Welcome

Empowering a healthy tomorrow

USP Activities in Vaccines

Dibyendu Saha Ph.D.
Senior Scientific Liaison,
United States Pharmacopeia

Who we are and where we work

- Founded in 1820, nonprofit, private, independent and self-funded
- Value-driven organization focused on quality standards to protect public health
- More than 1,100 employees worldwide

- Headquartered in Rockville, MD near Washington DC, NIH and FDA
- Laboratory facilities in U.S., India, China, Brazil and Ghana
- Offices in Switzerland, Ethiopia, Indonesia, Philippines and Nigeria

- Work with more than 900 scientists, practitioners and regulators to develop standards that help protect public health
- Internationally recognized and globally focused

What we do

We develop public, scientific-based quality standards that help protect people's health

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USP Standards

Monographs

- Specifications for pharmaceutical articles in commerce (from release through product shelf life)
- Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards

General Chapters

- Test chapters (numbered <1000) containing validated methods that users can verify are suitable for their use
- Informational (numbered >1000) containing best practices
- Support monographs by centralizing methods and procedures

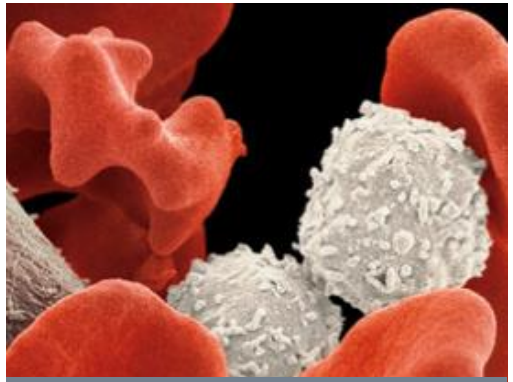
General Notices

- Provide definitions for terms used in the monographs, as well as information that is necessary to interpret the monograph requirements.

Official Recognition

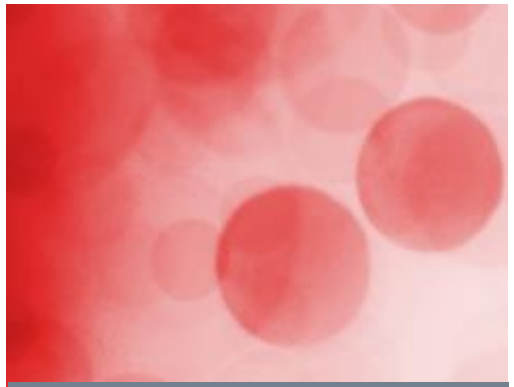
U.S. Federal Food, Drug, and Cosmetic Act designates the USP–NF as official compendia for drugs marketed in the United States.

