

- **European Directorate for the Quality of Medicines & HealthCare:**
- **Structure, Aims and Role in Providing Safety and Quality of Medicines in Europe**

Standardisation of Medicines

Harmonisation of Requirements

Cairo - Egypt, 22 March 2009

Jean-Marc Spieser, Head DBO-Healthcare

EDQM / Council of Europe



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CONTENT

GENERALITIES ON THE EUROPEAN ENVIRONMENT

EDQM Activities

Transfusion Medicine

European Pharmacopoeia

monographs, general methods /chapters,
reference materials

OMCL(Official Medicines Control Laboratories) Network

network activities

batch release

PTS



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European Directorate for the Quality of Medicines & HealthCare (EDQM)

- Mission: to contribute to the basic human right of access to good quality medicines and healthcare

- Health is a social human right indispensable for the exercise of all other human rights, for prosperity and democratic stability of people in Europe



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EDQM Activities

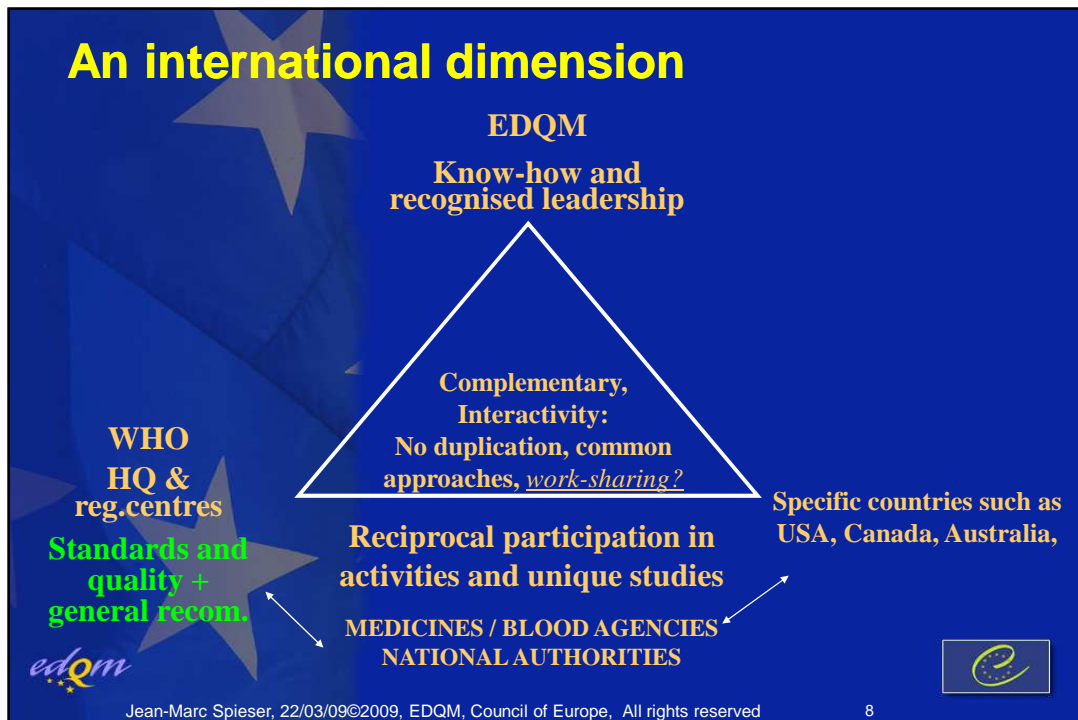
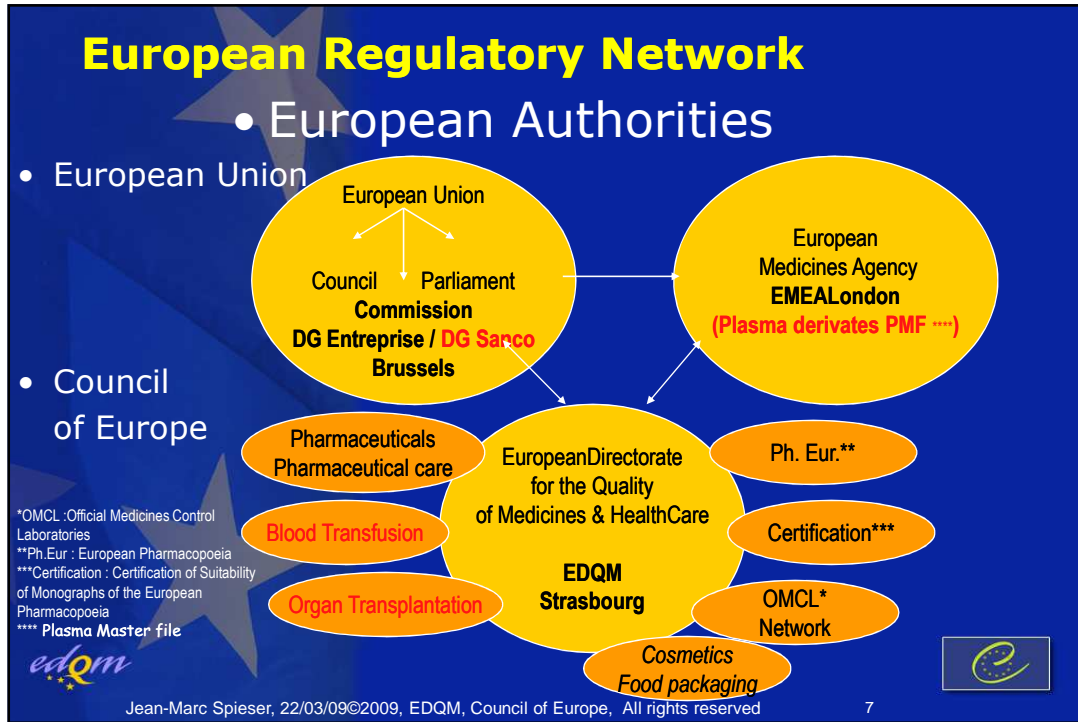
- Blood transfusion medicine
- Elaboration of the European Pharmacopoeia
 - Monographs, general methods
 - Biological reference preparations - BRPs
- OMCL network
 - Batch release
 - PTS



