Quality Standards for Challenge Strains

IABS - 2nd Human Challenge Trials in Vaccine Development

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Quality Standards for Challenge Strains

Proposal of a high-level structure of principal elements required in line with regulatory requirements for the CMC development of challenge strains used in human challenge trials

Concept (1)

The proposal is structured according to the CTD/EU-IMPD headings and consists of three columns:

- Points to consider listed according to the headings of the IMPD/CTD
- Applicable guidance (EU-, ICH guidelines, Ph. Eur. Monographs)
- Information required to comply with scientific standards and regulatory guidance

Concept (2)

- EU provisions applicable for IMPDs are specifically covered in the following two guidelines.
  - 16.) EMEA/CHMP/BWP/534898/08 - Requirements for quality documentation concerning biological investigational medicinal products in clinical trials
  - 17.) EMEA/CHMP/BWP/398498/2005 - Virus safety evaluation of biotechnological investigational medicinal products
- IMPDs are structured similarly to MAAs, namely according to the CTD format but may deviate in terms of comprehensiveness of information required, depending on the pharmaceutical development status
- As such, IMPD requirements are not specifically mentioned in the following slides

Module 3 - Quality Data
Drug Substance (DS)

Module 3 - S.2. Manufacture

Points to consider	Applicable guidance	Essential information
S.2.1. Manufacturer(s)	• ICH M4 The Common Technical Document	Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing
S.2.2. Description of Manufacturing Process and Process Controls	• Vaccine specific monographs and WHO recommendations	Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions • Batch(es) and scale definition • Cell culture and harvest • Purification and modification reactions • Filling, storage and transportation (shipping)

Module 3 - S.2. Manufacture (cont'd)

Points to consider	Applicable guidance	Essential information
S.2.3. Control of Materials	• Ph.Eur. 0153 Vaccines for human use • Ph.Eur. 2.6.1. Sterility • Ph.Eur. 2.6.7. Mycoplasmas • CHMP/BWP/457920/2012 Rev. 1 - Use of bovine serum in the manufacture of human biological medicinal products • EMA/CHMP/BWP/814397/2011 - Use of porcine trypsin used in the manufacture of human biological medicinal products • EMEA/410/01 Rev. 3 - Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (…)	Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding their source, manufacture, and characterisation.

Module 3 - S.2. Manufacture (cont'd)

Points to consider	Applicable guidance	Essential information
S.2.3. Control of Materials (con'd)	(…) • ICH Q5C Stability Testing of Biotechnological/Biological Products	• Control of Source and Starting Materials of Biological Origin • Source, history, and generation of the cell substrate • Cell banking system, characterisation, and testing

Module 3 - S.2. Manufacture (cont'd)

Points to consider	Applicable guidance	Essential information
S.2.4. Controls of Critical Steps and Intermediates	• Ph.Eur. 0153 Vaccines for human use • Ph.Eur. 2.6.1. (04/2011:20601): Sterility • Ph.Eur. 2.6.7. (01/2008:20607): Mycoplasmas • ICH Q5C Stability Testing of Biotechnological/Biological Products	• Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled • Information on the quality and control of intermediates isolated during the process • Stability data supporting storage conditions

S.3. Characterisation

Points to consider	Applicable guidance	Essential information
S.3.2. Impurities	• Vaccine specific monographs and WHO recommendations	Characterization of product and process related impurities

S.4. Control of Drug Substance

Points to consider	Applicable guidance	Essential information
S.4.1. Specification	• Vaccine specific monographs and WHO recommendations	Specification for DS should be provided

S.4. Control of Drug Substance (cont'd)

Points to consider	Applicable guidance	Essential information
S.4.4. Batch Analyses	• Vaccine specific monographs and WHO recommendations	Description of batches and results of batch analyses should be provided
S.4.5. Justification of specification	• Vaccine specific monographs and WHO recommendations	Justification for the drug substance specification should be provided

S.5. Reference Standards or Materials

Points to consider	Applicable guidance	Essential information
S.5. Reference Standards or Materials	• Vaccine specific monographs and WHO recommendations	Information on the reference standards or reference materials used for testing of the drug substance should be provided.

S.6. Container Closure System

Points to consider	Applicable guidance	Essential information
S.6. Container Closure System	• ICH M4 The Common Technical Document	• A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate • The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction

S.7. Stability

Points to consider	Applicable guidance	Essential information
S.7.1. Stability Summary and Conclusions	• ICH Q5C Stability Testing of Biotechnological/Biological Products	The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate
S.7.2. Stability Data/Results	• ICH Q5C Stability Testing of Biotechnological/Biological Products	• The post-approval stability protocol and stability commitment should be provided • Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Module 3 Quality Data
Drug Product (DP)

P.1. Description and Composition of the DP

Points to consider	Applicable guidance	Essential information
P.1. Description and Composition of the Drug Product	• Vaccine specific monographs and WHO recommendations	A description of the drug product and its composition should be provided. The information provided should include, for example: • Description of the dosage form; • Composition, i.e., list of all components of the dosage form, and their amount on a per- unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications) • Description of accompanying reconstitution diluent(s); and • Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable

P.2. Pharmaceutical Development (cont'd)

Points to consider	Applicable guidance	Essential information
P.2.4 Container Closure System	• ICH M4 The Common Technical Document	The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product)

P.2. Pharmaceutical Development (cont'd)

Points to consider	Applicable guidance	Essential information
P.2.5 Microbiological Attributes	• Ph.Eur. 5.1.7. (01/2008:50107): Viral safety • Ph.Eur. 2.6.1. (04/2011:20601): Sterility • Ph.Eur. 2.6.7. (01/2008:20607): Mycoplasmas • ICH M4 The Common Technical Document	The microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non- sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed
P.2.6 Compatibility	• ICH M4 The Common Technical Document	The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling

P.3. Manufacture

Points to consider	Applicable guidance	Essential information
P.3.1 Manufacturer(s)	• ICH M4 The Common Technical Document	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided
P.3.3 Description of Manufacturing Process and Process Controls	• Vaccine specific monographs and WHO recommendations	The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified

P.3. Manufacture (cont'd)

Points to consider	Applicable guidance	Essential information
P.3.4 Controls of Critical Steps and Intermediates	• Ph.Eur. 0153 Vaccines for human use • Ph.Eur. 2.6.1. (04/2011:20601): Sterility • Ph.Eur. 2.6.7. (01/2008:20607): Mycoplasmas • Vaccine specific monographs and WHO recommendations	• Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled. • Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

P.4. Control of Excipients (cont'd)

Points to consider	Applicable guidance	Essential information
P.4.4 Justification of Specifications	• Vaccine specific monographs and WHO recommendations	Justification for the proposed excipient specifications should be provided, where appropriate
P.4.5 Excipients of Human or Animal Origin	• ICH Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin • ICH Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products • Vaccine specific monographs and WHO recommendations	For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2).

P.4. Control of Excipients (cont'd)

Points to consider	Applicable guidance	Essential information
P.4.6 Novel Excipients	• Excipients labelling • ICH M4 The Common Technical Document	For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (non-clinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).

P.5. Control of the investigational DP (cont'd)

Points to consider	Applicable guidance	Essential information
P.5.4 Batch Analyses	• Vaccine specific monographs and WHO recommendations	A description of batches and results of batch analyses should be provided
P.5.5 Characterisation of Impurities	• ICH Q5C Stability Testing of Biotechnological/Biological Products • Vaccine specific monographs and WHO recommendations	Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities"
P.5.6 Justification of Specification(s)	• Vaccine specific monographs and WHO recommendations	Justification for the proposed drug product specification(s) should be provided

P.6. Reference Standards or Materials

Points to consider	Applicable guidance	Essential information
P.6. Reference Standards or Materials	• Vaccine specific monographs and WHO recommendations	Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials"

P.7. Container Closure System

Points to consider	Applicable guidance	Essential information
P.7. Container Closure System	• ICH M4 The Common Technical Document	A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate

P.8. Stability

Points to consider	Applicable guidance	Essential information
P.8.1 Stability Summary and Conclusion	• ICH Q5C Stability Testing of Biotechnological/Biological Products	The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.
P.8.2 Stability Data	• ICH Q5C Stability Testing of Biotechnological/Biological Products	• The post-approval stability protocol and stability commitment should be provided • Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included • Information on characterisation of impurities is located in 3.2.P.5.5

Module 3 - Quality Data
A. Appendices

A. Appendices

Points to consider	Applicable guidance	Essential information
A.1. Facilities and Equipment	• ICH M4 The Common Technical Document	• Manufacturing flow • Personnell flow • Material flow • Products manufactured • Dedicated or multi-use facility • Area classification • CIP/SIP procedures

A. Appendices

Points to consider	Applicable guidance	Essential information
A.2. Adventitious Agents Safety Evaluation	• ICH Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin • ICH Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products • Vaccine specific monographs and WHO recommendations	Information assessing the risk with respect to potential contamination with adventitious agents should be provided • For non-viral adventitious agents (TSE, bacteria, mycoplasma, fungi) • For viral adventitious agents (Materials of biological origin, testing at appropriate stages of production, viral testing of unprocessed bulks, viral clearance studies)

A. Appendices (cont'd)

Points to consider	Applicable guidance	Essential information
A.3. Excipients	• ICH M4 The Common Technical Document	Any additional drug substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance
Literature References	• ICH M4 The Common Technical Document	Key literature referenced should be provided, if applicable

Literature References

Points to consider	Applicable guidance	Essential information
Literature References		Key literature should be provided

GMP compliance

- GMP compliance is a must
- GMP starts with the MCB, MVS, etc.
- Research Cell Line from which the MCB is selected can be developed under non-GMP conditions
- Consider early enough that all starting materials used for process and excipients used for formulation need to be GMP manufactured
- Raw materials: pharma grade, tendency to expect that they also need to be GMP manufactured

End of presentation