Biologics product classes – Reference Standards

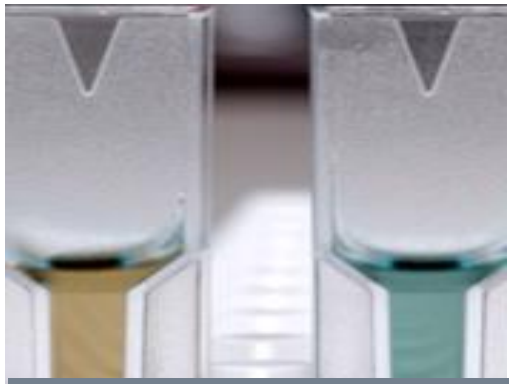


Blood products

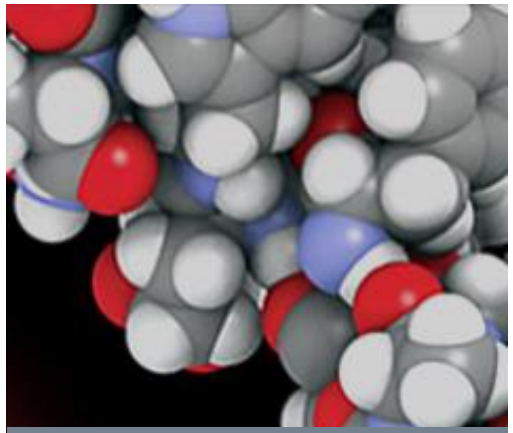
Cell & tissue



Glycosaminoglycans



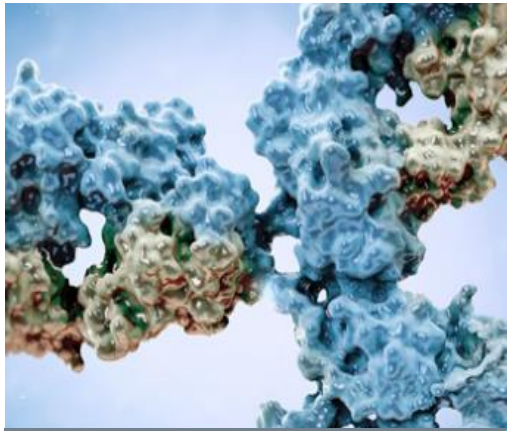
Performance standards



Peptides

Raw & ancillary materials

Vaccines



Proteins & enzymes

Role of General Chapters for biotech products

A broad chapter portfolio facilitates monograph development for all biotech products

Chapters support biological product development by providing validated procedures (numbered below 1000), as well as general quality guidance (numbered above 1000)

Chapters can provide key procedures that apply to and support products for which no monograph exists yet

Chapters can address materials/issues that would be challenging to address in a monograph, e.g. in the area of process, ancillary, and raw materials quality

Chapters allow choices and flexibility often needed for biologics, but also create consistency in analytical expectations and approaches

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Global regulations and standards

Human vaccines are regulated and licensed by FDA as biological products under the Public Health Service Act

- Applicable regulations include those in 21 CFR, sections 200 and 600
- FDA includes interpretation of requirements in guidance documents

Animal vaccines are regulated and approved by USDA

International guidances are available from the ICH and the WHO

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USP Reference Standard development process

Benefits of public international standards for biological medicinal products

- Promotes transparency
- Promotes international regulatory convergence
- Increases quality of and confidence in standards by utilizing and leveraging international scientific expertise
- Supports access to high-quality products worldwide by enabling multiple manufacturers
- Provides continuity of biological activity through changes in marketplace (e.g. helps identify drift within or between products)
- Helps protect against counterfeits and sub-standard products
- Helps address public health concerns/crisis

Public standards provide tools to industry, regulators, and other stakeholders that can be utilized throughout a product lifecycle - development, approval, compliance, market surveillance - to help ensure patient access to quality biological medicinal products