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EDQM Activities

- Blood Transfusion medicine



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Transfusion medicine - CD-P-TS

- Principles guiding our work

- Non commercialisation of substances of human origin
- Voluntary and non remunerated donation
- Protection of the health of donors and recipients of blood and blood products
- Networking, quality, efficiency, exchange of viewpoints and know-how and ?... eventually products ?



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EDQM Activities

- Blood Transfusion medicine
- resolution on « Donor responsibility and on limitations to donation of blood and blood components » approved in 2008 by committee of Ministers of CoE



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NEW: Blood Transfusion

- GUIDE including harmonised principles for
- Quality system for
- Blood establishments
- Blood collection
- Blood components
- Transfusion practices
- ...English + French edition
- National editions (It., Gr., Tu. ...)



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CD-P-TS

Guide for the preparation, use and quality assurance of blood components - 15th edition

currently under development

- revision of the technical and scientific content
- restructuring of the presentation

will be published early 2010 in English and French followed by Spanish and Russian version as soon as possible



CD-P-TS

15th edition **NEW STRUCTURE**

- > **chapters - methods - general principles**
- > **definition and specifications of blood components**
(presentation and content standardised : norms)



CD-P-TS

Guide 16th edition

-> information on products spc like and general principles

additionnal publication ?

Optimal clinical use of blood / blood components (including pediatric use and quality aspects such as best practice)



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Clinical use of blood

First step

Organisation of an international symposium to exchange view points between European clinical users of blood / components concerning optimal use of these products (on invitation) proceedings will be public.

