THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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Blood Proficiency Testing Scheme (B-PTS) Programme:

Considerations for Common Technical Specifications (CTS)

Keeping up with Reality and Quality: A Challenge for Blood Establishments

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Implementing Technical Standards and EU Legislation

Funded by the European Union and the Council of Europe — EUROPEAN UNION — COUNCIL OF EUROPE — CONSEIL DE L'EUROPE — Implemented by the Council of Europe

External Quality Assessments
B-PTS
Blood Proficiency Testing Scheme

Quality Management Programme
B-QM
Blood Quality Management Programme

- Dedicated to **European Blood Establishments** to support the development, implementation and improvement of BE Quality System (QS)
- The Programmes are co-funded by the EDQM and the European Commission
- To ultimately improve the quality and safety of blood components and plasma-derived medicinal products, and of patients undergoing blood transfusion

BLOOD-PROFICIENCY TESTING SCHEME (B-PTS) PROGRAMME

► **AIM: B-PTS** provides Blood Establishments (BEs) with an objective mean of assessing that the **testing results** for blood donations are **reliable**.

'Regular participation in a formal system of proficiency testing, such as an external quality-assurance programme'

EU Directive 2005/62/EC; Good Practice Guidelines ,Guide to the Preparation, Use and Quality Assurance of Blood Components

Nucleic Amplification Technique (NAT)
HBV, HCV, HIV

Serology
Anti-HCV
Anti-HIV/p24
Anti-treponema
HBsAg/Anti-HBC

Immunohaematology
ABO, Rhesus, Kell, extended phenotyping and irregular bodies

► **Since 2010:** **6** studies (300-400 participants)/year, over **50** studies to date covering **33** European countries

B-PTS Programme – Reflection and Consideration

While the aim of the B-PTS Programme is to assess the performance of blood establishment laboratories;

Information has been elicited from the results of the schemes related to the **use and performance of specific testing assays**

- Explored further through B-PTS studies (specifically HBsAg)
- Basis of consideration for the common technical specifications (CTS) for in vitro medical devices (IVD)

Common Technical Specifications (CTS)

What are the CTS?

They establish performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials;

As a general rule, manufacturers of IVD are required to comply with the CTS;

*Commission Decision **2002/364/EC** on Common Technical Specifications for In Vitro Diagnostics*

Updated by;

***2009/886/EC** - to reflect technical progress in the performance and analytical sensitivity of devices*

***2019/1244 -** Requirements for HIV and HCV antigen and antibody combined tests and requirements for nucleic acid amplification techniques with respect to reference materials and qualitative HIV assays;*

***2020/35 -** Definitions of first–line assays and confirmatory assays, requirements for devices for self-testing and requirements for HIV and HCV rapid tests, confirmatory and supplementary assays*

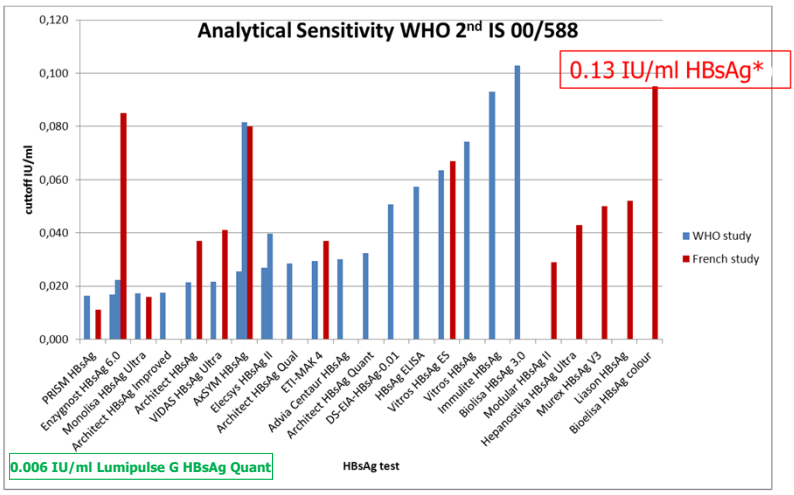
Common Technical Specifications – HBsAg Screening Assays

Table 1

"Screening" assays: anti-HIV 1 and 2, anti-HTLV I and II, anti-HCV, HBsAg, anti-HBc

		Anti-HIV-1/2	Anti-HTLV-I/II	Anti-HCV	HBsAg	Anti-HBc
Diagnostic sensitivity	Positive specimens	400 HIV-1 100 HIV-2 including 40 non-B-subtypes, all available HIV/1 subtypes should be represented by at least 3 samples per subtype	300 HTLV-I 100 HTLV-II	400 (positive samples) Including samples from different stages of infection and reflecting different antibody patterns. Genotype 1-4: > 20 samples per genotype (including non-a sub-types of genotype 4); 5: > 5 samples; 6: if available	400 Including subtype-consideration	400 Including evaluation of other HBV-markers
	Seroconversion panels	20 panels 10 further panels (at Notified Body or manufacturer)	To be defined when available	20 panels 10 further panels (at Notified Body or manufacturer)	20 panels 10 further panels (at Notified Body or manufacturer)	To be defined when available
Analytical sensitivity	Standards				0.130 IU/ml (Second International Standard for HBsAg, subtype adw2, genotype A, NIBSC code 00/583)	
Specificity	Unselected donors (including first-time donors)	5 000	5 000	5 000	5 000	5 000
	Hospitalised patients	200	200	200	200	200
	Potentially cross-reacting blood-specimens (RF+, related viruses, pregnant women, etc.)	100	100	100	100	100