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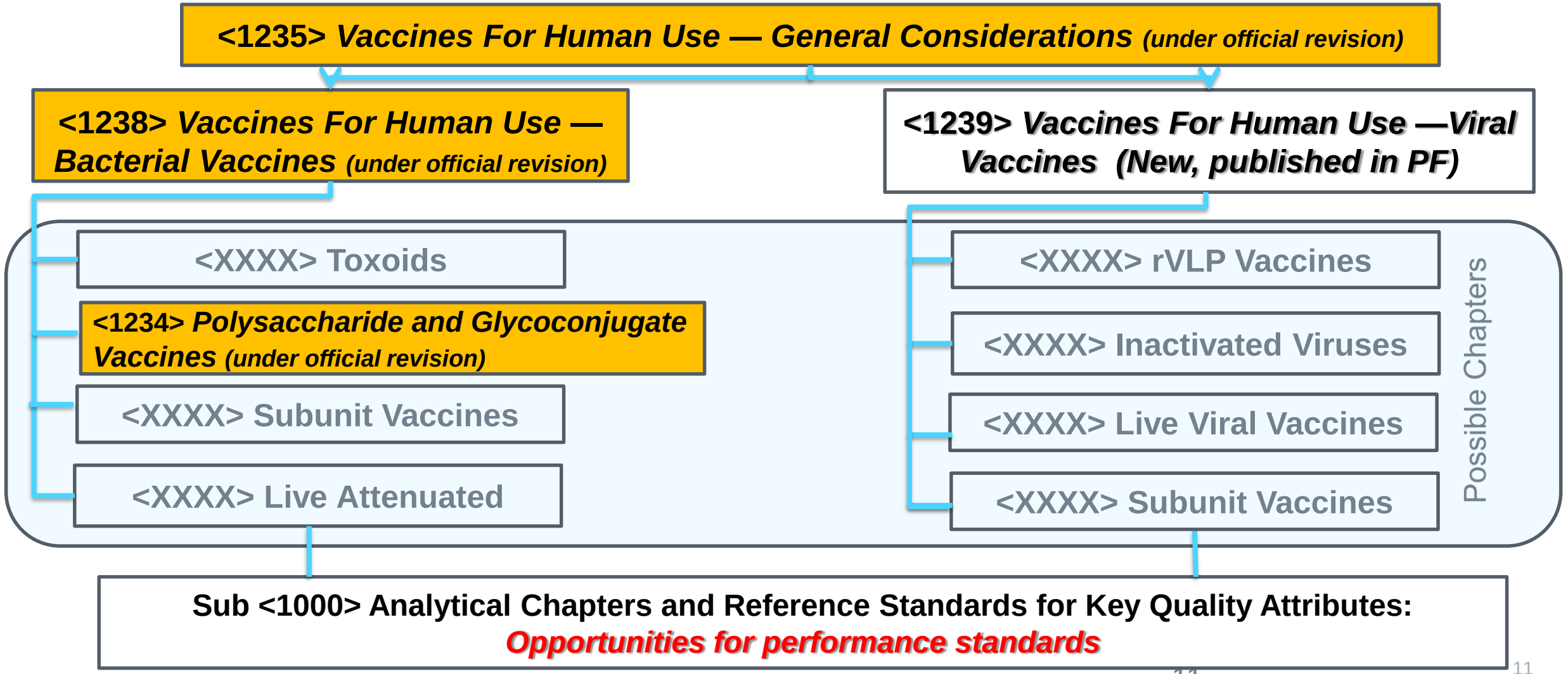
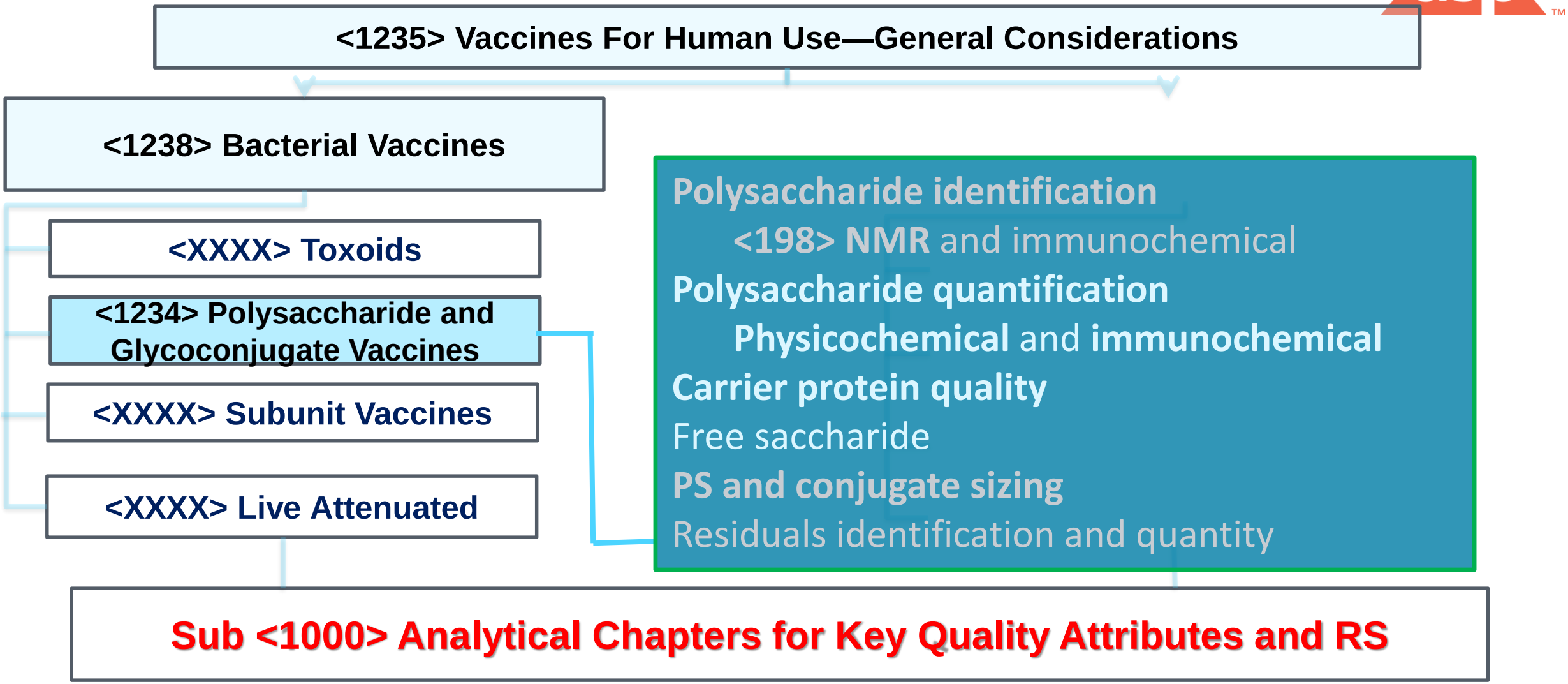
USP vaccine chapters