24-25 avril 2009 Wildbad-Kreuth Bavaria Germany



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CD-P-TS**European Bank of frozen rare groups of blood**

Creation of a working group aiming at updating the list and details concerning preservatives used, making the inventory of different stocks throughout Europe and eventually exploring the possibility of developing a central data base of those products



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**CD-P-TS****Donors management**

Creation of a working group the role of which would be to develop assistance tools for facilitating donor management and consultation by Member States



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Questionnaire on collection, controls and use of blood / components in Europe

- Yearly reporting by Member States

Trend analysis: 2001-2007 in progress
(soon available)



 

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Also planning:

assistance programme
proficiency testing studies (PTS) and external
quality assessment of control laboratories of
transfusion centres and blood banks
hopefully initiated in June 2009 with the support
of DG Sanco EC commission Brussels

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Resolution

Recommends to governments of member states:

1. to ensure that blood components are produced solely from blood collected from safe blood donors;
2. to foster cooperation and trust between blood establishments and blood donors, in particular by informing the public about the need and criteria for selection of blood donors;
3. to guarantee that blood establishments provide prospective donors with clear and appropriate information, including at least the following:



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- 3.1. essential nature of blood, blood donation procedure, testing of collected blood, components derived from collected blood;
- 3.2. possible risks to the health of the donor associated with blood donation;
- 3.3. possible risks for the recipient of blood or blood components of a given donor;
- 3.4. donor's duty to provide the blood establishment with all relevant information to the best of the donors' knowledge, in particular on factors and activities which may increase risks for the recipient;
- 3.5. right to withdraw from donation at any time during the procedure for any reason including doubts on suitability without the need to explain decision;
- 3.6. importance for the donor to give the blood establishment post-donation information if the donor doubts about his/her suitability or in the event of health status change after donation;
- 3.7. the consequences of failure to provide the information as specified above during the donor assessment procedure;
- 3.8. confidentiality of all personal information given by the donors to the blood establishment notably those related to health and behavior;



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4. to ensure that blood establishments are ultimately responsible for the quality and safety of the blood and blood components collected, in particular blood establishments should:

- 4.1. be responsible for the final acceptance or deferral of donors on grounds of a risk assessment based on regularly updated epidemiological data, and bearing in mind the right of blood recipients to the protection of their health, and the resulting obligation to minimise the risk of transmission of infectious diseases. Those rights and obligations override any other consideration including individuals' willingness to donate blood;
- 4.2. set up arrangements for fair compensation in case harm is caused to the recipient and/or the donor of blood and blood components.



EDQM Activities

- European Pharmacopoeia



The European Pharmacopoeia

- Objectives:
 - Provide authoritative quality standards for medicinal substances that are **IMPORTANT** for **PUBLIC HEALTH** in Europe (all different domains:chemicals,biologicals,herbals, radiopharmaceuticals, vaccines, **PLASMA DERIVATES**,etc)
 - **RESPOND RAPIDLY** to new risks to public health (mad cow's disease, counterfeit medicines, heparins,blood borne viruses screening by NAT etc.)
 - Facilitate the **FREE MOVEMENT** and trade of medicines among countries
 - Facilitate **ACCESS** to high-quality medicines
 - **ENSURING THE SAME QUALITY OF MEDICINES FOR ALL EUROPEAN CITIZENS and beyond**



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European Pharmacopoeia Today

- More than 2200 monographs and 300 general texts
- Periodically up-dated to the state of the art of production and control methods

“Life-cycle management” of monographs is vital to reflect the actual market situation and enable them to contribute to optimal protection of public health, e.g. in controlling impurities! (safety issues) – plasma for fractionation



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The European Pharmacopoeia : plasma derivatives

- 6 general chapters
- 15 general methods
- 28 monographs
- 19 Biological Reference Preparations (BRPs)
- = unique standards for guaranteeing safety, efficacy and quality of the products in clinical therapeutical use (batch consistency)



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Ph.Eur Chapters and related BRPs (general methods -1)

