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Quality Control of Polysaccharide Vaccines by the Belgian National Control Lab (OMCL) in the European Batch Release Framework : Activity Report 2012

Scientific Institute of Public Health

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List of Abbreviations

BELAC	Belgian Accreditation Body
$CCID_{50}$	Cell Culture Infectious Dose 50 %
DMAB	p-dimethylaminobenzaldehyde
EDQM	European Directory for the Quality of Medicines & Healthcare
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
Free PS	Free Polysaccharide
GC-FID	Gas-Chromatography-Flame Ionization Detector
Hib	Haemophilus influenza type b
HPLC-PAD	High Performance Liquid Chromatography-Pulsed Amperometric Detector
HPLC-SEC	High Performance Liquid Chromatography-Size Exclusion Chromatography
ICP-AES	Inductively coupled plasma-Atomic Emission Spectroscopy
ISO	International Standardisation Organisation
LAL	Limulus_amoebocyte_lysate
MAA	Marketing Authorisation Application
MJA	Mutual Joint Audit
OCABR	Official Control Authority Batch Release
OMCL	Official Medicine Control Laboratory
OPV	Oral Polio vaccine
Ph.Eur.	European Pharmacopoeia
PS	Polysaccharide
PTS	Proficiency Testing Scheme
UPLC	Ultra Performance Liquid Chromatography
VLP	Virus-like particle
WHO	World Health Organisation
WIV-ISP	Wetenschappelijk Instituut voor volksgezondheid - Institut de Santé Publique

PART 1: GENERAL SECTION

Introduction

The **Biological standardisation** unit of the Scientific Institute of Public Health (WIV-ISP) has a legal activity of quality control for vaccines intended for human use and plasma derived medicinal products. It checks the compliance of each batch of these biological medical products by laboratory analyses prior to their placing on the European market, independently of manufacturers and according to the European Batch release procedure **[1]**. For the international market, batches are released on basis of the protocol review. Testing is not mandatory but may be performed either on a random basis or at the request of local competent authority.

The unit carries out expert activities in these fields, specifically by assessing the "quality" part of registration files, participating in Good Manufacturing Practices (GMP) inspections and the accreditation of blood establishments, as well as participating in various opinion groups and drafting regulatory texts on these matters.
The aim of the service is also to carry out research and development activities in these fields, for normative purposes.

In Belgium, the Federal Agency for Medicines and Health Products **[2]**, founded on the 1st January 2007, is the competent authority responsible for the **quality**, **safety** and **efficacy** of medicines and health products, for granting the marketing authorisation namely to the vaccines manufacturers and for performing the GMP inspections.

The Scientific Institute of Public Health is declared as the Official Medicines Control Laboratory for immunological products in the Royal Decree of 14 December 2006 related to the medicines for human and veterinary use (revision of the Royal Decree of 6 June 1960).

The Biological Standardisation unit performs the OCABR procedure for the human vaccines according the Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC.

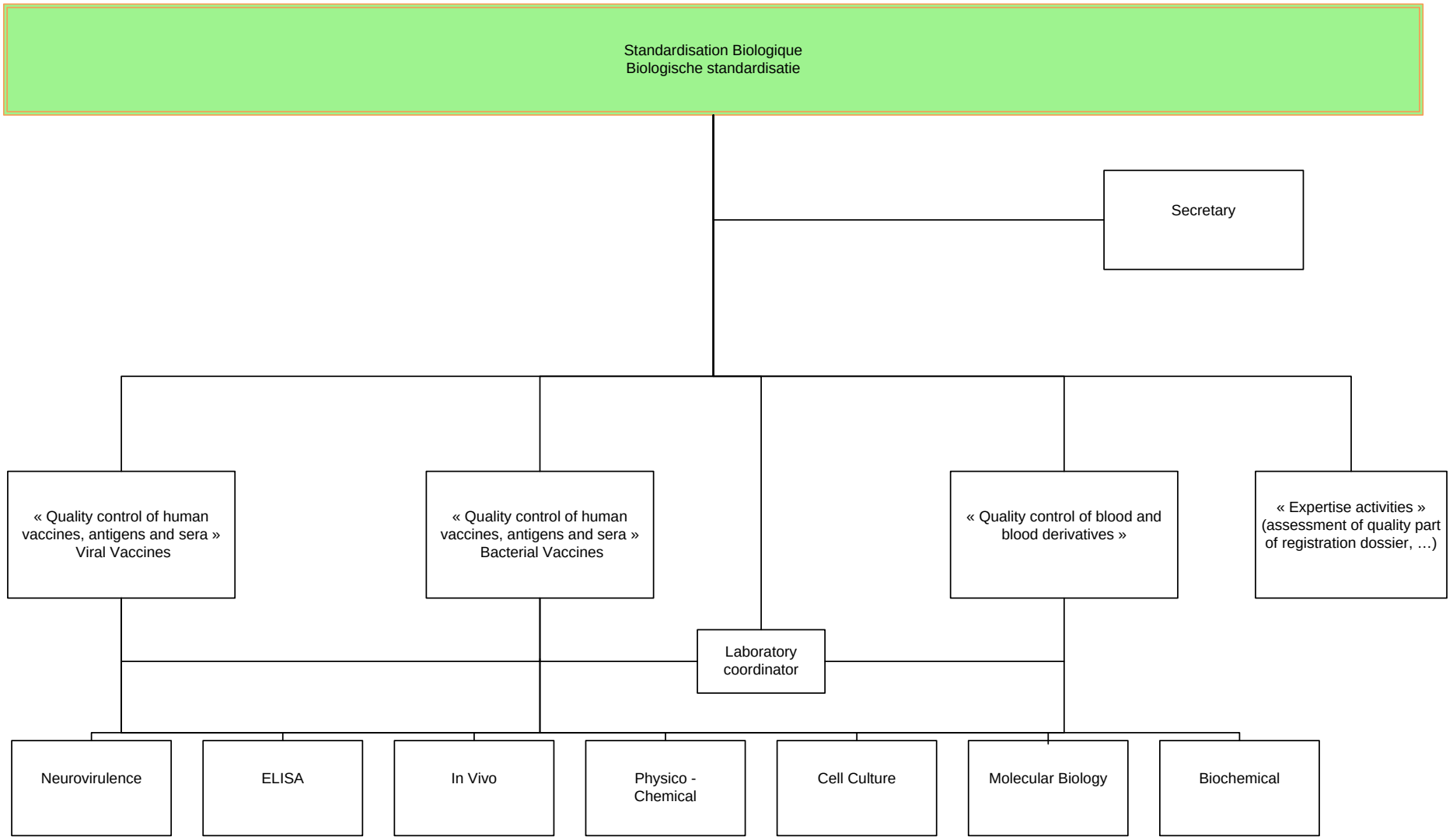
Section A: Organisation of the Competent Authority/OMCL

A.1 General Structure

The Biological Standardisation unit, OMCL for biological products, is part of the Operational Direction “Expertise, Service Provision and Customer Relations” of the Scientific Institute of Public Health.

The structure and the organization of the release activities of the Biological Standardisation unit are shown on the next two pages.


ORGANISATION CHART WIV-ISP
GENERAL DIRECTION
Services of the Executive director
Support services
Managerial posts
Advisor posts
COMMUNICABLE AND INFECTIOUS DISEASES
Food pathogens
Bacterial diseases
Viral diseases
Mycology and aerobiology
Immunology
Platform of animal facility
Laboratory of medical microbiology
Platform BSL3 and Metrology
FOOD, MEDICINES AND CONSUMER SAFETY
Medicines
Toxic and pharmacological residues
Emergent chemical risks
Pesticides
Platform for chromatography and mass spectrometry
PUBLIC HEALTH AND SURVEILLANCE
Toxicology
Healthcare services research
Surveys, lifestyle and chronic diseases
Infectious diseases among the general population
Healthcare associated infections & Antimicrobial resistance (NSIH)
Health and environnement
Cancer Centre
EPI methods for Public health crisis
Public health information system
Special survey
EXPERTISE, SERVICE PROVISION AND CUSTOMER RELATIONS
Biosafety and biotechnology
Biological standardization
Quality of medical laboratories
Platform Biotechnology and molecular biology
Coordination Cell for customer relations and orientation
Dispatching Centre


Standardisation Biologique
Biologische standardisatie
Secretary
« Quality control of human vaccines, antigens and sera » Viral Vaccines
« Quality control of human vaccines, antigens and sera » Bacterial Vaccines
« Quality control of blood and blood derivatives »
« Expertise activities » (assessment of quality part of registration dossier, …)
Laboratory coordinator
Neurovirulence
ELISA
In Vivo
Physico - Chemical
Cell Culture
Molecular Biology
Biochemical

A.2 Personnel Matters

Persons listed hereunder have actively participated in polysaccharide vaccine testing in 2012. Please see also reports to be published from other sections of the unit.

Physicochemical assays, all vaccines

Lorenzo Tesolin, M. Sc, Wim Van Molle, PhD. with technical assistance from Rita De Brandt, Betty Bracke, Saloua El Youssoufi, Dominique Pecher, Rachida Elkhalouki, Ind. eng., Innocent Habyalimana and Laurence Vifquin

Immunochemical assays, all vaccines

Isabelle Hansenne PhD. with technical assistance from Virginie Misplon, Camille Domicent, M.Sc., Hanh Van Dang, Sébastien Garcia-Sanchez, Véronique Massé and Romain Algoet.

Biochemical assays, all vaccines

Olivier Carabin, M.Sc, with technical assistance from Fatiha Rahmouni and Sabah Said, Ind. eng.,

Head of Biological Standardisation Unit:

Geneviève Waeterloos, M.Sc. with secretarial assistance from Pascale Prévédello.

Section B: Quality Assurance System

The Biological Standardisation unit was first EN 45001 accredited in 1999 and accredited ISO 17025 since 2002. The ISO 17025 accreditation was renewed after a last external audit performed in April 2011 by BELAC, the Belgian Accreditation body **[3]** .

See the accreditation' certificate n° 109-T (valid till 31/01/2015) in annex 1.

List of accredited tests

Assay Code	Sample type	Measured parameter Range of measurement	Description of the assay Equipment
42/III-01/F	Adsorbed Vaccines	Identification & quantification of the HAV antigens content	ELISA Principal equipment colorimeter, washing equipment
42/III-03/F	Adsorbed Vaccines	Identification & determination of the HBsAg antigen content	ELISA Principal equipment colorimeter, washing equipment
42/III-05/F	Bulks of Vaccines	Purity and Identity	PAGE , Coomassie blue and silver staining, and visual evaluation. Principal equipment: PAGE equipment, staining equipment
42/III-09/F	Histological slides - nervous system of monkeys injected with oral poliomyelitis vaccine	Number and lesion scores	Optical Microscopy Principal equipment: Optical microscope
42/III-10/F	Oral Poliomyelitis Vaccines	Number of cultivable live viral particles	Cytopathic effect of virus on cell culture by $CCID_{50}$, neutralisation with specific antiserum – calculation of titre Principal equipment:: laminar flow, incubator and optical microscope
42/III-17/F	Vaccines for human use	Osmolality	Measure of freezing temperature based on the osmolality Principal equipment: osmometer

Assay Code	Sample type	Measured parameter Range of measurement	Description of the assay Equipment
42/III-18/F	Haemophilus influenzae b (Hib) Vaccines	Molecular Size Distribution	HPLC by size exclusion with Refractive Index and UV detector Principal equipment: HPLC
42/III/19/F	Rotavirus vaccines	Number of cultivable live viral particles	Cytopathic effect of virus on cell culture by $CCID_{50}$, immunostaining /direct reading – calculation of titre Principal equipment: laminar flow, incubator and optical microscope
42/III-21/F	Measles, Mumps, Rubella, Varicella Vaccines	Number of cultivable live viral particles	Cytopathic effect of virus on cell culture by $CCID_{50}$, neutralisation with specific antiserum – calculation of titre Principal equipment: laminar flow, incubator and optical microscope
42/III-22/F	Varicella Vaccines	Number of cultivable live viral particles	Cytopathic effect of virus on cell culture by $CCID_{50}$, neutralisation with specific antiserum – calculation of titre Principal equipment: laminar flow, incubator and optical microscope
42/III-26/F	Vaccines for human use	pH and visual appearance	pH and visual inspection Principal equipment : pH-meter – Black & White boxes
42/III-28/F	Inactivated Poliomyelitis Vaccines	D-Antigen Content	ELISA Principal equipment colorimeter, washing equipment

Assay Code	Sample type	Measured parameter Range of measurement	Description of the assay Equipment
42/III-51/F	Vaccines	Determination of 3-O-deacyl-4'Monophoshoryl Lipid A content	GC-FID, Hydrolysis of MPL in fatty acid, derivatization and analysis on a gas chromatograph with flame ionization detector
42/III-52/F	Haemophilus influenzae type b vaccines	Analysis of the total polysaccharides content	HPLC-PAD Dionex, polysaccharide hydrolysis in ribitol-ribose–phosphate units and analysis on anionic column with pulsed amperometric detector (oxydation of carbohydrates).
42/III-54/F	Tetravalent Meningococcal Vaccines	Quantification & identity of polysaccharides ACWY	ELISA Principal equipment colorimeter, washing equipment
42/III-57/F	Human Papillomavirus Vaccines	Determination of HPV16 L1 VLP & HPV18 L1 VLP antigen content	ELISA Principal equipment colorimeter, washing equipment
42/III-59/NF	Monovalent pneumococcal conjugated bulks	Determination of total protein content	Lowry colorimetric assay. UV-VIS Spectrophotometer
42/III-60/NF	Monovalent pneumococcal conjugated bulks	Determination of total polysaccharide content	Resorcinol colorimetric assay. UV-VIS Spectrophotometer
42/III-61/F	Monovalent pneumococcal conjugated bulks	Determination of Free-PS4 content	ELISA Principal equipment colorimeter, washing equipment
42/III-62/F	Monovalent pneumococcal conjugated bulks	Determination of Free-PS18C content	ELISA Principal equipment colorimeter, washing equipment

During the last EDQM Mutual Joint Audit performed in March 2009, *in vivo* assays have been included in the scope.
The MJA attestation (EDQM/MJA045) is valid until 12/2014. See Annex 2.

PART 2: TECHNICAL SECTION

Section A: Status of application of Article 114

Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC is transposed in the Belgian legislation in the Royal Decree of 14/12/2006 related to the Medicinal Products for Human and Veterinary Use (published the 22/12/2006 in the Belgian official journal).

Article 89 describes the principle of batch release for the immunological products.
In conformity with the EU directive we perform the batch release testing on vaccines batches for the European market. Batch release certificates issued by other OMCLs are accepted.

Section B: Summary of batches tested for OCABR

It is noted that the difference between the submitted batches and released batches is due to the fact that the batches which were submitted in 2011, were released in 2012 and that a number of batches submitted at the end of 2012 were released beginning of 2013.
The report covers the batch release activities during the period January – December 2012.
Lots which do not comply to the approved specifications are rejected by the OMCL and can thus not be put on the market. Those are destroyed by the manufacturer.
Lots which are recalled from the market by the manufacturers are under the supervision of the Belgian Medicines Agency.