HBsAg CE Marked Screening Assays - Studies



Many assays performing significantly better than the CTS requirements;

Indicated higher analytical sensitivity in certain CE marked assays over others on the market

WHO study: Chudy et al. 2013; J Clin Virol 58:47-53;
French study: Servant-Delmas et al. 2012; J Clin Virol 53:338-345.
***CTS requirement, IVD Directive 98/79/EC**

B-PTS Studies - HBsAg

HBsAg:		re+/total	re+ percent
➢ ***0.10 IU/ml***			
B-PTS007	not defined	43/43	100.0%
B-PTS021	core *	64/64	100.0%
B-PTS028	core	71/71	100.0%
B-PTS035	core *adw2*/gt A	80/81	98.8%
	core *ayw3*/D2	77/81	95.1%
B-PTS041	core *adw2*/gt A	76/76	100.0%
	core *ayw3*/D2	76/76	100.0%
B-PTS048	core *adw2*/gt A	67/67	100.0%
	core *adr*/C2	67/67	100.0%
➢ ***0.05 IU/ml***			
B-PTS007	not defined	42/43	97.7%
B-PTS021	non-core**	64/64	100.0%
B-PTS028	core	70/71	98.6%
B-PTS035	core *adw2*/gt A	73/81	90.1%
B-PTS041	core *adw2*/gt A	75/76	98.7%
B-PTS048	core *adw2*/gt A	64/67	95.5%

***Core Sample**

Sample that has to be correctly determined as reactive or non-reactive for a satisfactory performance:

****Non Core Sample**

Sample that does not require to be found reactive or non-reactive for a satisfactory performance - used for educative purpose in the study:

Trend analysis performed -B-PTS Advisory Group
M. Chudy, M.L Hecquet, D. Sondag, S.Pupella, G.Pisani, E. Regourd

Where unsatisfactory performance has occurred – cases where this could be attributed to the analytical sensitivity of the assay

HBsAg – Consideration for CTS

HBsAg assays used for screening of blood donors and for diagnosis of patients suspected of having HBV infection;

Performance requirements should correspond to the expected HBsAg Levels

Blood Donors – better analytical sensitivity needed – low HBsAg levels

Diagnosis of Patients – high analytical sensitivity not as critical? – HBsAg levels generally high;

Candotti D et. Al Transfusion Transmission of Hepatitis B Virus: still learning more about it. ISBT Science Series (2011) 6, 234–240
World Health Organisation – Performance Evaluation Acceptance Criteria for HBsAg In vitro diagnostics in the context of WHO Prequalification
Jaroszewicz J et. al. Hepatitis B Surface Antigen (HBsAg) levels in the natural history of hepatitis B virus (HBV) infection: A European perspective. J Hepatology 2010 vol 52 j 514-522

HBsAg – Consideration for CTS

Taking into account the performance and use of CE Marked HBsAg assays on the market,

For HBsAg assays Should the CTS requirements distinguish between the analytical sensitivity requirements for **screening versus diagnostic** use??

B-PTS Programme – Perspectives and Objectives

Continue to **monitor and improve** the programme based on trends and observations;

Immunohematology – IA for patient testing

CONCLUDED STUDIES	2017	2018	2019
HCV/HBV/HIV NAT	97.40%	100%	100%
Anti-HCV	94.30 %	100%	100%
Anti-HIV/p24	88.70%	100%	100%
Anti-Treponema	94 %	94 %	94 %
HBsAg/anti-HBc	82,4% (HBsAg) 100% (anti-HBc)	98 % (HBsAg) 100 % (anti-HBc)	98 % (HBsAg) 100 % (anti-HBc)
ABo, Rh Grouping	96% (ABO, Rh) 94% (Ext. phenotyping) 76% (Ir. Antibodies)	97 % (ABO, Rh) 93 % (Ext. phenotyping) 75 % (Ir. antibodies)	97 % (ABO, Rh) 93 % (Ext. phenotyping) 75 % (Ir. antibodies)

Quality Control

Bacterial Screening Study

B-PTS Advisory Group

MEMBERS	ORGANISATION
M. Chudy	*Paul Ehrlich Institut, Germany*
G. Pisani	*Istituto Superiore di Sanità, Italy*
S. Pupella	*National Blood Center, National Institute of Health, Italy*
D. Sondag	*Croix Rouge, Belgium*
M. Riley	*National Blood Transfusion Centre, Malta*
M. Prax	*Paul Ehrlich Institut, Germany*

- Proposals for annual B-PTS programme and future studies;
- Nomination of Scientific Advisors for B-PTS studies;
- Provide support for scientific, technical and logistical issues of the activity;
- Provide advice regarding the improvement of the studies and the activity;
- Produce additional material (e.g. guidance) in relation to the B-PTS activity, based on evidence collected during the B-PTS activity;
- Provide recommendations to relevant parties on scientific/regulatory aspects based on outcomes and evidence collected during the B-PTS activity,

Acknowledgments

- **B-PTS Advisory Group;**
- **Perrine Arnould – Scientific Assistant;**
- **Elena Regourd – Statistics**
- **Marie-Laure Hecquet – Head of SoHO section**

Thank you

- **EDQM Colleagues;**
- **CD-P-TS;**
- **EC/DG-SANTE;**

Thank you for your attention

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