CHAPTER N°	TITLE	BRP	COMMENTS
2.6.15	Prekallikrein activator	<i>Prekallikrein activator in albumin BRP</i>	
2.6.17	Test for anticomplementary activity of immunoglobulin	<i>Human immunoglobulin BRP</i>	
2.6.20	Anti-A and anti-B haemagglutinins (indirect method)	<i>Anti-A and anti-B haemagglutinins +positive / negative BRP</i>	Ongoing Revision to implement a direct method and BRPs (17-19 march 2009)
2.6.21.	Nucleic acid amplification techniques	<i>Validation of nucleic acid amplification techniques (NAT) for the detection of hepatitis C virus (HCV) RNA in plasma pools : guidelines; B 19 virus</i>	Guideline on B19 will be soon implemented (Group 6B should examine the comments received after Pharmedeuropa enquiry)
2.6.22	Activated coagulation factors		
2.6.26	Test for anti-D antibodies in human immunoglobulin for intravenous administration	<i>Immunoglobulin (anti-D antibodies test) BRP & Immunoglobulin (anti-D antibodies test negative control) BRP</i>	



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Ph.Eur Chapters and related BRPs (general methods -2)

CHAPTER N°	TITLE	BRP	COMMENTS
2.7.4	Assay of human coagulation factor VIII	<i>Human coagulation factor VIII BRP</i>	
2.7.9	Test for Fc function of immunoglobulin	<i>human immunoglobulin BRP.</i>	Recently updated, addition of a micromethod
2.7.10	Assay of human coagulation factor VII	<i>Human coagulation factor VII concentrate BRP</i>	
2.7.11	Assay of human coagulation factor IX	<i>Human coagulation factor IX concentrate BRP</i>	
2.7.12	Assay of heparin in coagulation factors		
2.7.13	Assay of human anti-D immunoglobulin	<i>Human anti-D immunoglobulin BRP</i>	
2.7.17	Assay of human antithrombin III		
2.7.18	Assay of human coagulation factor II		



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**Ph.Eur Chapters and related BRPs (general methods -3)**

CHAPTER N°	TITLE	BRP	COMMENTS
2.7.19	Assay of human coagulation factor X		
2.7.21	Assay of human von Willebrand factor		
2.7.22	Assay of human coagulation factor XI		
2.7.25	Assay of human plasmin inhibitor		
2.7.30	Assay of human protein C		
2.7.31	Assay of human protein S		
2.7.32	Assay of human α -1-proteinase inhibitor		



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Ph.Eur Monographs and related BRPs (individual specific products -1)

MONOGRAPH N°	TITLE	BRP	COMMENTS
0024	Human fibrinogen		
0209	Anticoagulant and preservative solutions for human blood		
0255	Human albumin solution	<i>Human albumin for electrophoresis BRP</i>	
0275	Human coagulation factor VIII	<i>BRP available</i>	
0338	Human normal immunoglobulin	<i>-Human immunoglobulin for electrophoresis BRP -Human immunoglobulin (molecular size) BRP - Human hepatitis A immunoglobulin BRP</i>	
0397	Human measles immunoglobulin		



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**Ph.Eur Monographs and related BRPs (individual specific products -2)**

MONOGRAPH N°	TITLE	BRP	COMMENTS
0398	Human tetanus immunoglobulin	<i>Human tetanus immunoglobulin BRP</i>	Currently proposal to replace <i>in vivo</i> by <i>in vitro</i> potency assay
0554	Human prothrombin complex		
0557	Human anti-D immunoglobulin	<i>BRP available</i>	
0617	Human rubella immunoglobulin		
0722	Human hepatitis B immunoglobulin		
0723	Human rabies immunoglobulin	<i>Human rabies immunoglobulin BRP</i>	
0724	Human varicella immunoglobulin		



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Ph.Eur Monographs and related BRPs (individual specific products -3)

