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# Quality Guidelines

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| | **Pharmaceuticals** | **Biological and Biotechnological Products** |
|---|---|---|
| **GMP** | • GMP for active pharmaceutical ingredients (ICH Q7) CPMP/ICH/4106/00 | |
| **General consideration** | • Pharmaceutical development (ICH Q8 R2) EMA/CHMP/ICH/167068/2004<br>• Note for guidance on development pharmaceutics CPMP/QWP/155/96<br>• Quality risk management (ICH Q9) EMA/CHMP/ICH/24235/2006<br>• Pharmaceutical quality system (ICH Q10) EMA/CHMP/ICH/214732/2007<br>• Development and manufacture of drug substances (ICH Q11) EMA/CHMP/ICH/425213/2011 (Q&A document regarding selection and justification of starting material Q11 Q&As)<br>• Note for guidance on quality of water for pharmaceutical use CPMP/QWP/158/01 Revision | |

| | Pharmaceuticals | Biological and Biotechnological Products |
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| **General consideration** | • Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning IMPs in clinical trials CHMP/QWP/185401/2004 (NOTE: Currently under revision: EMA/CHMP/QWP/834816/2015) | • Guideline on the requirements for quality documentation concerning biological IMPs in clinical trials EMA/CHMP/BWP/534898/2008 (NOTE: Currently under revision: EMA/CHMP/BWP/534898/2008 Rev.1)<br>• Development pharmaceutics for biotechnological and biological products (Annex to note for guidance on development pharmaceutics) CPMP/BWP/328/99 |
| **Active Substance** | • Guideline on summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97 Rev 1 corr<br>• Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances EMA/CHMP/QWP/104223/2015<br>• Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances EMA/448443/2014<br>• Guideline on active substance master file procedure CHMP/QWP/227/02 Rev 3/Corr<br>• Guideline on the chemistry of new active substances CPMP/QWP/130/96, Rev 1 (NOTE: Currently under revision new guideline EMA/454576/2016 effective from 21.05.2017)<br>• Investigation of chiral active substances 3CC29a | • Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products EMA/CHMP/BWP/429241/2013 |

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| **Manufacturing** | • Note for guidance on manufacture of the finished dosage form CPMP/QWP/486/95 (NOTE: Currently under revision: Draft published 09.07.2015: EMA/CHMP/QWP/245074/2015)<br>• The use of ionising radiation in the manufacture of medicinal products 3AQ4a<br>• Annex 12 Use of ionizing radiation in the manufacture of medicinal products | |
| | | • Comparability of biotechnological/biological products subject to changes in their manufacturing process (ICH Q5E) CPMP/ICH/5721/03<br>• Guideline on the quality of biological active substances produced by stable transgene expression in higher plants EMEA/CHMP/BWP/48316/2006<br>• Guideline on human cell based medicinal products EMEA/CHMP/410869/2006<br>• Guideline on quality of biological active substances produced by transgene expression in animals EMA/CHMP/BWP/151897/2013<br>• Position statement on the use of tumourigenic cells of human origin for the production of biological and biotechnological medicinal products CPMP/BWP/1143/00 |
| **Specifications** | • Evaluation and recommendation of pharmacopoeial texts for use in ICH regions (ICH Q4B) EMEA/CHMP/ICH/222007/2006 | |
| | • Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances (ICH Q6A) CPMP/ICH/367/96 | • Specifications: Test procedures and acceptance criteria for biotechnological/biological products (ICH Q6B) CPMP/ICH365/96 |
| **Process Validation** | • Guideline on process validation for finished products EMA/CHMP/CVMP/QWP/BWP/ 70278/2012-Rev1, Corr1 | • Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission EMA/CHMP/BWP/187338/2014 |