USP vaccine chapters



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⟨198⟩ Nuclear Magnetic Resonance Spectroscopy Identity Testing of Bacterial Polysaccharides Used in Vaccine Manufacture

^{1}H NMR spectroscopy applied to the **identity testing** of **bacterial polysaccharides**

The identity of the saccharide component in polysaccharide and glycoconjugate vaccines should be confirmed for bulk monovalent polysaccharide, blended polysaccharide bulk, activated polysaccharide (if isolated), bulk monovalent conjugate, blended conjugate bulks, and final fills.

NMR is most useful for bulk monovalent polysaccharides and activated polysaccharides (if isolated).

This approach is compatible with polysaccharides that lack O-acetylation, such as ***Haemophilus influenzae*** type b or many pneumococcal polysaccharides, or O-acetylated polysaccharides, such as ***Neisseria meningitidis***, and many pneumococcal polysaccharides where the product and spectral consistency allow identity to be established through direct comparison of test and reference spectra.

Strategy

Standards **may** or **may not** be supported by a monograph but will be accompanied by an **analytical chapter**.

Find out industry/stakeholder requirements

Engage with the industry to develop relevant standards

Potential USP vaccine standards for the future

Following candidates have been identified for new analytical chapters with associated reference standards :

- Identity standards

System suitability standards to verify method performance (e.g., USP PS NMR System Suitability RS associated with <198>), currently being extended to *Meningococcal*, *Pneumococcal*, *Hib* and *S. Typhi* Vi polysaccharides (Product-specific Reference Standards). Work in progress with *Meningococcals*.