MONOGRAPHN°	TITLE	BRP	COMMENTS
0769	Human hepatitis A immunoglobulin	<i>Human hepatitis A immunoglobulin BRP</i>	
0853	Human plasma for fractionation	<i>Hepatitis C virus RNA for NAT testing BRP , B19</i>	
0878	Human antithrombin III concentrate		
0903	Fibrin sealant kit		
0918	Human normal immunoglobulin for intravenous administration	<i>Human immunoglobulin for electrophoresis BRP human immunoglobulin (molecular size) BRP</i>	
1016	Human hepatitis B immunoglobulin for intravenous administration		



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**Ph.Eur Monographs and related BRPs (individual specific products -4)**

MONOGRAPHN°	TITLE	BRP	COMMENTS
1223	Human coagulation factor IX	BRP avail.	
1224	Human coagulation factor VII	BRP avail.	
1527	Human anti-D immunoglobulin for intravenous administration	<i>B19 virus DNA for NAT testing BRP</i>	
1528	Human varicella immunoglobulin for intravenous administration		
1644	Human coagulation factor XI		
1646	Human plasma (pooled and treated for virus inactivation)	<i>-Hepatitis C virus RNA for NAT testing BRP -B19 virus DNA for NAT testing BRP -Human hepatitis A immunoglobulin BRP</i>	



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Ph.Eur Monographs and related BRPs (individual specific products -5)

MONOGRAPH N°	TITLE	BRP	COMMENTS
1928	Anti-T lymphocyte immunoglobulin for human use, (animal)		
2298	Human von Willebrand factor		
2387	Human α -1-proteinase inhibitor		

BUT ALSO GENERAL CHAPTERS OF INTEREST SUCH AS

STERILITY, MICROBIAL DETERMINATION etc.

Guidelines hematopoietic stem cells



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Membership & Observership

- 36 member countries + the European Union
- Ph. Eur. is the official Pharmacopoeia in Europe for all issues more than one Member State is interested in
- 23 observer countries and international organisations including World Health Organisation (WHO) and USA (FDA)
- In 2008: 3 new observers (Armenia, Argentina and Moldova)



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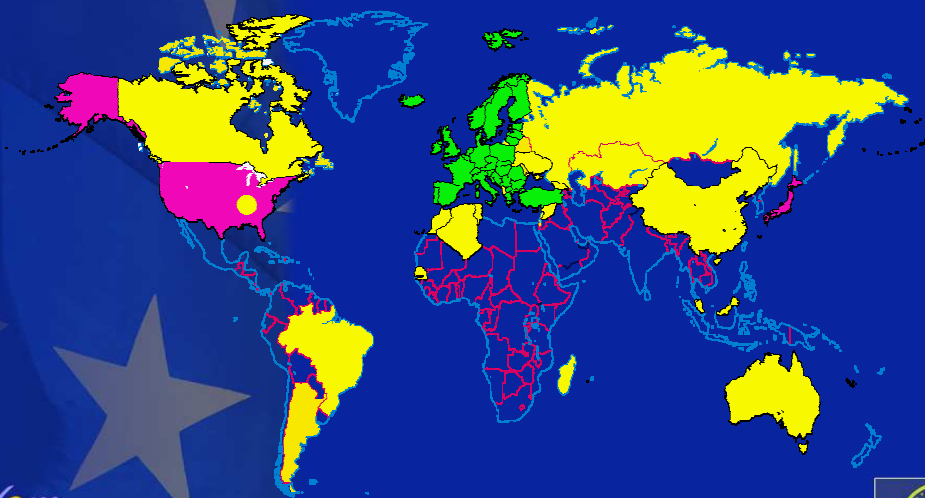
Ph. Eur. Member States & Observers



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In the World



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EDQM Activities

- Establishment and provision of **reference standards and materials** (chemical and biological)



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EDQM Activities

- The OMCL Network

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EDQM Activities

- The **OMCL Network**
- General coordination of activities fostering of mutual confidence & recognition of data & results
 - Implementation of quality assurance system
 - Audits of OMCLs by peers (EDQM and Network members) periodical
 - Proficiency testing studies (PTS)
 - Training courses (Procedures, QA and analytical techniques in OMCLs)

Work sharing in Market surveillance

OFFICIAL CONTROL AUTHORITY BATCH RELEASE (OCABR) for vaccines and plasma derivatives

Data bases of results with secured access for Auth.