Vaccine type	Status	Release information's		
		EU	Non-EU	Total
Purified meningococcal polysaccharide vaccine, serotypes ACWY	Submitted	46	68	114
	Tested	46	0	46
	Released	46	68	114
	Rejected	0	0	0

Vaccine type	Status	Release information's		
		EU	Non-EU	Total
Lyophilised Haemophilus influenzae type b conjugate Vaccine, Manufacturer A	Submitted	60	133	193
	Tested	60	0	60
	Released	60	133	193
	Rejected	0	0	0

Vaccine type	Status	Release information's		
		EU	Non-EU	Total
Haemophilus influenzae type b conjugate vaccine, Manufacturer B	Submitted	20	0	20
	Tested	20	0	20
	Released	20	0	20
	Rejected	0	0	0

WIV-ISP also performs testing and release of pneumococcal monovalent conjugated bulks used for the formulation of a multivalent pneumococcal conjugated vaccine. A certificate of approval is issued by WIV-ISP and transferred to two other OMCL's who are responsible for testing and release of the final container. In 2012 only EU approval certificates where provided.

Vaccine type	Status	Release information's		
Pneumococcal Monovalent bulk conjugate		**EU**	**Non-EU**	**Total**
	Submitted	76	0	76
	Tested	59	0	59
	Released	36	0	36
	Rejected	0	0	0

Since 2012, WIV-ISP also performs the release of a conjugated meningococcal polysaccharide vaccine ACWY.

Vaccine type	Status	Release information's		
Conjugated Meningococcal polysaccharide vaccine ACWY		**EU**	**Non-EU**	**Total**
	Submitted	3	0	3
	Tested	1	0	1
	Released	1	0	1
	Rejected	0	0	0

Section C: Technical Details of tests methods applied for OCABR

Batch release of final products is based on the critical evaluation of key parameters of the production and control protocol, and on laboratory testing. The tests performed at WIV-ISP are listed in the following tables, according to Ph.Eur. Monographs or the Marketing authorisation (MA) when applicable:

	Release test	Brief description
Diphtheria toxoid containing vaccines	Potency on final bulk or final lot	Single or multiple dilution, lethal challenge assay on guinea-pigs vs. in house reference (Ph. Eur.)
	Identity on final lot	Immunodiffusion after desorption
Tetanus toxoid containing vaccines	Potency on final bulk or final lot	Single or multiple dilution, lethal challenge assay on mice vs. in house reference (Ph. Eur.)
	Identity on final lot	Immunodiffusion after desorption
Whole cell Pertussis containing vaccines	Potency on final bulk	Multiple dilution, B.pertussis intracerebral challenge assay (Kendrick test) on mice vs in house reference (Ph.Eur.)
	Specific toxicity on final bulk	Mouse weight gain test (Ph. Eur.)
	Endotoxin content on final lot	LAL test (kit) by kinetic method (Ph.Eur.)
Acellular Pertussis containing vaccines	Potency on final bulk or final lot	Single dilution serological assay on mice vs in house reference. Quantification of serological response by ELISA (MA)
	Residual pertussis toxin on final bulk	Histamine Sensitising Assay (Ph. Eur.)
	Identity on final lot	ELISA (MA) or immunodiffusion (MA)
Purified meningococcal polysaccharide vaccine, serotypes ACW & ACWY	Appearance	Visual inspection (Ph Eur)
	Endotoxin content	LAL test (Kit) (Ph.Eur.)
Bulk conjugate and lyophilised Haemophilus influenzae type b conjugate Vaccine	Polysaccharide content	HPLC-PAD(Dionex™ method)
	Molecular size	Size exclusion chromatography
Haemophilus influenzae type b conjugate Vaccine	Appearance	Visual inspection (Ph.Eur.)
	pH	pH measurement (Ph.Eur.)
	Endotoxin content	LAL test (Kit) (Ph.Eur.)
	Free polysaccharide content	ELISA (MA)
	Molecular size	Size exclusion chromatography
Pneumococcal monovalent bulk conjugates	Protein content	Lowry method (MA)
	Polysaccharide content	Resorcinol colorimetric method with in house standard and reference (MA)
	Free-polysaccharide content	ELISA (MA)
	Molecular size distribution	HPLC-SEC with dextran cut-off (MA)
Conjugated Meningococcal polysaccharide vaccine ACWY	O-acetyl content on purified polysaccharide A, C, W and Y bulks	Spectrophotometry (MA)
	Total and free-polysaccharide content on conjugated polysaccharide A bulk	Inductively Coupled Plasma – Atomic Emission Spectrometry (ICP-AES) (MA)

	Total and free-polysaccharide content on conjugated polysaccharide C bulk	DMAB colorimetric method with in house standard and reference (MA)
	Total and free-polysaccharide content on conjugated polysaccharide W and Y bulks	Resorcinol colorimetric method with in house standard and reference (MA)
	Molecular size distribution on conjugated polysaccharide A, C, W and Y bulks	HPLC-SEC with dextrane cut-off (MA)
	Appearance on final lot	Visual inspection (Ph.Eur.)
	Endotoxin content on final lot	LAL test (Kit) (Ph.Eur.)
	Total polysaccharide A content on final lot	Inductively Coupled Plasma – Atomic Emission Spectrometry (ICP-AES) (MA)
	Total polysaccharide C+W+Y content on final lot	Ultra Performance Liquid Chromatography (UPLC) with fluorometric detection (MA)
	Total polysaccharide W content on final lot	Ultra Performance Liquid Chromatography (UPLC) with fluorometric detection (MA)
	Total polysaccharide Y content on final lot	Ultra Performance Liquid Chromatography (UPLC) with fluorometric detection (MA)
	Identity on final lot	ELISA (MA)

Section D: Summary of test results

Preliminary remarks

The batch release of final products is based on the critical evaluation of key parameters of the production and control protocol, and on laboratory testing.

On the one hand, the testing verifies the compliance of the key parameters against approved specifications (cf. Marketing authorisation).

On the other hand, consistency limits are set up from a statistical point of view according to yearly historical data of the product. Data from manufacturer and National Control Lab are then evaluated from a consistency point of view.

Out of consistency cases are discussed transparently with the manufacturer and properly justified when needed, ensuring the high quality, safety and efficacy of the final product.

All data have been anonymized.

D.1. Meningococcal polysaccharide vaccine, serotypes ACWY

D.1.1 Product description

This is a vaccine directed against meningococcal invasion (*Neisseria Meningitidis*). Four different polysaccharide serotypes (A,C,W and Y) are formulated directly to obtain the final bulk, followed by filling into final containers and lyophilisation.

D.1.2 Number of batches released

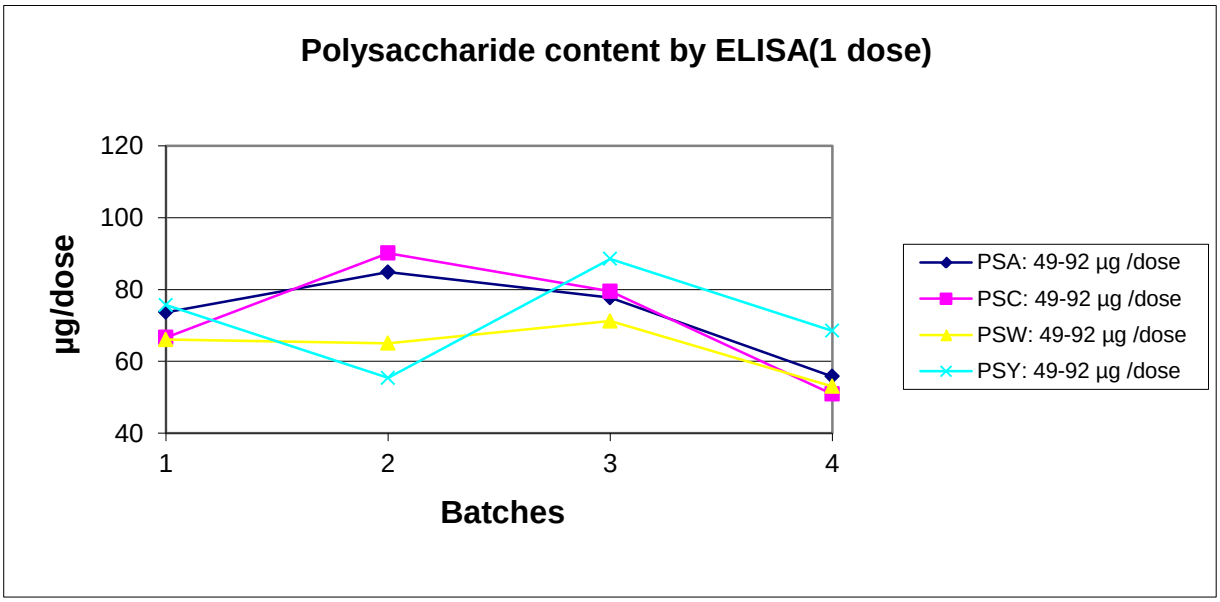
Vaccine type	submission	Release information's		
		EU	Non-EU	Total
Purified meningococcal polysaccharide vaccine, serotypes ACWY	Submitted	46	68	114
	Tested	46	0	46
	Released	46	68	114
	Rejected	0	0	0

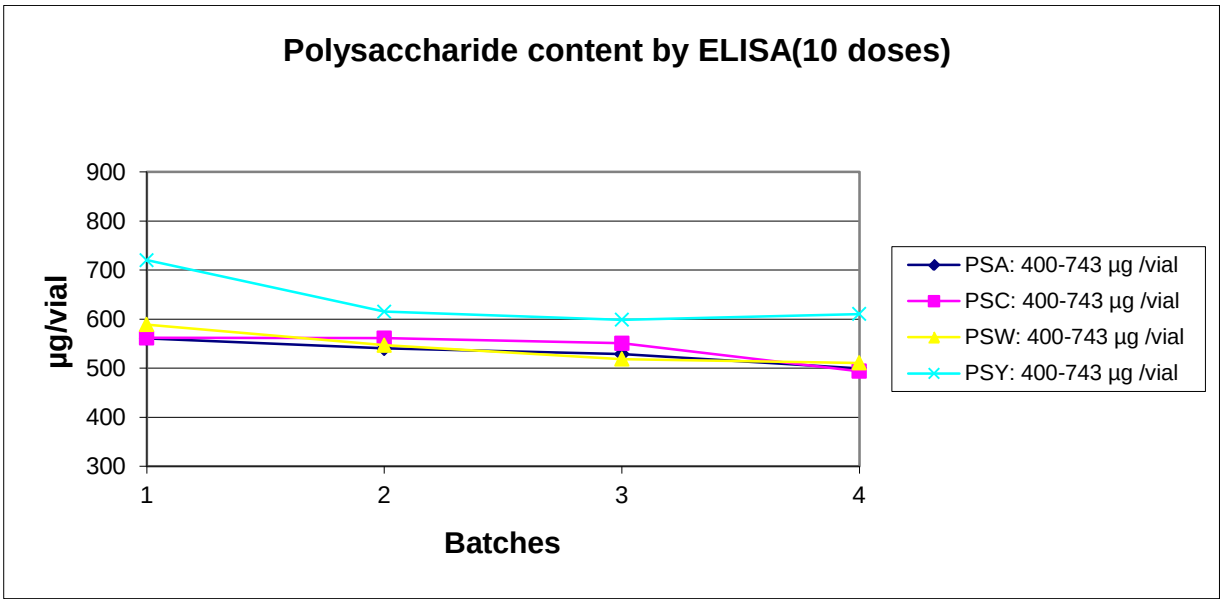
D.1.3 WIV-ISP data

Polysaccharide content

Polysaccharide content is determined by ELISA for each serotype (A,C,W,Y) on the final container.
The results remain within specifications. See consistency and graph.

Serotype	Consistency 2010(mean ±2SD)	Consistency 2011(mean ±2SD)	Consistency 2012(mean ±2SD)
	7 lots	**4 lots**	**4 lots**
PSA 1D	72,6 µg ± 20,8	70,0 µg ± 18.6	73,0 µg ± 24,8
PSC 1D	64,8 µg ± 12,4	67,9 µg ± 16,6	71,8 µg ± 33,8
PSW 1D	65,1 µg ± 25,8	68,8 µg± 13,2	63,8 µg± 15,4
PSY 1D	68,2 µg ± 16,2	69,1 µg± 9,0	72,0 µg± 27,8
	8 lots	**8 lots**	**4 lots**
PSA 10D	582,7 µg ± 138,0	547,3 µg ± 63,8	532,5 µg ± 51,2
PSC 10D	537,6 µg ± 113,0	544,3 µg ± 74,4	542,0 µg ± 64,8
PSW 10D	561,3 µg ± 154,6	558,5 µg ± 152,2	541,4 µg ± 70,8
PSY 10D	588,3 µg ± 143,8	565,5 µg ± 66,2	636,2 µg ± 113,0





Endotoxin content:

For the year 2012, results for the endotoxin content are lower than 20 IU/dose and usually lower than 5 IU/doses (specification is lower than 48 IU/dose).

lot	1	2	3	4	5	6	7	8
endotoxin content (EU/dose)	15.1	<2,5	<2,5	8.5	<5	12.5	<5	9.1

D.1.4 Conclusion and remarks

All the results from the manufacturer and WIV-ISP are still compatible with a consistent production ensuring the high quality of the vaccine.

Data of the manufacturer have been submitted with the production protocol for each lot, reviewed and found consistent compared to previous years.

D.2. Lyophilized Haemophilus influenzae type b conjugate Vaccine, Manufacturer A

D.2.1 Product description

This is a vaccine directed against *Haemophilus influenza type b*. The polysaccharide is conjugated with a protein carrier (Tetanus Toxoid). The monovalent conjugated bulks may be adsorbed on aluminium or directly formulated to obtain the final bulk, followed by filling into final containers and lyophilisation.

D.2.2 Number of batches released

The Hib vaccines in the table hereunder have been released separately. However, Hib vaccines may also be included as a component in combination vaccines. Results in graph may thus show a higher number of batches.

