the Network and for the organization of the scientific assessment within his or her own organization, making sure that all the available relevant scientific and regulatory expertise is utilized adequately. An alternative expert shall be designated by each Regulatory Authority as a substitute representative, in case the principal Representative is not available. Each Member should provide the WHO Secretariat with the curriculum vitae of both the Representative and Alternative experts. Each participating Regulatory Authority and the WHO Secretariat should ensure that a rapid contact is always available in case of emergencies.

10. To ensure that the Network can meet its objectives, it is important to keep its character as a "peer regulators group". The Network needs to maintain a workable size with 12 Members in maximum in order to assure the ability to react quickly and flexibly to critical situations. Consideration should be given to a broad representation of WHO regions.

11. In reviewing membership applications from additional regulatory authorities, the following criteria should be considered:

The applicant:

(a) represents a leading Regulatory Authority that has responsibility for the regulation of blood, blood products and associated drugs and medical devices, including IVDs;

(b) has the necessary expertise and capacity to address emerging public health challenges;

(c) has a well established, demonstrated institutional capacity and national legal standing to address the delineated objectives of the Network;

(d) is able to provide the necessary information and evidence that the criteria are met, by first completing a questionnaire and if necessary by an oral explanation and discussion with the Network upon invitation of a Representative of the applicant authority by the WHO Secretariat;

(e) nominates a designated Representative and/or the substitute Representative of the applicant Regulatory Authority which contributes in providing the necessary information.

12. A Regulatory Authority interested in becoming a Member should send an application letter to the WHO Secretariat, explaining its interest in membership as well as its potential contribution to the Network. Alternatively, the Members of the Network and the WHO Secretariat can also propose new candidates for membership. The WHO Secretariat will then request the applicant Regulatory Authority to provide the necessary information and evidence for meeting the criteria. At the request of the Network, the WHO Secretariat may invite the applicant candidate to partially participate at the meeting as an observer. If the application and the information provided is found acceptable by unanimous recommendation of the Network Members, the WHO Secretariat shall, in consultation with the ECBS members, decide on whether to approve the application of an applicant candidate. The WHO Secretariat shall thereafter inform the applicant of the decision taken.

13. Whereas Membership in the Network is not time limited, any Member may decide to terminate its involvement in the Network by providing written notice to the WHO Secretariat. The WHO Secretariat shall inform other Members of the Network and remove the Member in question from the List of Members accordingly. In addition, WHO reserves the right to terminate the Membership of any Member with the provision of 30 days prior notice in writing.

D. Invited Experts

14. At the request of the Network, the WHO Secretariat may invite individual relevant experts ("Invited Experts") to participate in certain meetings of the Network, for the purpose of sharing information and/or advising the Network on matters within the sphere of their competence. Invited Experts will not, however, be considered as Members. Such experts will be required to complete a WHO Declaration of Interests form to be provided and assessed by the WHO Secretariat.

E. Operations

15. A Representative is elected by consensus of the Members as Chairperson of the Network. The term of office of the Chair shall normally consist of two years. A Chair should not be elected for more than two consecutive two-year terms. The WHO Secretariat shall facilitate the Chair election procedure. The Chair will work closely with the WHO Secretariat, especially for the organization of the meetings and with regard to reporting on the activities of the Network.

16. The Network provides the Members and other participants with the opportunity to discuss matters and formulate proposals and recommendations which fall within the Terms of Reference. Such proposals and recommendations shall be addressed to the WHO Secretariat for its presentation to the ECBS in a timely manner.

17. The Network may establish adhoc Working Groups composed of Invited Experts to support specific areas of expertise, as necessary. A Member of the Network will be elected as a Chair of each Working Group. The Chair of the Working Group will report to the Network the conclusions reached by the Working Group.

18. The recommendations of the Network are made by consensus of the Members. Recommendations of the Network shall not be binding on WHO or the participating Regulatory Authorities and are not overriding the authority of the respective governing bodies of the Members or of WHO. They constitute expert advice from which the Members, other Regulatory Authorities and WHO may utilize.

19. The Network is not an independent legal entity, but a collaborative mechanism between the Members. Whereas the Members may freely share the issues discussed and the consensus considerations and recommendations of meetings of the Network, the Network cannot be formally represented by individual participants at any other fora. The Chair of the Network or a designated Representative, could however report on the activities of the Network with the agreement of all the Members and the WHO Secretariat.

20. The Network shall conduct its activities by any method of communication that is efficient and appropriate to discharge its objectives, including by in person meetings, videoconference, exchange of written reports and communications, e-mail communications and telephonically. The working language of the Network shall be English.

21. It is understood that Members of the Network have to comply with the rules of their respective authorities regarding confidentiality of privileged information and conflict of interest. It is further understood that the Network operates under the rules, regulations and administrative practices of WHO.

F. Secretariat support

22. Secretariat support for the Network is provided by WHO, acting through the Department of Essential Medicines and Pharmaceutical Policies and the programme responsible for blood products and related biologicals at the Organization's headquarters in Geneva. In this connection, the WHO Secretariat: (a) coordinates the organization of the meetings and other communications of the Network, and of any Working Groups, (b) prepares and distributes, in consultation with the Chair, draft agendas, meeting reports, progress reports, etc, (c) receives and submits applications for membership in the Network to the Members, and (d) receives and informs the Members of notices of termination.

23. In addition, WHO, as part of its secretariat support for the Network, acts as a central repository of information and documentation relevant to the Network (including in particular reports of the Network and Working Groups), and disseminates and distributes such information and documentation to the regulatory authorities of WHO Member States and the public as appropriate, including through the WHO web site.