The next informational class chapter that can be considered is for toxoids, with carrier protein testing likely to follow, ***based on industry requirements****.*

Future analytical chapters

1. Molecular sizing System Suitability Reference Standards using HPSEC for Polysaccharide and Glycoconjugate Vaccines (can use current USP Dextran RS's for SST)

2. Analytical Methods on Process Impurities in Vaccines (with associated Reference Standards)

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Establishing Procedural Standards for Molecular Size Determination of Polysaccharide and Glycoconjugate Vaccines by HPSEC

The proposed approach is based on work published by GSK for polysaccharide vaccines

***Development and validation of a molecular size distribution method for polysaccharide vaccines**. G Clément, J-F Dierick, C Lenfant, D Giffroy • Pharmeuropa bio & Scientific Notes • 2014*

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Importance of molecular sizing

Polysaccharide size is CQA for polysaccharide vaccines, and a critical release test:-

- WHO requirements
- EP monographs

[WHO] Specifications are based on K_d of the [soft-gel] column

A key in-process test in the manufacture of glycoconjugate vaccines – CPS size reduction prior to conjugation

It is a key test for batch consistency in glycoconjugate vaccines

The method is based on size-exclusion chromatography

- Originally Sepharose CL-2B or -4B soft gel columns (still in use for some legacy products)
- Now using HPSEC columns with RI or UV detection

Advantages and challenges

- **Disadvantages of CGPC**: Time consuming, requires careful handling and large amount of product.
- **Advantages of HPSEC:** Quicker analysis, small amount of product requirement and large choice of detectors.

Challenges

- Ensuring consistent intra-laboratory measurement (between column matrices, matrix batches etc.)
- Consistent measurement following method transfer between analytical platforms (e.g. soft gel to HPSEC)
- NRA/NRL comparison of products from different manufacturers

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Establishing analytical methods and associated (quantitative/identity) reference standards for process impurities in vaccines

Process impurity type	Relevant vaccines
Inactivation and toxoiding agents (e.g. formaldehyde, glutaraldehyde)	Inactivated viral and bacterial vaccines, toxoid vaccines
Host cell proteins/cell culture residuals (e.g. albumin, ovalbumin, antibiotics, etc.)	Viral vaccines
Purification reagents (e.g. Caesium, CTAB - Cetyl trimethylammonium bromide, etc.)	Live viral vaccines, polysaccharide vaccines
Conjugation reagents e.g. EDC (1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide)	Glycoconjugate vaccines
Endotoxin	Most vaccines

Future considerations on vaccines

Glycoconjugate vaccines – Standards (PS **ID** & PS **quantity**)

Polysaccharide characterization – **quantity** – rate nephelometry

Carrier protein quality – toxoids (% monomer HPLC, BSA monomer and dimer standards for system suitability)

Test methods for modern adjuvants, e.g. squalene

Sterility Testing – USP <71> would benefit from a revision. Can the Industry and USP come up with a viable generic rapid sterility test method?

Proposed vaccine course outline

- Global vaccine course targeting the GMP aspects of manufacturing and control
- Amalgamation of excerpts from WHO, ICH and USP
- Deeper insights and understanding of industrial challenges against regulatory expectations
- Modular design to help manufacturers choose as per their needs
- A five-day course consisting of class room learning and activities to help the attendees correlate the theory with practical experiences
- Case studies to help the attendees understand the underlying regulatory aspects

Proposed vaccine course outline, *continued*

- Essentials of GMP for manufacture and control of vaccines (all vaccines) fully aligning with the USP's mission of ensuring global public health
- Introduce USP and its role across the globe in promoting the quality of medicines, foods and dietary supplements with special emphasis on the vaccines for human use
- Uniquely positioned course prepared with the current industry scenario in mind
- Provide education on end-to-end solutions for vaccine industry, right from the cell banking to the challenges in shipping and logistics of drug products and solutions to overcome these challenges

Modular approach

Module 1
General introduction

Module 2
Cell banking

Module 3
Production

Module 4
Quality control

Module 5
Regulatory

Module 6
Packaging and logistics

Call for Candidates: 2020-2025 Council of Experts

- Seeking technical and scientific volunteers for Council of Experts, Expert Committees
  - Pharmaceutical, biologics, and food industries, academia, regulatory and government sectors to volunteer for USP's Council of Experts and Expert Committees
- Help develop quality standards for medicines, dietary supplements and foods
- Learn more:

https://callforcandidates.usp.org

email: **uspvolunteers@usp.org**

Questions

Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow