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Trusted Standards
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A light gray world map is centered in the background of the slide, showing the outlines of all continents.

Welcome

Vaccine Standards – a USP perspective

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What is USP's Role in U.S. Law?

- ▶ **Adulteration** – Drug/biologic “shall” be deemed adulterated “If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.” FDCA 501(b)
 - “Official compendium” means the current version of *USP* or *NF* deemed official by USP, including any supplements. FDCA 201(j)
Current official version is *USP37-NF32*, 5/1/2014 – 4/30/2015
- ▶ **Tests** – “Such determination as to strength, quality or purity shall be made in accordance with the tests or methods of assay set forth in such compendium,” FDCA 501(b)
- ▶ **Misbranding** – Drug/biologic “shall” be deemed misbranded “if it purports to be a drug the name of which is recognized in [*USP-NF*],” unless “packaged and labeled as prescribed therein.” FDCA 502(g)
- ▶ **Enforcement** – USP has no role in enforcement of USP standards; responsibility of FDA and other authorities in U.S. and elsewhere.

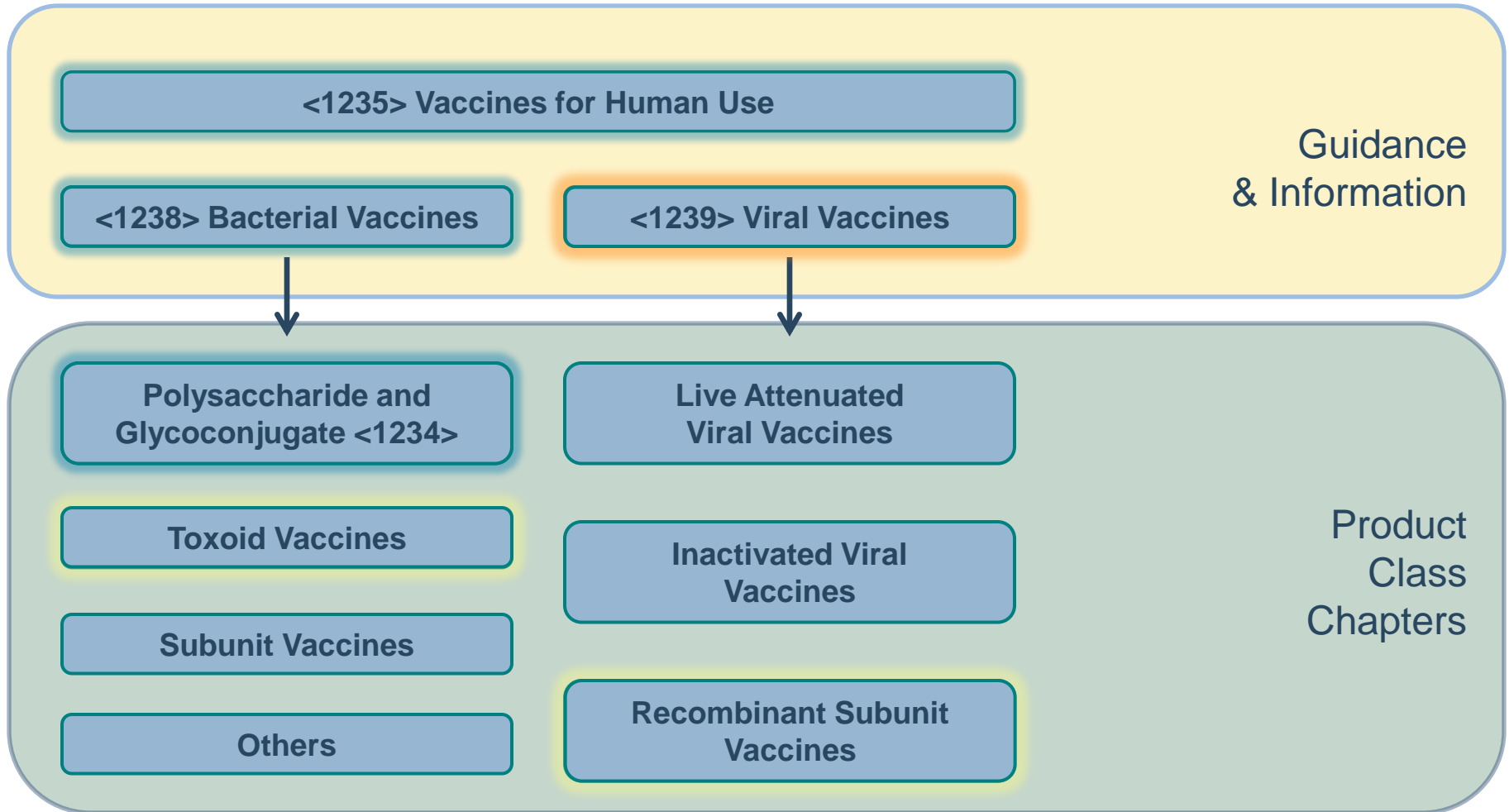
- ▶ **Monographs**
 - Specifications for pharmaceutical articles in commerce (from release through product shelf life)
 - Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards
- ▶ **General Chapters**
 - Required when monograph cites them (numbered <1000)
 - Informational (numbered >1000)
 - Support monographs by centralizing methods and procedures
- ▶ **Physical Reference Materials**
 - Provide traceable standards to demonstrate broad-based acceptability of procedures