Vaccine type	Submission	Release information's		
Lyophilised Haemophilus influenzae type b conjugate Vaccine		EU	Non-EU	Total
	Submitted	60	133	193
	Tested	60	0	60
	Released	60	133	193
	Rejected	0	0	0

D.2.3 WIV-ISP tests data

On the bulk conjugate:

- identity and molecular size distribution

On the final lot:

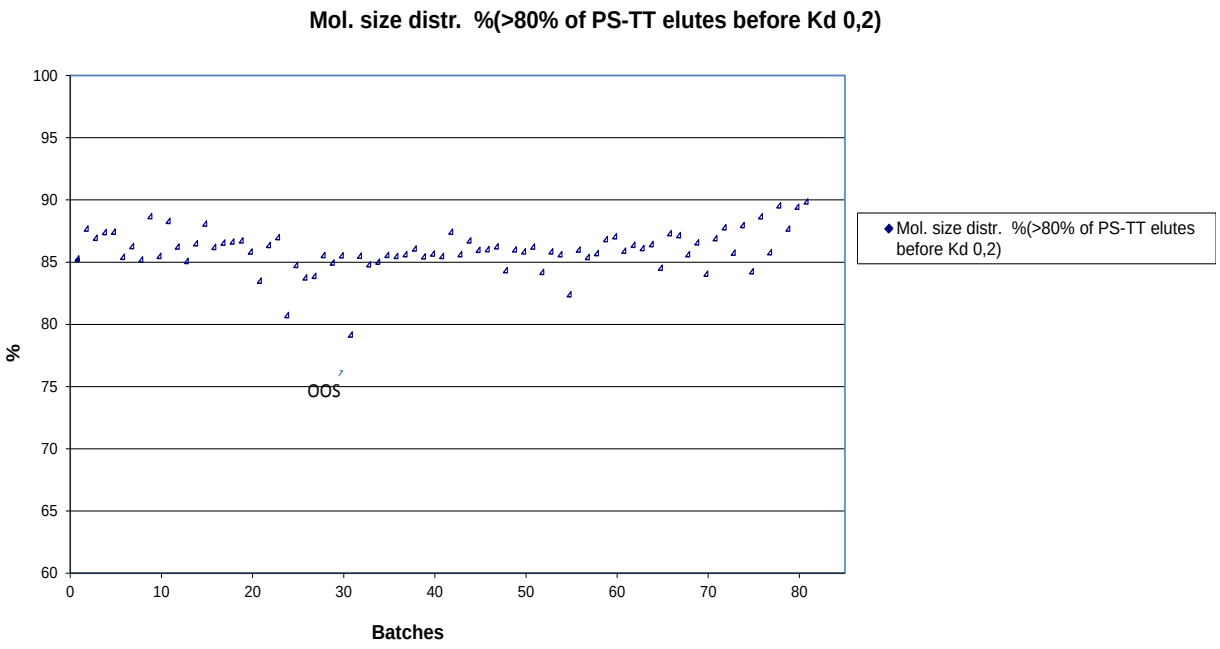
- polysaccharide content by Dionex method
- free polysaccharide content by ELISA.
- description-appearance
- endotoxin content by LAL (Kit)

D.2.3.1. Bulk Conjugate

Molecular Size Distribution : (Specification: >80% of the conjugate PS-TT eluted before Kd 0.2).
The molecular size distribution shows a high consistency of production.

Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 83)	87.9	91.9	83.9
2011 (N = 78)	87.4	90.2	84.6
2012 (N =81)	85.9	89.3	82.5

All WIV-ISP results are below manufacturer's results due to time lag between testing of both labs and the short shelf life of the product itself. One lot has been found OOS due to expired shelf life. Release Sample has been submitted too late but the batch has been formulated in due time. The lot has been released under deviation as manufacturer's result was within specification and all others results from WIV-ISP for this lot were within specification. Another lot is out of alert limits of consistency for the same reason.

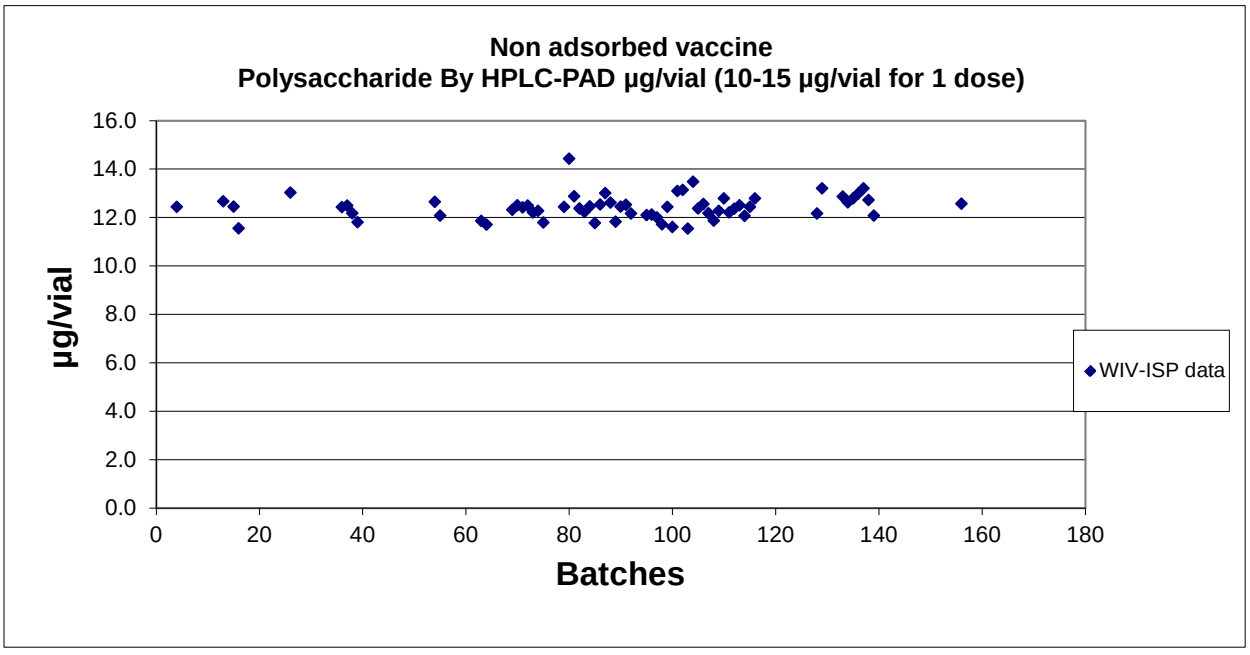


D.2.3.2. Final container

Total polysaccharide content by HPLC with pulsed amperometric detector (refer to section B)

Total polysaccharide non-adsorbed vaccines (10-15µg/dose)
Please note that, in all graphs, all lots are sorted by increasing number. Some 'missing results' may appear. In fact, those lots have not been tested by our lab but released for the international market (Non EU market) based on the production protocol review.
The polysaccharide content shows a high consistency during 2012.

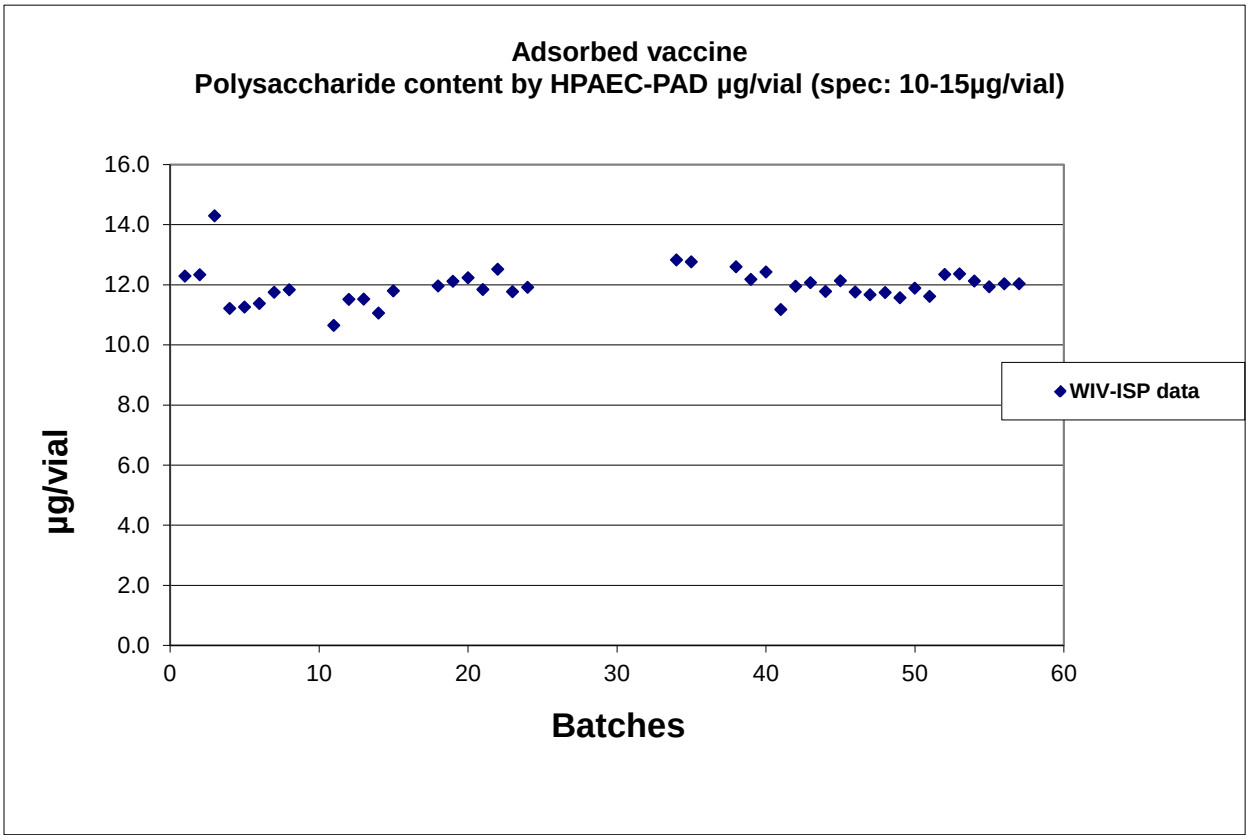
Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 43)	12.6	14.6	10.6
2011 (N = 20)	12.1	13.4	10.8
2012 (N =52)	12.4	13.4	11.4



Total polysaccharide adsorbed vaccines(10-15µg/dose)

The polysaccharide content shows a high consistency during 2012 except for one lot still within specifications.

Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 94)	12.3	13.5	11.1
2011 (N = 57)	11.6	13.0	10.2
2012 (N =59)	12.0	13.0	11.0



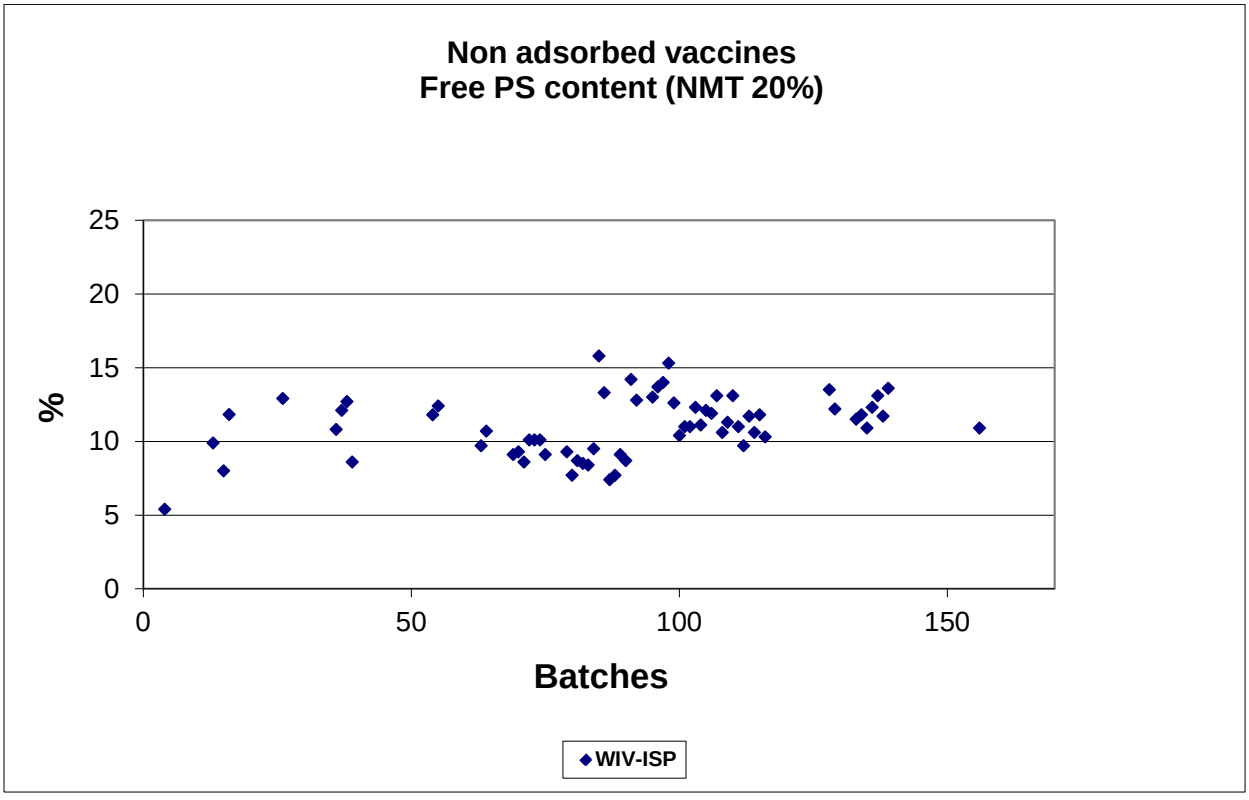
Free polysaccharide content by ELISA (Specification : nmt 20% for non-adsorbed Hib and nmt 20% for adsorbed Hib for use in combination vaccines).

Rem: the specification has been adapted to 20% for adsorbed and non-adsorbed vaccine in 2010.

Free polysaccharide non adsorbed Vaccines (NMT 20%):

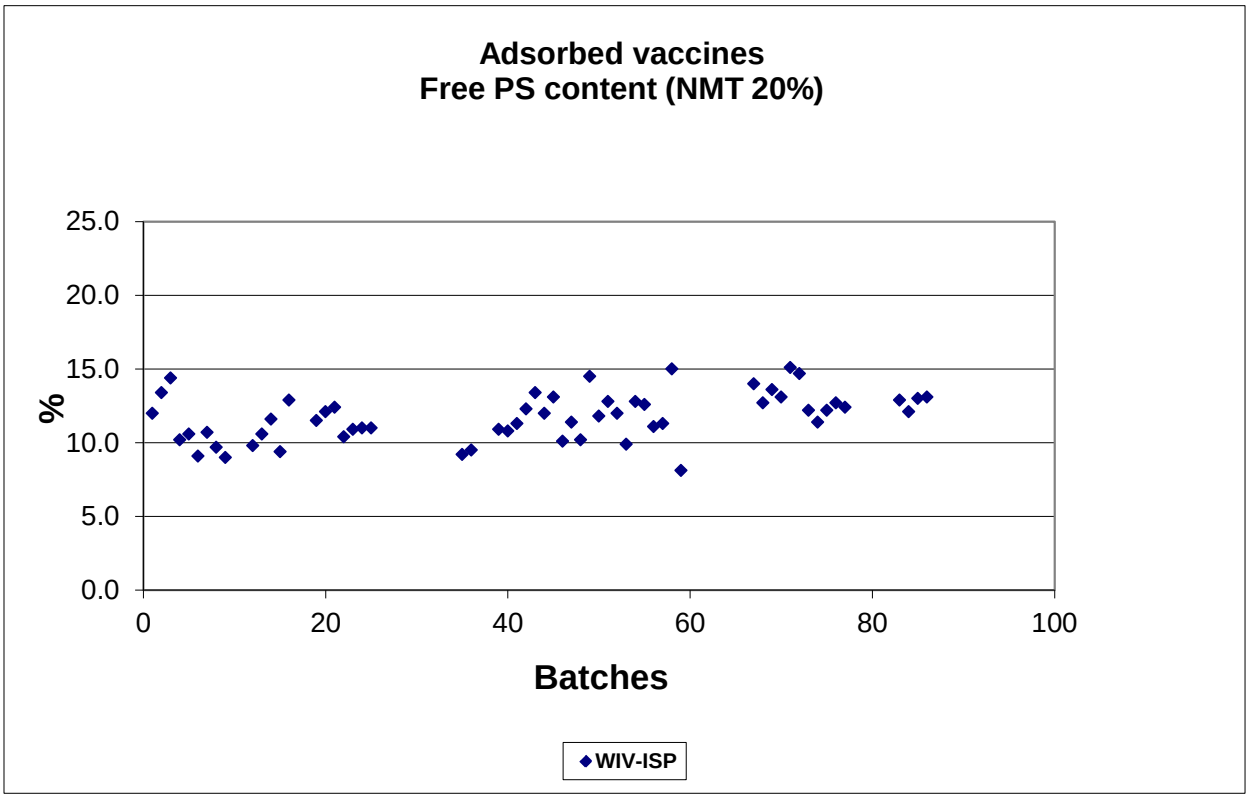
Results are higher for WIV-ISP lab in some cases due to the high variability of the ELISA test.

Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 43)	10.7	15.9	5.5
2011 (N = 20)	9.3	11.9	6.7
2012 (N =52)	11.0	15.0	7.0



Free polysaccharide adsorbed vaccines(NMT 20%):.

Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 94)	12.0	16.8	7.2
2011 (N = 57)	11.4	15.2	7.6
2012 (N =59)	11.8	15.0	8.6



Endotoxin content by LAL (Specification : <5.00 IU/dose)

Data show that the endotoxin content by LAL test is mostly below 2.5 IU/dose.
The specification is already very low compared to whole cell vaccines, the level of endotoxin of which can reach thousands of IU/dose.

D.2.4 Conclusion

All the results, from the manufacturer as well as from the National Control lab, point towards a highly consistent production ensuring the high quality and safety of the product.

D.3. Lyophilized Haemophilus influenzae type b conjugate vaccine, Manufacturer B

D.3.1 Product description

This is a vaccine directed against *Haemophilus influenza type b*. The polysaccharide is conjugated with a protein carrier (Tetanus Toxoid). The monovalent conjugated bulks are directly formulated to obtain the final bulk, followed by filling into final containers and lyophilisation.

D.3.2 Number of batches released

Vaccine type	submission	Release information's		
Haemophilus influenzae type b conjugate vaccine		EU	Non-EU	Total
	Submitted	20	0	20
	Tested	20	0	20
	Released	20	0	20
	Rejected	0	0	0

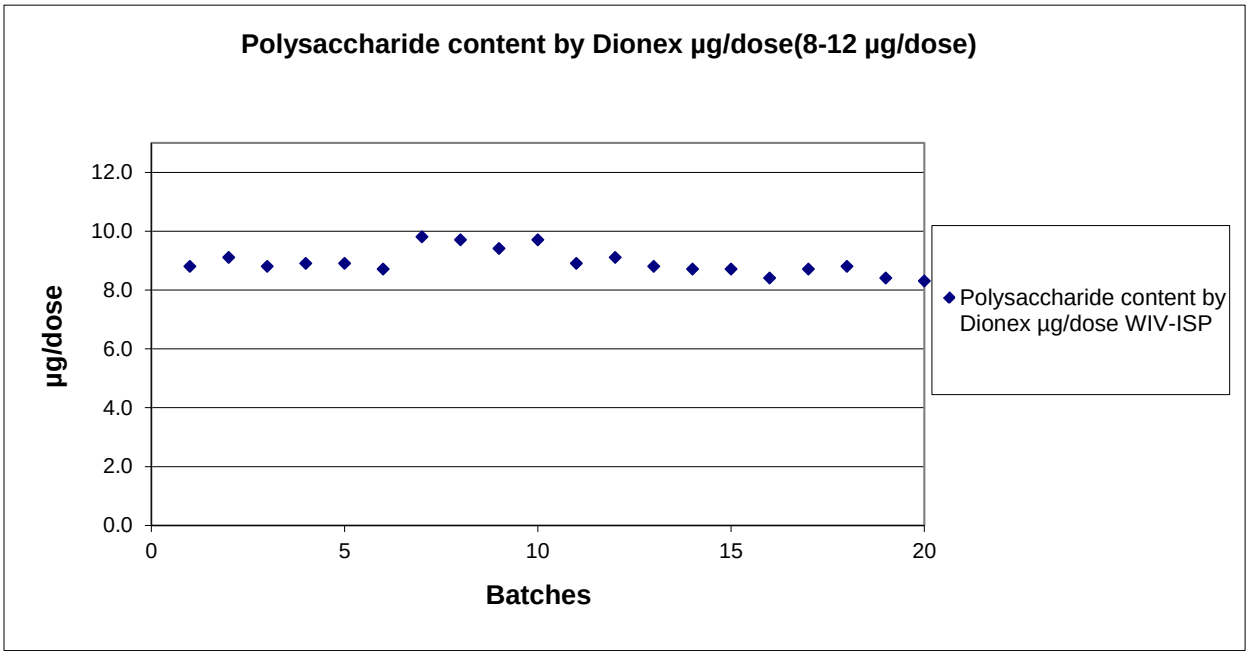
D.3.3 WIV-ISP tests data

All tests performed on final container except molecular size distribution.

Polysaccharide content by HPLC-PAD (Specifications: 8-12µg/ dose)

Results remain within the specifications and shows a high consistency. Note that manufacturer's results have been rounded to unit. WIV-ISP results are below manufacturer's results.

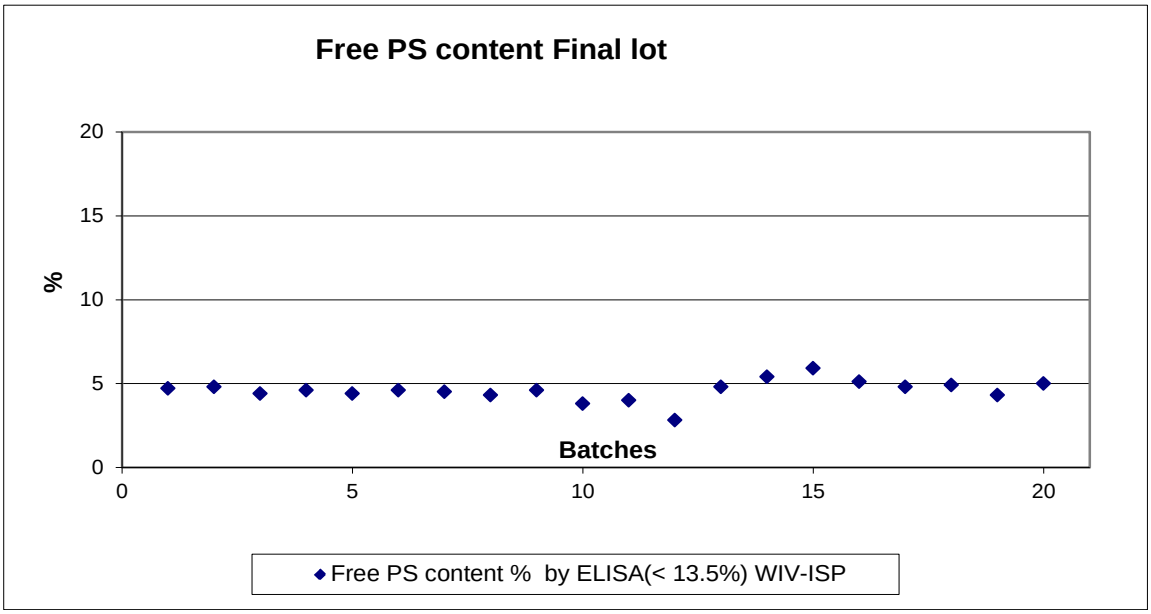
Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 20)	8.7	9.6	7.8
2011 (N = 20)	9.1	10.1	8.1
2012 (N =20)	8.9	9.8	8.0



Free polysaccharide content by ELISA (Specification: <13.5%)

Most of our results were below 5%, while the current specification is <13.5%. WIV-ISP results are below manufacturer's results. This is most probably due to the difference in methodology to separate free polysaccharide from conjugated polysaccharide and from the testing itself (HPLC-PAD versus ELISA for WIV-ISP lab).

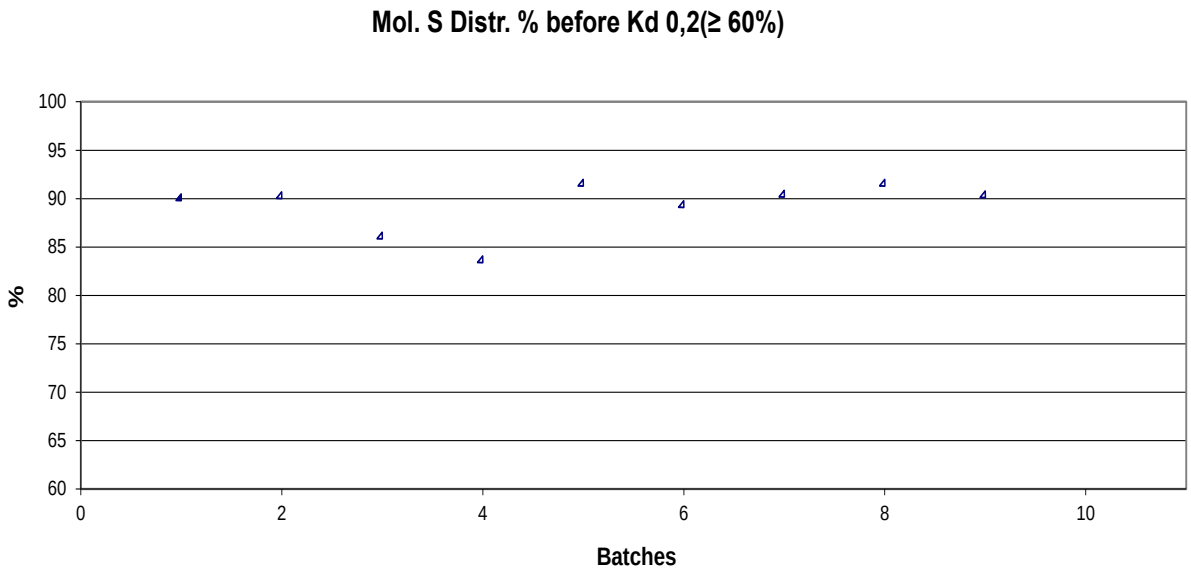
Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 20)	5.0	7.3	2.7
2011 (N = 20)	4.3	4.9	3.7
2012 (N =20)	4.6	5.8	3.4



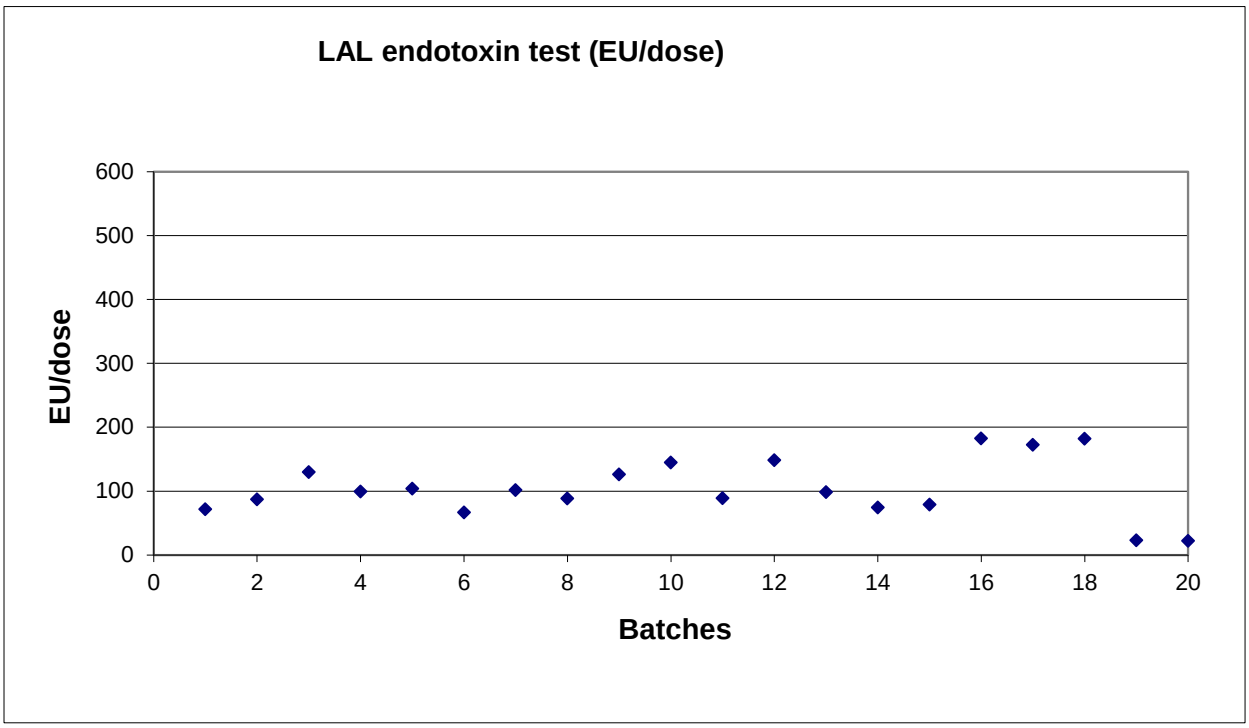
Molecular size distribution, percentage of conjugate PS-TT eluted before KD 0.2 (Specifications: >60% of the conjugate elutes before Kd 0.2).

In 2010 the specification was expressed as Kd <0,2; at least 60 % of polysaccharide elutes). The Manufacturer has submitted at that time a variation dossier to express the molecular size with a multiple Angle light scattering equipment : Hydrodynamic radius, Mega Dalton. The variation dossier has demonstrated measurement equivalence.

Years	Mean	Mean + 2*SD	Mean - 2*SD
2010 (N = 12)	89.6	92.9	86.3
2011 (N = 11)	89.3	92.9	85.7
2012 (N =9)	89.0	91.7	86.3



LAL endotoxin content LAL (<200 EU/dose).
All results are within specification.



D.3.4. Conclusion

All the results, both from the manufacturer and from WIV-ISP, point towards a consistent production.

D.4. Pneumococcal vaccine: monovalent conjugated bulks

D.4.1 Product description

This multivalent vaccine is directed against pneumococcal invasion (S*treptococcus pneumoniae*). The different polysaccharide serotypes are conjugated with a protein carrier. The monovalent conjugated bulks are adsorbed on aluminium before final formulation into the final container.

D.4.2 Number of released batches

It is possible that batches released in 2012 were tested in 2011, batches tested in 2012 released or to be released in 2013 and batches submitted in 2012, tested and released in 2013.