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EDQM Activities

- **OFFICIAL CONTROL AUTHORITY BATCH RELEASE (OCABR) for vaccines and plasma derivatives**
- Specific regulation in Europe
- Each product must have a Marketing Authorisation but in addition each batch will be submitted to a double control
 1. Manufacturer Lot release
 2. OCABR independent batch release (protocol review and some keys tests for safety and potency)
- Prior to placing each lot on the market
- **Only products which have passed both controls can be used in patients**



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PTS - Goals

- Measure performance of **participating labs** regarding biologicals especially for methods used for
 - Official Control Authority Batch Release
 - Market Surveillance Studies
- Open to
 - OMCLs
 - Labs testing for OMCLs
 - Private labs (manufacturers); since 2003



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PTS - Scope

- Biologicals
 - Vaccines
 - Plasma derived products
 - Biotech products
- Biological methods (no animal tests)
 - Assay
 - SEC
 - Contaminants (HCV, Parvovirus B19)



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PTS - Achievements

- 36 studies concluded since 1997
- 16 studies on vaccines, blood products
 - potency assay FVIII, FIX, influenza vaccine, IPV-D-antigen, acellular pertussis vaccine, Hep A Ig
 - SEC for Hib vaccine, albumins
 - Endotoxin in vaccines, heparins
 - Igs - protein content
 - PKA content of albumin
- 15 studies on HCV-NAT
- 5 study on B19-NAT



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Examples

- PTS Studies on HCV-NAT (e.g. PTS061)
- PTS Studies on Parvovirus B19



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HCV RNA Testing of Plasma Pools by NAT

- EP mono. *Human plasma for fractionation:*
NAT testing of all plasma pools
- “... using a validated NAT (2.6.21).”
- “... complies if found non-reactive..”
- Controls to be included:
 - 100 IU/ml positive control
 - positive internal control (for inhibitors)



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PTS061: Materials & Methods

- Panel:
 - 20 test samples: 0.6 ml (frozen)
 - Negative samples
 - Genotypes: 1, 3a, 4a, 6a
 - various titres
 - known to participants
- NAT Methods: routine in-house
 - Details mentioned in report



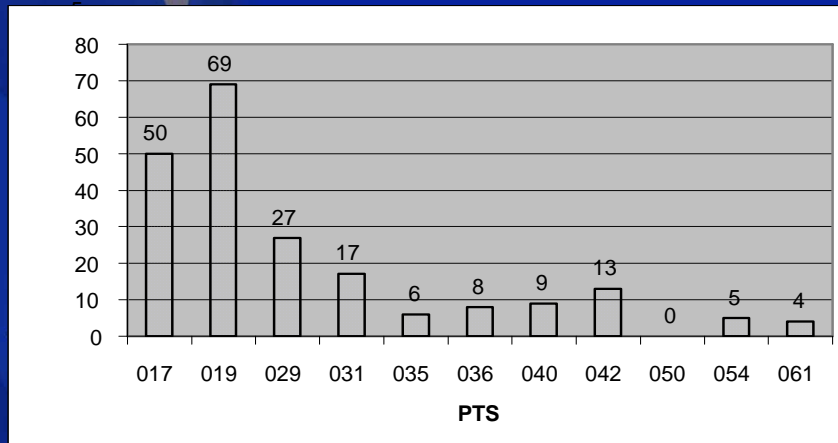
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HCV-NAT: PTS 2000-2006

% undetected 100 IU/ml samples



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Conclusion HCV-NAT PTS

Significant improvement in performance of HCV NAT between 2000 and 2006



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PTS FOR BLOOD TRANSFUSION

- Based on this experience EDQM will develop a PTS programme for control labs in the transfusion medicine customised to the needs and adapted to the requirements set up in the EU Directive namely demonstration that an External quality assessment is in place
- The participation will be eligible for EU but also BEYOND



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