- **Chemical**
 - Analytical Chemistry
 - Synthetic Chemistry
 - Reference Standards Laboratory
 - Lab Operations

- **Biology**
 - Biochemistry and Protein Characterization
 - Vaccines
 - Microbiology
 - Cell Biology
 - Virology

- **Development of General Chapter and Monographs**
- Development of **USP Reference Standard materials**
 - Collaborate with International Groups – NIBSC & WHO
- **Training Programs** in different areas of biologics
 - USAID Training Program in Microbiology for Sub-Saharan Govt. Testing Lab employees
 - Biotech training program for Govt. Laboratory employees from other countries, e.g., Russia
 - Pharmacopeial Training Program – Theory and Practical in Microbiology and Protein analysis
 - Training program in Biotechnology – USP-IIBT-NIPER

USP Vaccine Chapters – Strategy



- ▶ <1235> *Vaccines for Human Use – General Considerations*
 - Covers general guidance applicable to all types of vaccines
 - Seed lot systems
 - Manufacturing
 - Fermentation, Propagation/Harvest, Purification, Intermediates, Bulks, Final Containers
 - Stability, Analytical, Label/Pack, Lot Release

- ▶ <1238> *Vaccines for Human Use – Bacterial Vaccines*
 - Covers guidance specifically for bacterial based vaccines
 - Types of vaccines
 - Polysaccharide, Polysaccharide-protein conjugates, Toxoids
 - Details on seed lot systems, manufacturing, fermentation, purification, process development, monitoring, testing.

- ▶ *<1239> Vaccines for Human Use – Viral Vaccines*
 - Ready to go to PF 40(5)
 - Structure and content similar to *<1238>*
 - Covers guidance specifically for viral vaccines

▶ <1239> *Vaccines for Human Use – Viral Vaccines*

– Introduction

- List of available viral vaccines,
 - 4 Categories of viral vaccines
 - Live attenuated, Inactivated, Subunit, VLP
 - Table listing information on characteristics, advantages and challenges for each of the 4 categories
- General discussion of each category
- Chapter subsections:
 - Raw Materials
 - Seed banking, fermentation, harvest, purification, and formulation
 - Should conform to applicable compendial standards
 - Links to relevant tests e.g., *Elemental Impurities - Limits <232>*, *Elemental Impurities – Procedures <233>*, *Bacterial Endotoxins Test <85>*, *Growth Factors and Cytokines used in Cell Therapy Manufacturing <92>*

- Eggs and Primary Cell Lines
 - Control cultures and Adventitious agent testing guidance
 - ✓ <1050> *Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin*
 - Link to <1237> *Virology Test Methods*, for guidance on screening cell lines
- Seed Lot systems, Cell Banks
 - General information in <1235> *Vaccines for Human Use – General Considerations*.
 - For recombinant technology see <1048> *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of r-DNA Derived Protein Products*
 - For guidance on cryopreservation of cell lines see <1044> *Cryopreservation of Cells*

- Culture and Harvest
 - Detailed descriptions of viral culture and harvest
 - For Extractables / Leachables see <1031> *The Biocompatibility of Materials Used In Drug Containers, Medical Devices, and Implants* for guidance
- Purification
 - Details for each category of viral vaccine
- Intermediates
 - Tables with lists of appropriate tests for different types of intermediates, links to compendial tests where appropriate, e.g., <71> *Sterility Tests*, <791> *pH*, <85> *Bacterial Endotoxins Test*

USP Vaccine Chapters <1239>

- Drug Substance
- Drug Product & Lot Release Tests
- Other Requirements

Each of these three subsections contain references to appropriate parts of CFR where governing requirements are located as well as references to specific USP required tests.