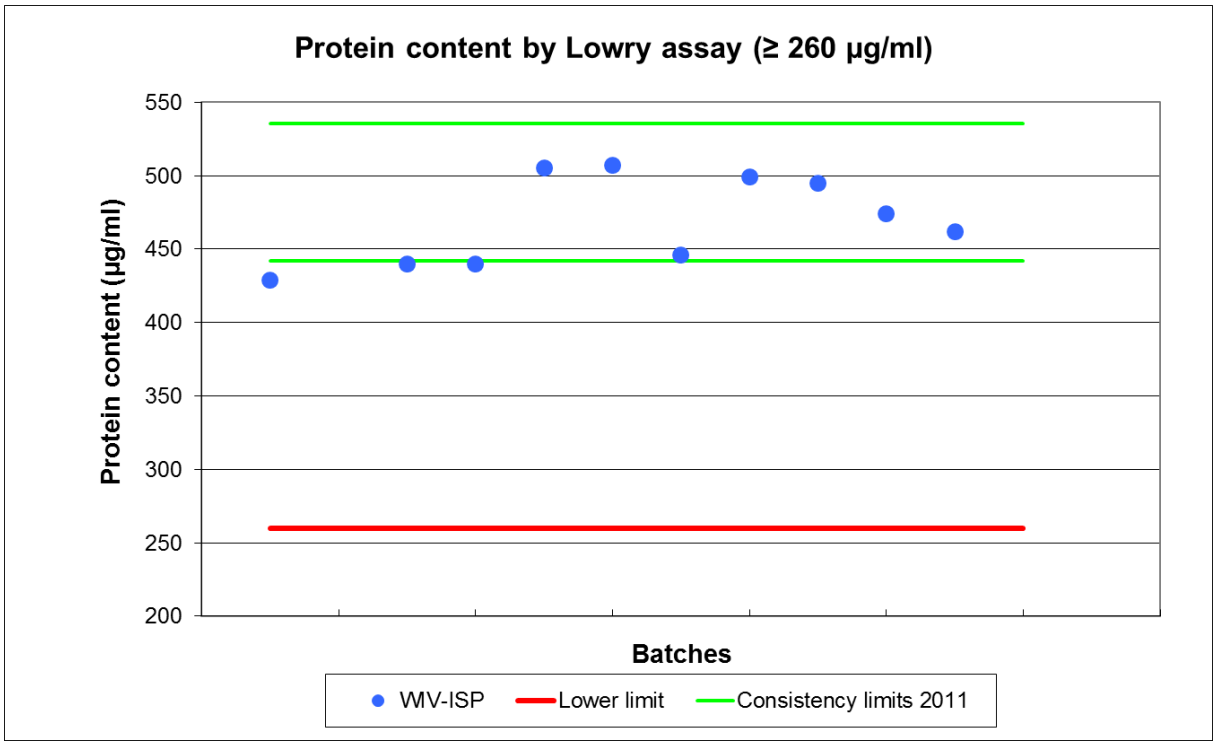
Vaccine type	Status	Release information's		
Pneumococcal Monovalent bulk conjugate (non-adsorbed)		**EU**	**Non-EU**	**Total**
	Submitted	76	0	76
	Tested	59	0	59
	Released	36	0	36
	Rejected	0	0	0

D.4.3 Results

D.4.3.1 Monovalent conjugated bulk PS4-PD

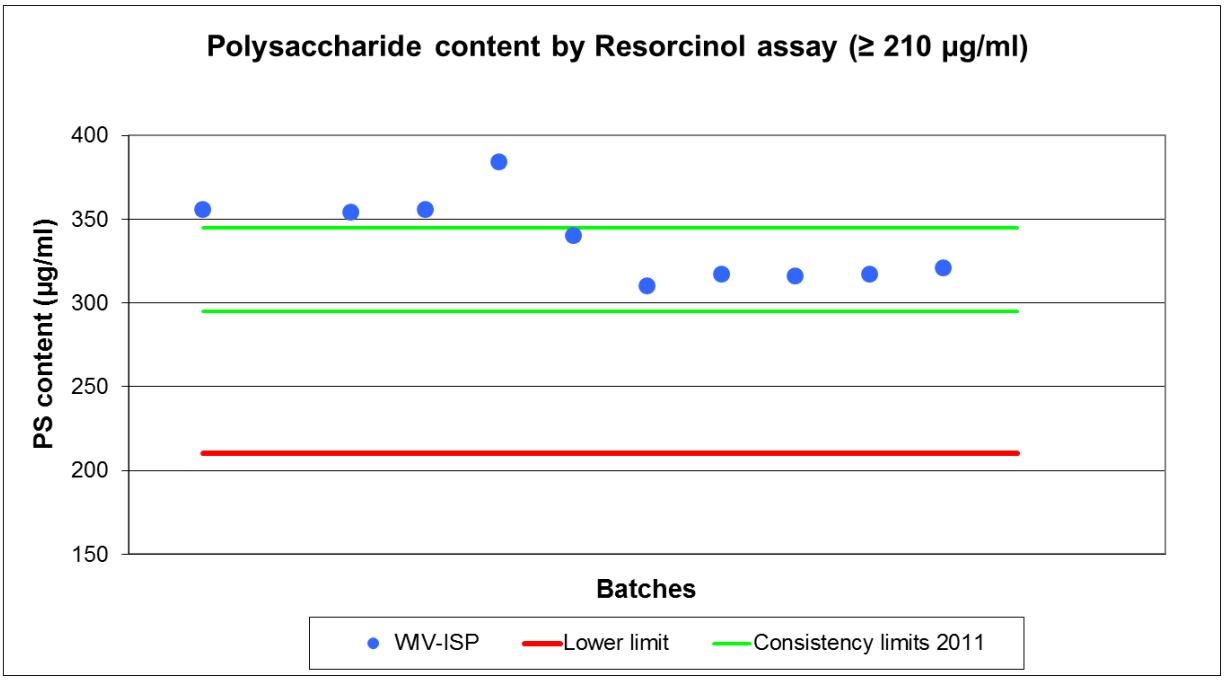
D.4.4.1.1 Protein content

The number of monovalent conjugated bulk batches released in 2012 is limited. The data obtained by WIV-ISP were compared to the consistency limits obtained for the batches produced in 2011 (data submitted by the manufacturer). From the graph below, it is clear that all but one of the results obtained for protein content fall inside the consistency limits set. All the results obtained are within the specifications.



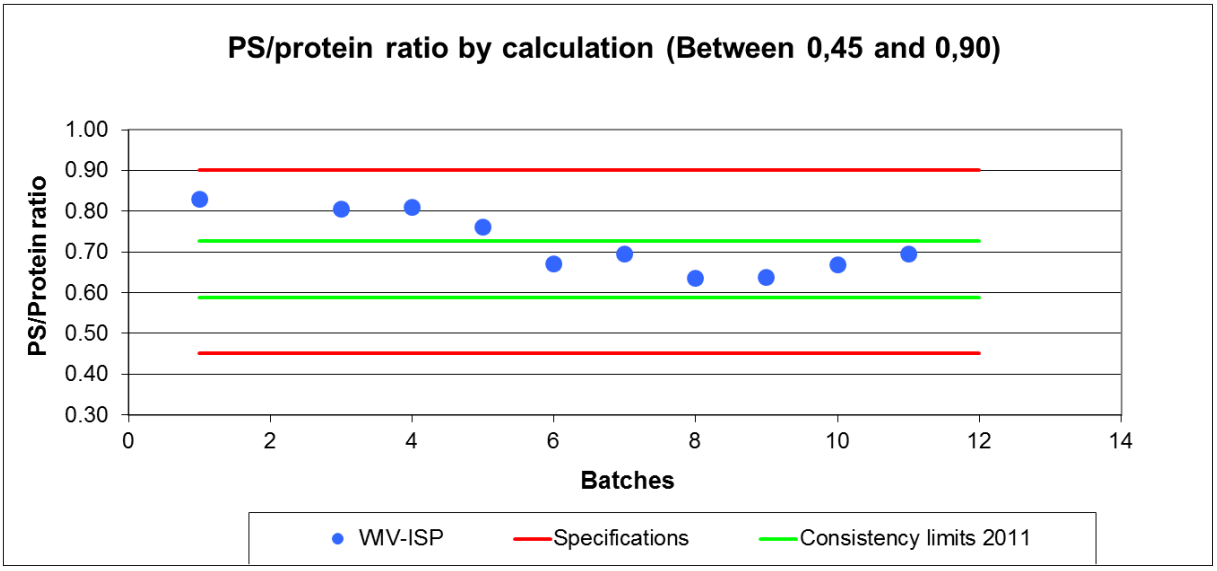
D.4.3.1.2 Polysaccharide content

Also for the polysaccharide content, the results from 2012 are within the consistency of the batches produced in 2011, with the exception of some batches. Since the amount of batches released by WIV-ISP is low, no conclusions can be drawn concerning a potential out of consistency. Result remain within the specifications with no risk of OOS results.



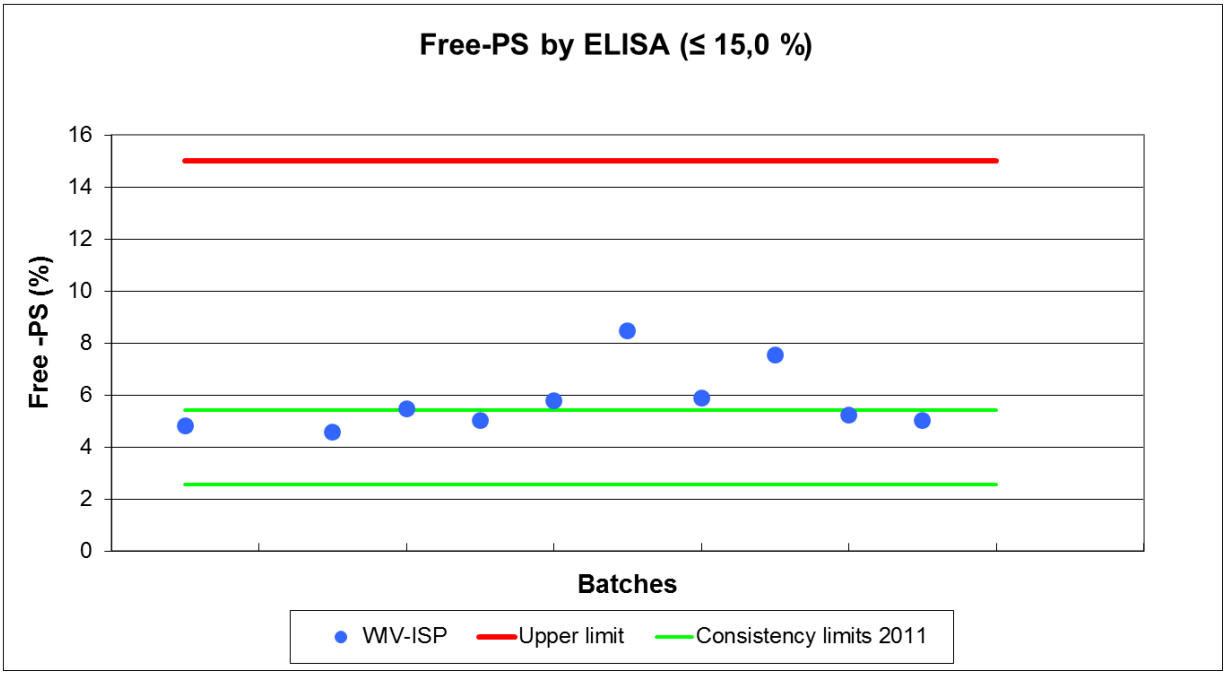
D.4.3.1.3 PS/protein ratio

For the PS/protein ratio, which is obtained by calculation using the protein and PS content data, the graph below shows that the 2012 batches are mostly within the 2011 consistency. For the batches with increased PS/protein ratio, the result is related to an increased PS ratio (see above). No OOS results were reported.



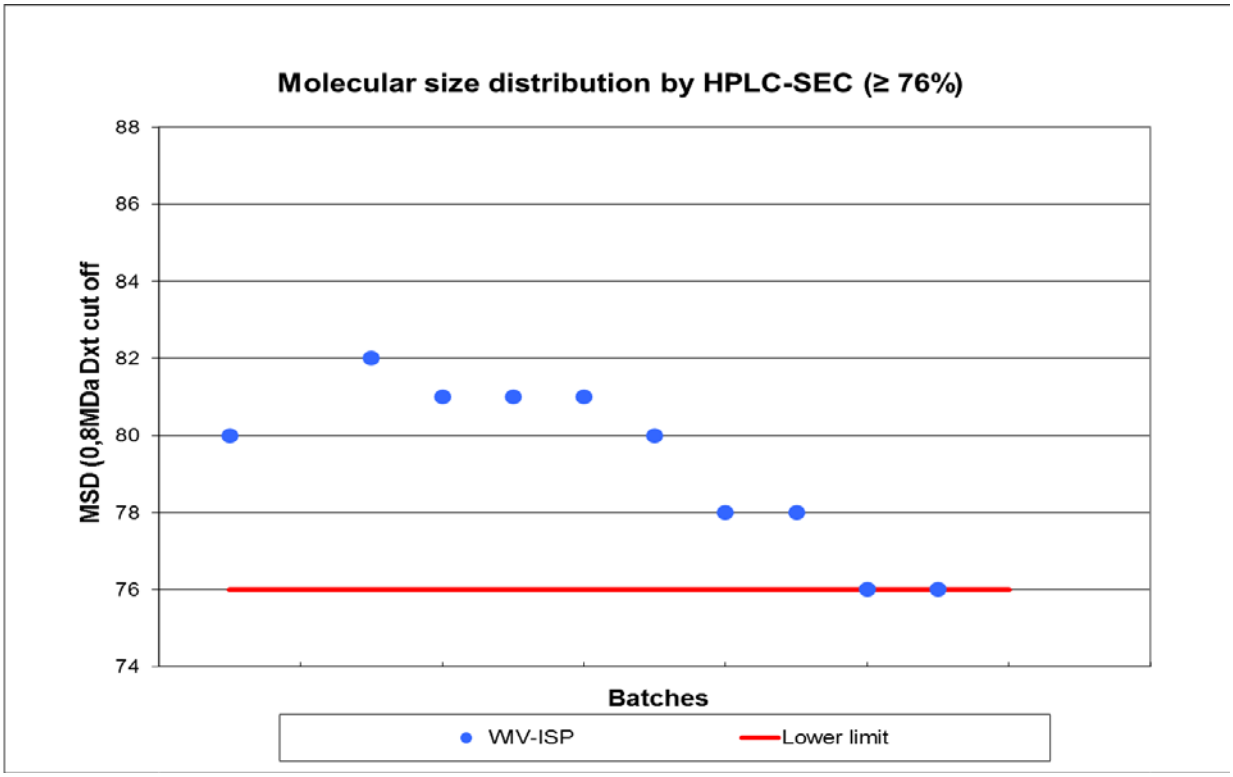
D.4.3.1.4 Free-PS

The 2012 results all meet the specifications and are consistent compared to the consistency of the 2011 batches as shown in the graph below. The fact that some batches seem to fall outside the consistency is related to the fact that there is a time delay between testing by the manufacturer and testing by WIV-ISP. It is reasonable to believe that free-PS is a parameter which can be influenced by the age of the bulk, so that the free-PS will increase over time. It should also be mentioned that the percentage of free PS is calculated based on two test results, each test with its intrinsic variability No OOS data were obtained.