Vaccine Monographs

- ▶ Only 3 vaccine monographs currently official in USP/NF
 - Anthrax Vaccine Adsorbed
 - BCG Vaccine
 - BCG Live

- ▶ 3 Immune Globulin Monographs
 - Pertussis
 - Vaccinia
 - Rabies

- ▶ BB-2 voted to omit most previously official monographs since they contained little quality information and minimal requirements

- ▶ Vaccine members of Expert Committee drafted proposed revision to the USP Request for Revision (RFR) Guideline
 - The Guideline aims to outline what a modern vaccine monograph should look like *i.e.* structure of the monograph
 - These edits will be considered as USP is revising the entire RFR Guideline in 2014

▶ Name

- Unique identity
- Able to differentiate from other vaccines
- Disease designation are first words
- If adsorbed, last word is *Adsorbed*
- If combination all components included separated by “and”

▶ Definition

- Defines scope of monograph
- Should include potency limits (each component)
- Should include antimicrobial agent(s) if present

- ▶ **Manufacturing steps prior to Drug Product**
 - Brief description of each key manufacturing step from Seed to Drug Substance to Drug Product
 - For each key manufacturing step provide information for appropriate release and stability testing as appropriate

▶ Seeds

- Identity, Purity, Safety, Genetic Stability Test, Specific Test, Storage conditions

▶ Intermediates

- Identity, Purity, Sterility <71>, Endotoxin <85>, Safety, Mycoplasma <63> (21 CFR 610.30: cell cultured live viral at harvest and pre-inactivation for inactivated viral vaccines)
- Intermediate Specific Tests (e.g. content, impurity) for each key Drug Substance Component
- Reference Standards

▶ Packaging and Storage

- Indicate the type of container (When container type [plastic or glass] is not included, USP will assume that either is adequate)
- Indicate storage temperature (definitions under *General Notices*)
- Storage temperatures (conform to 21 *CFR* 610.53)

▶ Other Requirements

- Expiration (conform to 21 *CFR* 610.53)

- ▶ Labeling (conform to 21 *CFR* 610.60, 610.61, and 610.62)
 - instructions for use, storage temperatures, recommended dose, and route of administration
- ▶ Reference Standards
 - Indicate which tests require RS
 - CBER, WHO, USP
- ▶ Specification
 - Proprietary information treated as confidential
 - Procedures detailed for competent analyst use

- ▶ Identification Test (conform to 21 *CFR* 610.14)
 - Typically contain multiple orthogonal procedures
- ▶ General Safety (conform to 21 *CFR* 610.11)
- ▶ Antimicrobial Preservatives Content
 - See General Chapter *Antimicrobial Agents–Content* <341>
 - See General Chapter *Antimicrobial Effectiveness Testing* <51> (minimal amount shown to be effective)
- ▶ Adjuvant
 - If present, quantitation test required
 - If aluminum, conform to 21 *CFR* 610.15

▶ Impurities

- Procedures and approved limits if impact to safety and/or efficacy
- For lyophilized products per 21 *CFR* 610.13, include the limits for residual moisture <921>

▶ Related Substances

- Degradation products, starting materials
- All constituent materials meet requirements of 21 *CFR* 610.15

▶ Potency Test

- by an Animal-Based Procedure
- By In-Vivo Antigen Content if no animal test
 - Commercially available kits should be qualified for suitability using an in-house, US, USP, or WHO standard

▶ Specific Tests

- Specific tests, in addition to the ones described above, may be included to better describe and control the purity, quality, and potency of a vaccine. Reference should be made to appropriate General Chapters, where applicable. If the procedure is not included in a General Chapter, the Request for Revision should include complete validation data (see General Chapter *Validation of Compendial Methods* <1225>).

▶ Specific tests

- *Sterility Tests* <71>
- *Bacterial Endotoxins Test* <85> or *Pyrogen Test* <151>
- Container Closure Test
 - test demonstrates integrity (see *Sterility Tests* <71>)
- Determination of Volume see *Injections* <1>
- Particulate Matter* <787> <788>

All RS are being developed in collaboration with NIBSC

Currently Under Development

- ▶ Hib PRP RS – USP-NIBSC-WHO
- ▶ Hepatitis B Antigen RS – USP & NIBSC
- ▶ Tetanus Toxoid – USP-NIBSC-WHO
- ▶ Diphtheria Toxoid – USP-NIBSC-WHO
- ▶ Pertussis antigen (whole cell) – USP-NIBSC

Development will start shortly

- ▶ Tetanus Toxoid for flocculation – USP-NIBSC-WHO – Dec., 2014
- ▶ Meningococcal A polysaccharide - USP-NIBSC-WHO

- ▶ **Global Expertise, Trusted Standards, Improved Health**
 - Utilize Your Expertise
 - Advance Your Profession
 - Improve Drug and Food Quality
 - Improve Public Health

- ▶ **Seeking experts in pharmaceutical, biological, and food sciences; pharmacy; medicine; and related disciplines to volunteer for USP's Council of Experts and Expert Committees for the 2015-2020 cycle**

- ▶ **Contact USPVolunteers@usp.org to receive related email announcements, including next cycle's expert committee structure and the official launch (Fall 2013) of the Call for Candidates**



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A light gray world map is centered in the background of the slide, showing the continents of North America, South America, Europe, Africa, Asia, and Australia.

Thank You