D.4.3.1.5 Molecular size distribution

All the results for molecular size distribution met the specifications but fall outside the consistency. This has been discussed with the manufacturer and properly justified.

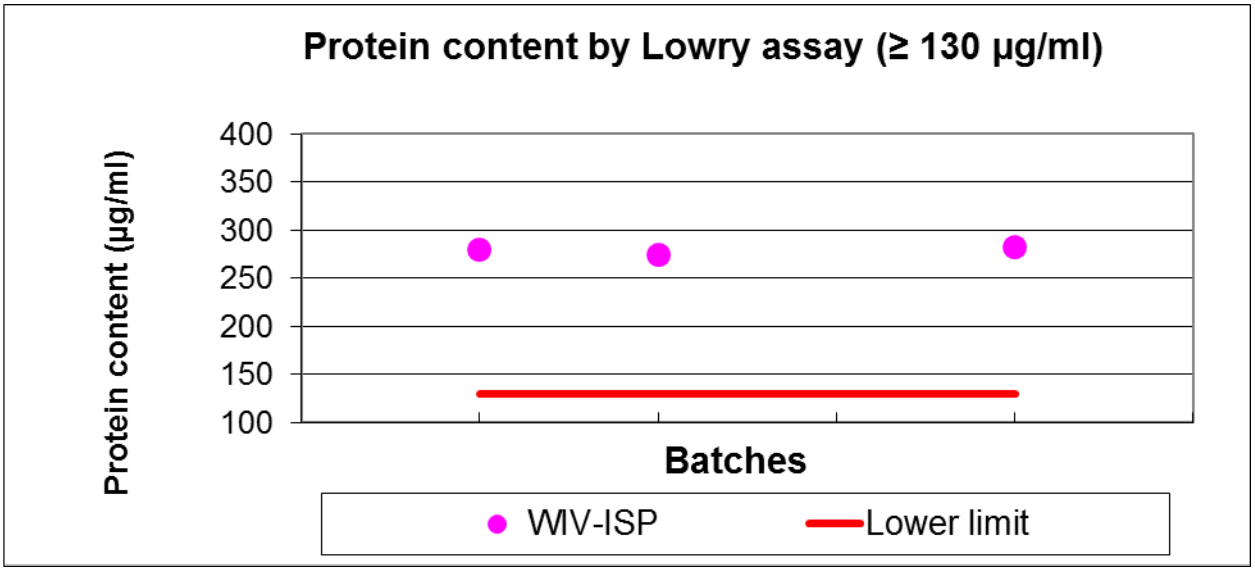


Molecular size is a characteristic that is influenced by the age of the bulk. Since testing was performed later than release testing by the manufacturer, the lower results are not unexpected. Some results close to the limit were obtained, but no OOS results were generated.

D.4.3.2 Monovalent conjugated bulk PS6B-PD

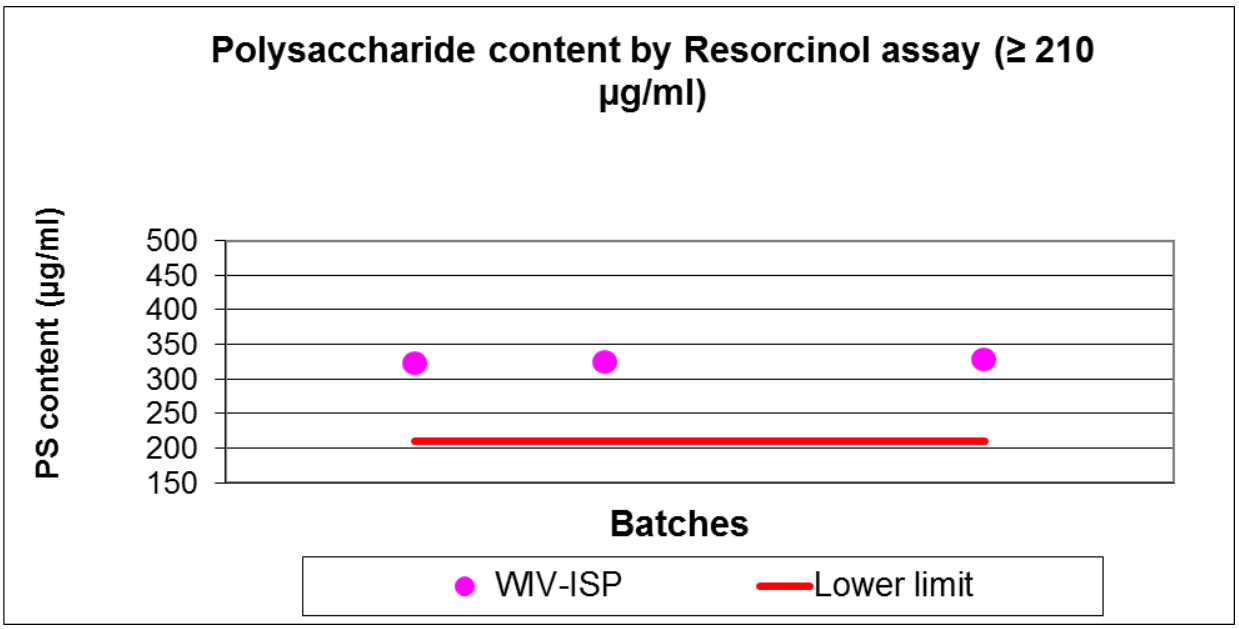
D.4.3.2.1 Protein content

From the graph below, is clear that all tested batches meet the specifications. Due to the limited amount of batches, a comparison against the 2011 consistency limits is not useful.



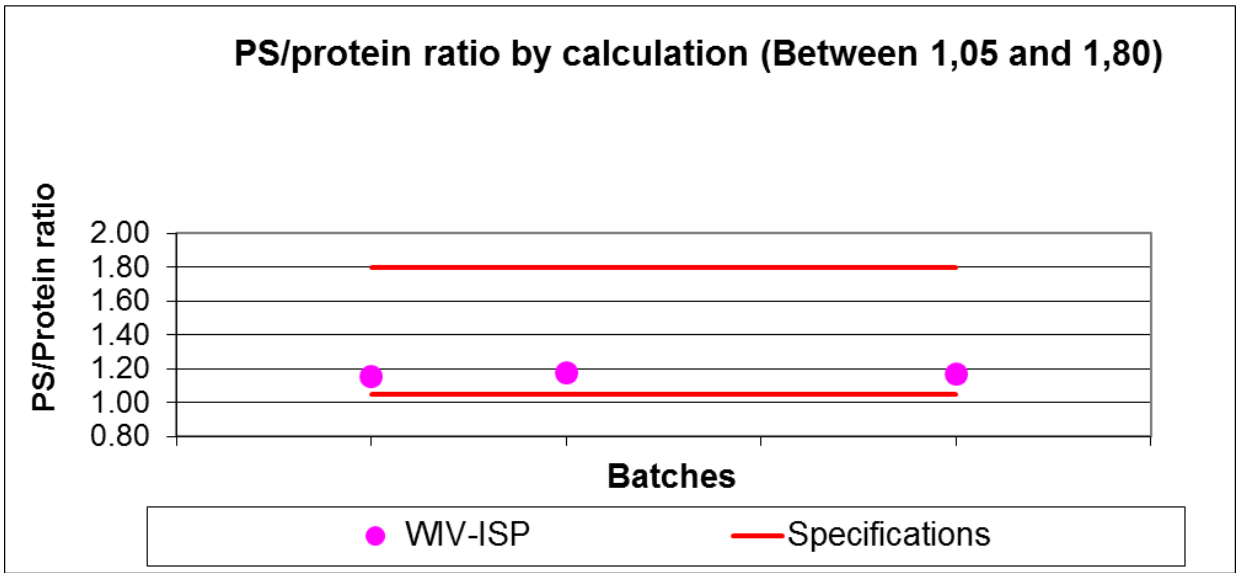
D.4.3.2.2 Polysaccharide content

Also for the polysaccharide content, the results meet the specifications.



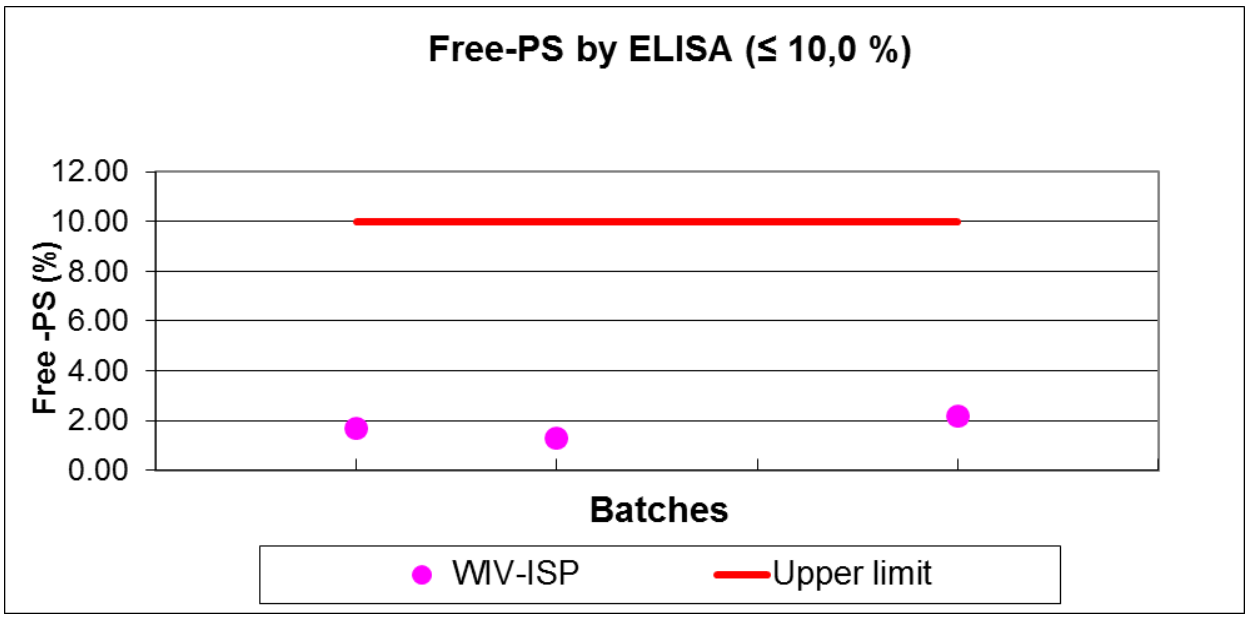
D.4.3.2.3 PS/protein ratio

For the PS/protein ratio, which is obtained by calculation using the protein and PS content data, the graph below shows that the 2012 data all meet the specifications.



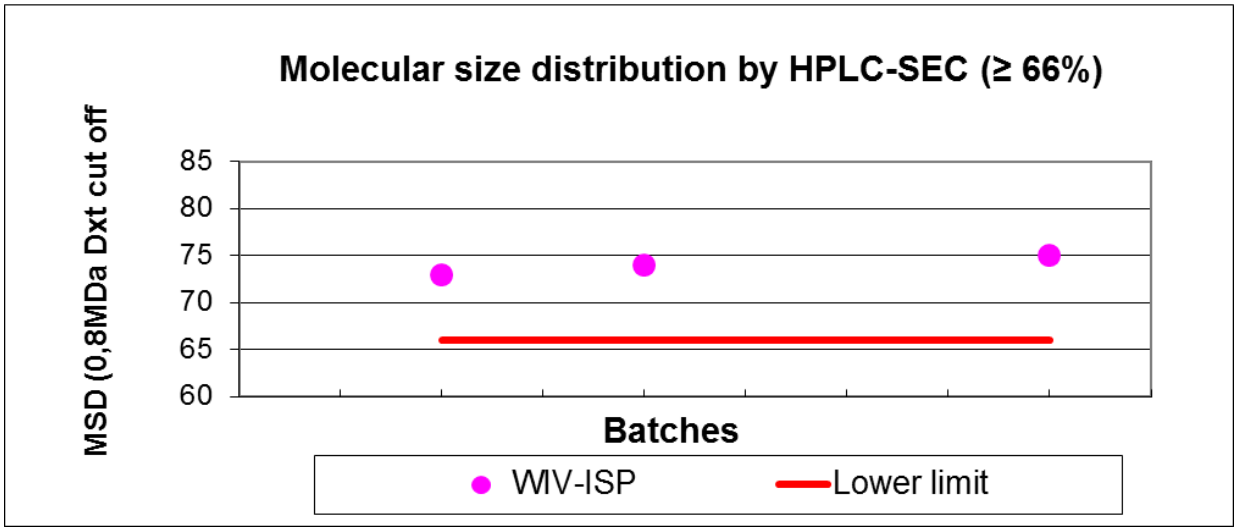
D.4.3.2.4 Free-PS

For the 2012 batches, the results obtained by WIV-ISP are far below the upper specification limit. No OOS data were obtained.



D.4.3.2.5 Molecular size distribution

All the results for molecular size distribution met the specifications.



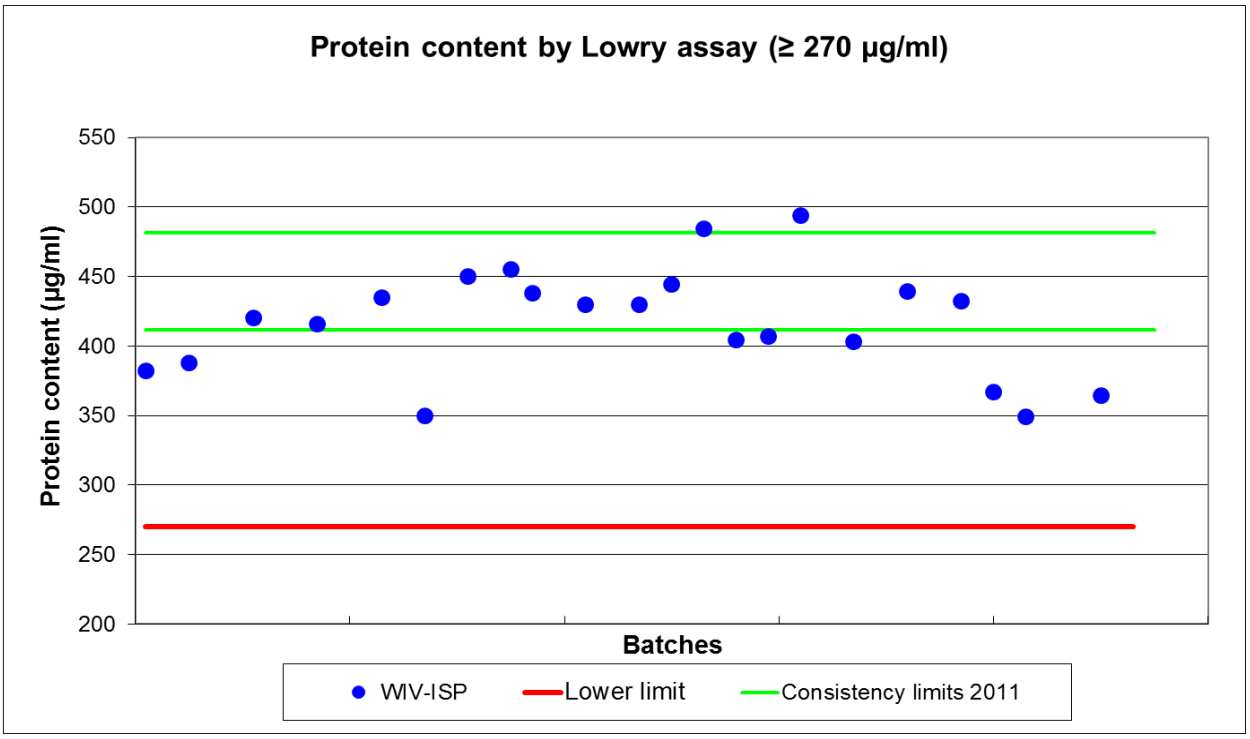
D.4.3.3 Monovalent conjugated bulk PS7F-PD

Only one batch of PS7F-PD monovalent conjugated bulk was released in 2012. Test results on protein content, polysaccharide content, PS/protein ratio, free-PS, molecular size distribution all met the specifications.

D.4.3.4 Monovalent conjugated bulk PS18C-TT

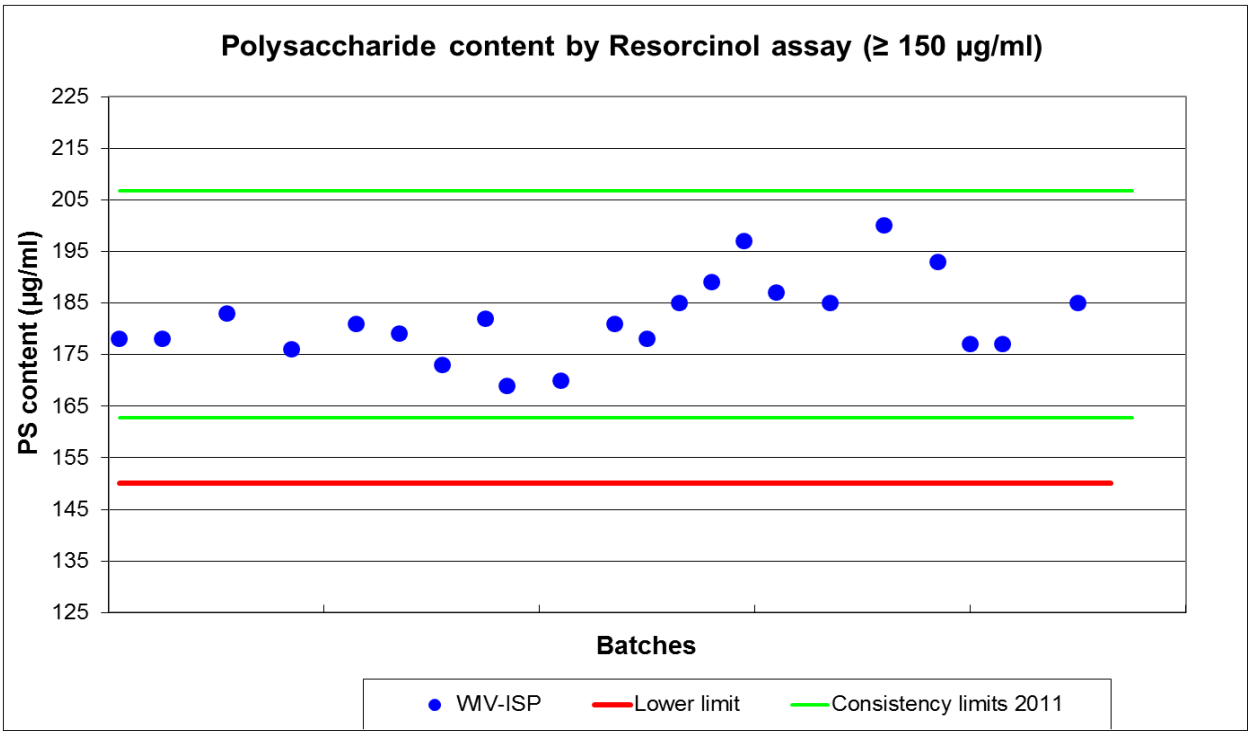
D.4.3.4.1 Protein content

Most of the results obtained by WIV-ISP for protein content are within the consistency limits provided by the manufacturer. No OOS data were generated.



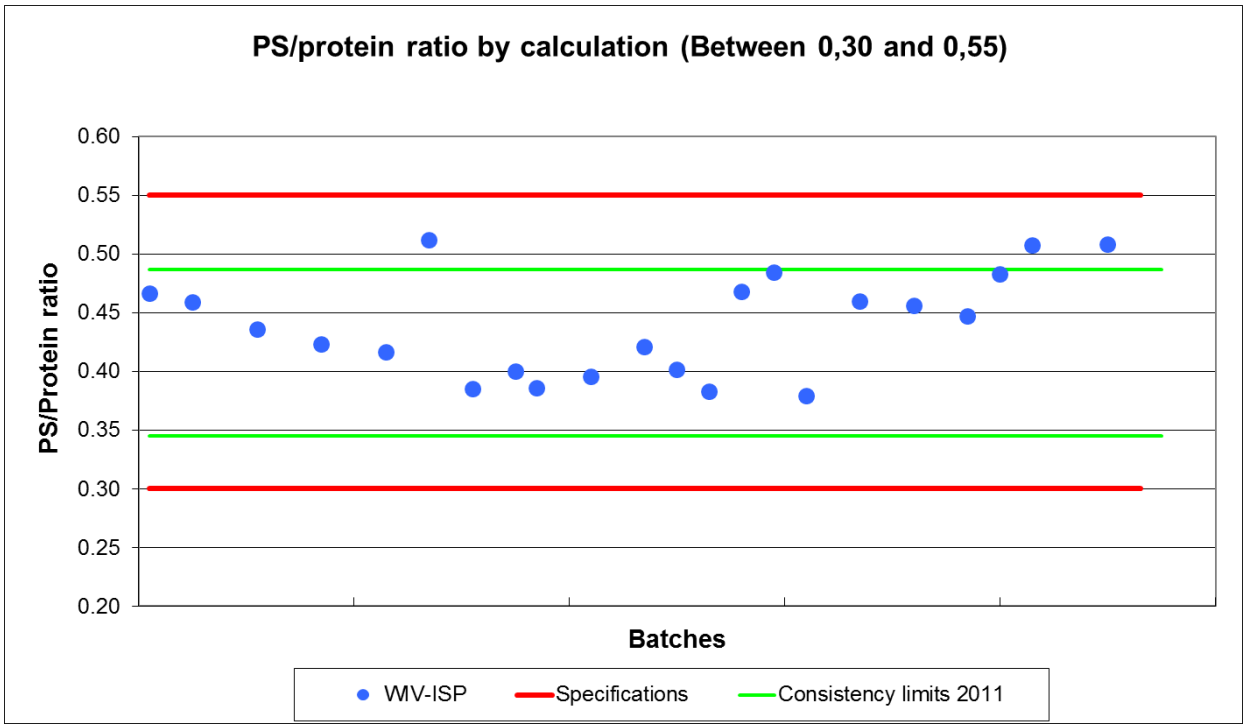
D.4.3.4.2 Polysaccharide content

For the polysaccharide content, the graph below demonstrates that the results are within the specifications and that all the results fit within the consistency limits of the 2011 batches.



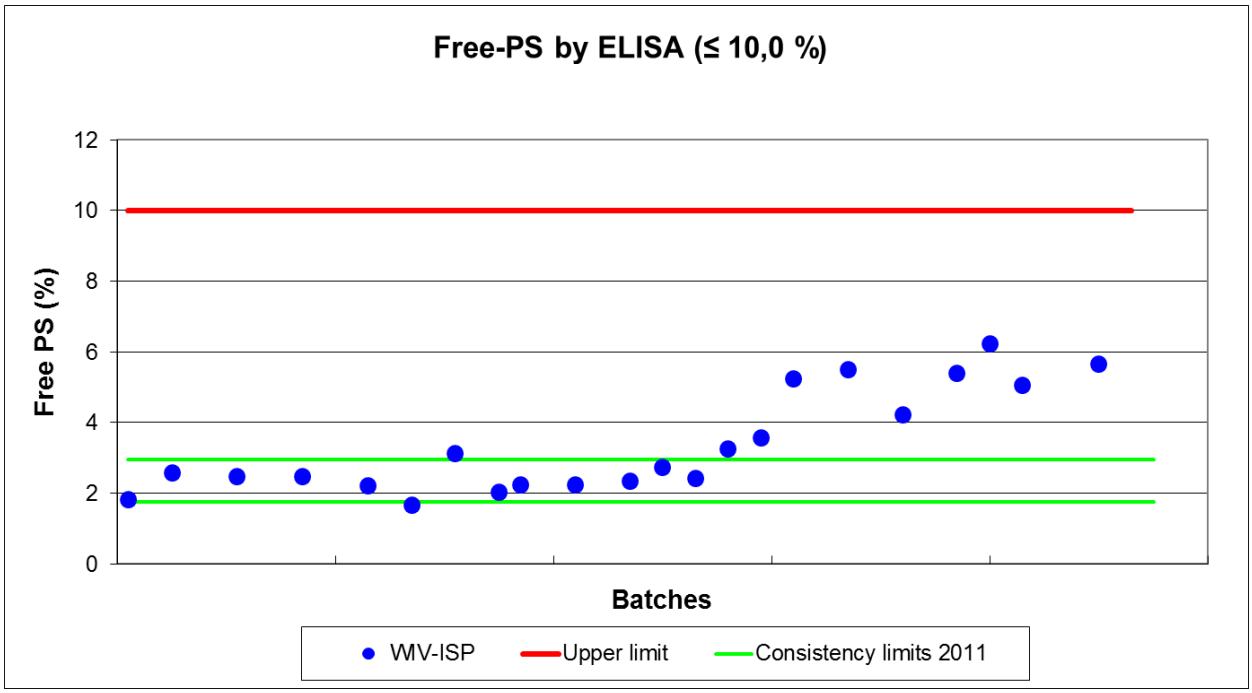
D.4.3.4.3 PS/protein ratio

All the results for the PS/protein ratio are within the specifications and are consistent compared to the 2011 batches. For the batches that are slightly outside the consistency, the protein content was lower resulting in a higher PS/protein ratio value.



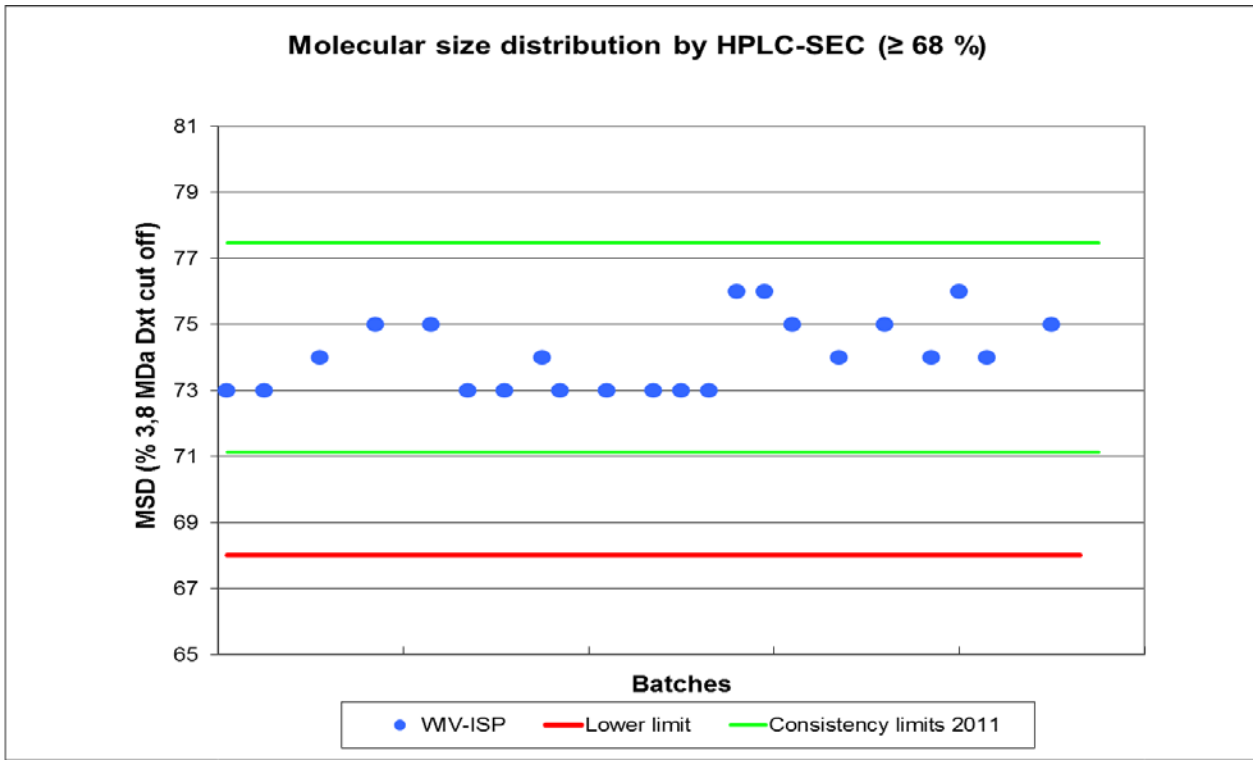
D.4.3.4.4 Free-PS

The results in the graph below demonstrate that the 2012 results very well fit into the consistency of 2011 for the initial results. For the later batches, the results seem to be out of consistency, but this is related to the fact the batches were tested later on during the shelf life. Free-PS can be considered as a stability indicating factor that increases in function of bulk age. No OOS results were obtained. it should also be taken into account that the consistency limits set by the manufacturer are very tight.



D.4.3.4.5 Molecular size distribution

All the results for molecular size distribution met the specifications and the results were consistent compared to the 2011 results.



D.4.3.5 Monovalent conjugated bulk PS23F-PD

Only one batch of PS23F-PD monovalent conjugated bulk was released in 2012. Test results on protein content, polysaccharide content, PS/protein ratio, free-PS, molecular size distribution all met the specifications.

D.5 Conjugated meningococcal polysaccharide vaccine, serotypes ACWY

D.5.1 Product description

This is a vaccine directed against meningococcal invasion (*Neisseria meningitidis*). Four different polysaccharide serotypes (A,C,W and Y) are separately conjugated with a Tetanus Toxoid protein carrier. The monovalent conjugated bulks are mixed to obtain the final bulk, followed by filling into final containers. Only one final lot was released by WIV-ISP (launch of the product on the market).

D.5.2 Number of released batches

In 2012, 3 batches were submitted and one batch was fully tested and released

Vaccine type	Status	Release information's		
		EU	Non-EU	Total
Conjugated meningococcal polysaccharide vaccine, serotypes ACWY	Submitted	3	0	3
	Tested	1	0	1
	Released	1	0	1
	Rejected	0	0	0

In order to release the batch, 2 purified polysaccharide batches were tested and two conjugated polysaccharide batches (serotype A and C). The purified PSW and PSY and conjugated PSW-TT and PSY-TT batches were tested by another OMCL.

D.5.3 Release specifications and limits

Tests	Manufacturer	WIV-ISP
Purified PSA bulks		
O-acetyl content	≥ 2,5 µmole per mg PS dry weight (by spectrophotometry)	same as manufacturer
	≥ 0.80 mole/ mole PS (by NMR)	Test not performed at WIV-ISP

Tests	Manufacturer	WIV-ISP
Purified PSC bulks		
O-acetyl content	≥ 1,5 µmole per mg PS dry weight (by spectrophotometry)	same as manufacturer
	≥ 0.81 mole/ mole PS (by NMR)	Test not performed at WIV-ISP

Tests	Manufacturer	WIV-ISP
Purified PSW bulks		
O-acetyl content	≥ 0,3 µmole per mg PS dry weight (by spectrophotometry)	same as manufacturer
	≥ 0.49 mole/ mole PS (by NMR)	Test not performed at WIV-ISP

Tests	Manufacturer	WIV-ISP
Purified PSY bulks		
O-acetyl content	≥ 0,9 µmole per mg PS dry weight (by spectrophotometry)	same as manufacturer
	≥ 0.62 mole/ mole PS (by NMR)	Test not performed at WIV-ISP

Tests	Manufacturer	WIV-ISP
Conjugated PSAah-TT bulks		
polysaccharide content	≥ 240 µg/ml	same as manufacturer
free-polysaccharide	≤ 15 %	same as manufacturer
molecular size distribution	≥ 65 % before dextran 0,8Mda/≥ 65 % before cut off 875 KDa	same as manufacturer

Tests	Manufacturer	WIV-ISP
Conjugated PSCah-TT bulks		
polysaccharide content	≥ 300 µg/ml	same as manufacturer
free-polysaccharide	≤ 15 %	same as manufacturer
molecular size distribution	≥ 60 % before dextran 3,8Mda/≥ 60 % before cut off 2900 KDa	same as manufacturer

Tests	Manufacturer	WIV-ISP

Conjugated PSW-TT bulks		
polysaccharide content	≥ 360 µg/ml	same as manufacturer
free-polysaccharide	≤ 15 %	same as manufacturer
molecular size distribution	≥ 50 % before dextran 3,8Mda/≥ 50 % before cut off 2300 KDa	same as manufacturer

Tests	**Manufacturer**	**WIV-ISP**
Conjugated PSY-TT bulks		
polysaccharide content	≥ 220 µg/ml	same as manufacturer
free-polysaccharide	≤ 20 % or ≤ 15 % (depending on manufacture date)	≤ 15 %
molecular size distribution	≥ 60 % before dextran 3,8Mda/≥ 60 % before cut off 2600 KDa	same as manufacturer

Tests	**Manufacturer**	**WIV-ISP**
Final container		
Appearance	White cake or powder. After reconstitution with diluent: clear and colourless liquid.	same as manufacturer
Identity of all four serotypes	Positive	same as manufacturer
Endotoxin content	≤ 10.00 IU per dose	same as manufacturer
PS A content	≥ 80% of target value	same as manufacturer
PS C + W + Y content	≥ 80% of target value	same as manufacturer
PS Y content	≥ 80% of target value	same as manufacturer
PS W content	≥ 80% of target value	same as manufacturer
PS C content	≥ 70 % of target value (by ELISA)	≥ 65 % of target value (by calculation)

D.5.4 Results

In 2012, only one batch was released. WIV-ISP also tested one purified polysaccharide A and C and one conjugated PSAah-TT and PSCah-TT conjugated bulk.
All test results met the specifications.

D.6 General conclusion

Vaccines are heterogeneous immuno-biological products containing various components such as antigens, adjuvants, excipients and preservatives. Due to this complexity and the intrinsic variability of the vaccine production process, each vaccine batch (lot/serial) of final product is regarded as unique and it is therefore required that quality control is performed on each batch of a vaccine before its release on the market.

Testing is only one component of an operational quality system, which includes careful validation and maintenance of the manufacturing process.

On the other hand, the follow up of the consistency in production through the review of in-process characteristics and parameters (and not only the licensed release specifications) measured on the intermediates and the final product represent a major improvement in quality evaluation.

Nowadays it is a well-established philosophy that the quality of a vaccine is not ensured by testing alone, but also built through the strict application of the quality assurance system.
To reinforce the quality evaluation and the overview of the quality product, the Biological Standardisation has participated, in 2012, as product expert to **15 GMP inspections** on site with GMP auditors from the Inspectorate (FAMHP).

In addition, our quality experts have also been involved in evaluation of dossiers (**4 licensing dossiers as well as 91 process variation dossiers in 2012).**

This combination of different points of view (Batch release, GMP inspection, review of quality dossier) is quite unique and allows the Scientific Institute of Public Health to be one of the major key players in the field of vaccines within Europe.

Section E: Network Activity

➢ The Biological Standardisation Programme (BSP) [4]

One of the missions of the Biological Standardisation Programme is to elaborate European Pharmacopoeia Reference Standards and working standards for biologicals in order to improve international harmonisation.

To achieve such a goal, the secretariat of the Biological Standardisation, OMCL and HealthCare Department (DBO) of the EDQM coordinates collaborative studies run under the BSP with those planned by the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA).

The BSP studies may include national labs as well as labs of different European manufacturers in order to provide Biological Reference Preparations (BRP) to the network.

The full reports of the concluded collaborative studies are published in 'Pharmeuropa Bio & Scientific Notes' **[5]** .

➢ The Proficiency Testing Scheme (PTS) [6]

In order to build mutual trust between OMCLs, the concept of Proficiency Testing Scheme has been introduced within the European network of OMCLs.

The Proficiency Testing Scheme is an external assessment of quality control management systems using inter-laboratory comparisons. It is organized by the EDQM to ensure the performance of individual laboratories.

PTS studies are carried out on a regular basis on biological and physico-chemical methods.

This helps to build a homogeneous quality level of analysis between members as well as a mutual recognition within the network.

Studies foreseen for 2013:

- PTS 127: Hepatitis B
- PTS 137 : MMR vaccine – potency
- PTS 139 : pH
- PTS: Transgenic mice neurovirulence test : clinical scoring (NIBSC)

Monkey neurovirulence test: scoring of scanned slides (NIBSC)

➢ Mutual joint audit (MJA) [7]

A common approach for developing and implementing Quality Management systems (QMS) in all OMCLs of the Network is an essential step to mutual recognition. This was especially important due to the increasing exchange of results and data (e.g. batch release of biologicals, market surveillance of centrally authorised products) among members.

In order to harmonize the quality management systems of the OMCLs, the mutual joint audit program has been adopted and refers to the ISO/IEC 17025 quality standard.

MJAs of OMCLs are carried out by experts, from the Network. They check that OMCLs quality management systems comply with the requirements laid down in ISO/IEC 17025, in the General European OMCL Network Quality Management Guidelines and in the European Pharmacopoeia. They take place on a routine basis.

In 2012 a workshop for technical auditors of the Network was held at the EDQM premises in order to exchange experience and to harmonize requirements during audits.

Two experts from the Biological Standardisation unit participated in 2 different mutual joint audits in 2012.

- **Quality Management Guidelines**

They have been drafted by experts from the OMCL Network in order to support laboratories in implementing the ISO/IEC 17025 requirements, while taking into account the specific OMCL environment.

The following new or updated OMCL guidelines were adopted by correspondence and presented at the 2012 annual OMCL meeting: “Management of Reagents” (PA/PH/OMCL (11) 157 5R) and “Handling and Use of Reference Standards in the OMCL Network” (PA/PH/OMCL (11) 204 3R).

Currently, new guidelines on “Qualification of Balances” and “Qualification of Analytical Columns” are under elaboration, other guidelines are being revised.

Section F: Batch release at the request of WHO

Among its activities, our Biological Standardisation unit ensures the control and the release of batches of vaccines for human use before their marketing. Within this framework, our unit developed, thanks to its expertise acquired during the two last decades, a close collaboration with the World Health Organisation**[8]**.

Our collaboration is based on the following 3 activities/expertise:

A) The technical expertise for the analysis and the evaluation of new "candidate vaccines" subjected to a pre-qualification procedure or already pre-qualified vaccines. This is a procedure of acceptance of the vaccines by WHO for use at the time of vaccination campaigns of the UNICEF. **[9]**

The TSA contract (Technical Service Agreement) **[10]** lists the type of vaccines and the number of batches which will be sent by WHO as well as the tests to carry out. The samples come from the company who wishes to enter the pre-qualification process or to maintain its pre-qualified status.

WHO sends samples 2 or 3 times a year accompanied by the documentation relative to their production and control by the company.

During this pre-qualification procedure, the experts of the WIV-ISP are invited to evaluate the dossier submitted according to the WHO standards (Product Summary file) and take also part in a GMP quality audit of the manufacturer.

Batches tested in 2012 are listed in the table below

Others: WHO (TSA)	Nr of tested batches
bOPV (bivalent OPV type 1 & type 3)	**5**
Bulk Hib	**3**
Hib	**7**
HepB	**5**

B) The participation in the drafting of recommendations related to quality (production and control), safety and effectiveness of new "candidate vaccines" as well as the revision of existing recommendations. **[11]**

C) Scientific advice in direct connection with problems occurring on the field (e.g. when an out of specification result is detected on a critical test) or research projects (impact of temperature on vaccine activity). **[12]**

This expertise is also valuable during the evaluation of national regulatory authorities of other countries. Indeed, the competent authorities of a country are audited by their peers in order to standardize the dossier evaluation and analysis practices. This allows WHO to guarantee an equivalent quality level of assessment of the pre-qualification procedure, whatever the country of manufacturing. Within this framework, our scientists are invited as technical experts to share their expertise and knowledge of the vaccines.

In 2012, one of our experts has been involved in a national regulatory authority evaluation.

Acknowledgment

We would first like to thank the Manufacturers for the exchange of information on batches and the associated transparency in the European batch release framework

We would like to thank the European Directorate for the Quality of Medicine & Healthcare (EDQM) for giving us the opportunity to take part, as vaccine experts, to PTS & BSP testing and auditing.

We also would like to thank the World Health Organisation (WHO) for the fruitful collaboration in the field of testing and auditing.

Finally, We would like to thank all Biological standardisation teams for their expertise and support during testing, especially Geneviève Waeterloos, Head of the Biological standardisation unit, Isabelle Hansenne, Fabrice Ribaucour, Olivier Carabin and Koen Brusselmans, senior scientists.

Conflict of Interest Statement

The authors have neither any professional nor personal conflicts of interest.

see also:

http://www.ema.europa.eu/docs/en_GB/document_library/contacts/ltesolin_DI.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/contacts/wmolle_DI.pdf

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[1] http://www.edqm.eu/en/human-biologicals-611.html
[2] http://www.fagg-afmps.be/en/
[3] Belac: http://economie.fgov.be/en/entreprises/life_enterprise/quality_policy/Accreditation/
[4] BSP: http://www.edqm.eu/en/Biological-Standardisation-Programme-mission-60.html
[5] Pharmeuropa : http://www.edqm.eu/en/pharmeuropa-bio-and-scientific-notes-584.html
[6] PTS: http://www.edqm.eu/en/Proficiency-Testing-Scheme-47.html
[7] MJA: http://www.edqm.eu/en/quality-management-19.html
[8]Tesolin L., Le WIV-ISP, partenaire clé de l'OMS dans le contrôle qualité des vaccins. WIV-ISP rapport d'activités 2011-2012 ; numéro de dépôt : D/2013/2505/23 ; Bruxelles, 2013.
[9] http://www.who.int/topics/prequalification/en/
[10] http://www.who.int/biologicals/areas/vaccines/lot_release/en/
[11]http://www.who.int/immunization_standards/vaccine_quality/pq_consultation_2010/en/index.html
[12] Zipursky S. et al, Vaccine, JVAC-D-11-00507R1 (http ://dx.doi.org/10.1016/j. vaccine.2011.06.011)

List of Annexes

Annex 1 : ISO 17025 Belac accreditation certificate
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Annex 1 : BELAC certificate

Organisme belge d'Accréditation
Belgische Accreditatieinstelling
Belgische Akkreditierungsstelle
Belgian Accreditation Body

Signatory to EA, ILAC and IAF Multilateral Agreements

Certificat d'Accréditation n° 081-TEST

En application des dispositions de l'arrêté royal du 31 janvier 2006 créant BELAC, le Bureau d'Accréditation atteste que le laboratoire d'essais

SERVICE PUBLIC FEDERAL (SPF)
SANTE PUBLIQUE, SECURITE DE LA CHAINE ALIMENTAIRE
ET ENVIRONNEMENT
INSTITUT SCIENTIFIQUE DE LA SANTE PUBLIQUE
Rue Juliette Wytsman, 14
1050 BRUXELLES - Belgique

possède, conformément aux critères de la norme NBN EN ISO/IEC 17025:2005, la compétence pour effectuer les essais décrits dans l'annexe qui fait partie intégrante du présent certificat. Le respect des conditions d'accréditation fait l'objet de surveillances régulières.

La Présidente du Bureau d'Accréditation BELAC,

Nicole MEURÉE-VANLAETHEM

Date d'émission : **2010-06-22**

Date de validité : **2015-01-31**

La version originale de ce certificat est en néerlandais.

Annex 2: MJA Attestation

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE

COUNCIL OF EUROPE

European Directorate for the Quality of Medicines & HealthCare

OMCL NETWORK QUALITY MANAGEMENT SYSTEM

ATTESTATION

The EDQM, European Directorate for the Quality of Medicines & HealthCare, hereby declares that

Scientific Institute of Public Health
Juliette Wytsman, 14, B-1050 Brussels, Belgium
Biological Standardisation Section

has been audited in accordance with the EDQM instruction *IS7/02* on the OMCL Network Mutual Joint Audit Scheme.

The above-mentioned OMCL is entitled to declare that it has satisfactorily implemented a Quality Management System in accordance with ISO/IEC 17025.

Detailed information can be found in the Audit Report, which is consigned in document *PA/PH/OMCL-QA (09) 04 DEF* corresponding to the *MJA 01/09*, and in the enclosed Scope of Assessment. The original documents are archived at the Department of Biological Standardisation, OMCL Network & HealthCare (DBO) of the EDQM and the Director of the OMCL has received a certified copy.

Attestation number: EDQM/MJA-045

Strasbourg, 30 June 2011

Valid until: 12/2014

Karl-Heinz Buchheit
Deputy Head of the DBO, EDQM