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| **Impurities** | • Guideline on impurities: Guideline for residual solvents (ICH Q3C (R5)) EMA/CHMP/ICH/82260/2006 + Annexes<br>• Guideline on the specification limits for residues of metal catalysts or metal reagents EMEA/CHMP/SWP/4446/2000<br>• Guideline on the limits of genotoxic impurities EMEA/CHMP/QWP/251344/2006<br>• Guideline for elemental impurities (ICH Q3D) EMA/CHMP/ICH/353369/2013 | |
| | • Impurities in new drug substances (ICH Q3A R2) CPMP/ICH/2737/99<br>• Impurities in new drug products (ICH Q3B (R2)) CPMP/ICH/2738/99 | • Guideline on setting specifications for related impurities in antibiotics EMA/CHMP/CVMP/QWP/199250/2009 corr<br>• Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (ICH Q5A (R1)) CPMP/ICH/295/95<br>• Position statement on DNA and host cell proteins impurities (HCP), routine testing versus validation studies CPMP/BWP/382/97 |
| **Adventitious agents** | | • Guideline on virus safety evaluation of biotechnological IMPs EMEA/CHMP/BWP/398498/2005<br>• Note for guidance on virus validation studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses CPMP/BWP/268/95<br>• Guideline on the use of bovine serum in the manufacture of human biological medicinal products EMA/CHMP/BWP/457920/2012 rev 1<br>• Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products EMA/CHMP/BWP/814397/2011<br>• Guideline on the investigation of manufacturing processes for plasma-derived medicinal products with regard to variant Creutzfeldt-Jakob disease risk CPMP/BWP/5136/03 |

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| **Adventitious agents** | | • Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products EMA/410/01 rev 3 |
| **Analytical Procedure** | • Note for guidance on validation of analytical procedures: Text and methodology (ICH Q2 (R1)) CPMP/ICH/381/95 | |
| | | • Quality: Analysis of the expression construct in cell lines used for production of r-DNA derived protein products (ICH Q5B) CPMP/ICH/139/95<br>• Quality: Derivation and characterisation of cell substrates used for production of biotechnological/biological products (ICH Q5D) CPMP/ICH/294/95 |
| **Excipients** | • Guideline on excipients in the dossier for application for marketing authorization EMEA/CHMP/QWP/396951/2006<br>• Note for guidance: Inclusion of antioxidants and antimicrobial preservatives CPMP/CVMP/QWP/115/95 | |
| **Packaging** | • Guideline on plastic immediate packaging materials CPMP/QWP/4359/03 | |
| **Stability** | • Stability testing of new drug substances and products (ICH Q1A (R2)) CPMP/ICH/2736/99<br>• Photostability testing of new drug substances and products (ICH Q1B) CPMP/ICH/279/95<br>• Evaluation of stability data (ICH Q1E) CPMP/ICH/420/02<br>• Stability data package for registration in climatic zones III and IV (ICH Q1F) CPMP/ICH/421/02 | • Stability testing of biotechnological/biological products (ICH Q5C) CPMP/ICH/138/95 |
| **Qualified Person** | • Guidance for the template for the QP's declaration concerning GMP compliance of active substance manufacture EMA/196292/2014<br>• The QP declaration template WC500167853 | |

## Additional Guidelines:

### Manufacture, characterisation and control of the active substance

- ICH considerations: Oncolytic viruses EMA/CHMP/ICH/607698/2008
- Allergen products: Production and quality issues EMEA/CHMP/BWP/304831/2007
- Development and manufacture lentiviral vectors CHMP/BWP/2458/03
- Development, production, characterisation and specification for monoclonal antibodies and related products EMEA/CHMP/BWP/532517/2008
- Gene therapy product quality aspect in the production of vectors and genetically modified somatic cells 3AB6a
- Production and quality control of animal immunoglobulins and immunosera for human use EMA/CHMP/BWP/3354/1999 rev.1
- Production and quality control of medicinal products derived by recombinant DNA technology 3AB1a
- Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells EMA/CAT/GTWP/671639/2008
- Quality, preclinical and clinical aspects of gene transfer medicinal products CPMP/BWP/3088/99
  (NOTE: Currently under revision: Draft Guideline EMA/CAT/80183/2014)
- Xenogeneic cell-based medicinal products EMEA/CHMP/CPWP/83508/2009

### Stability

- Stability testing for new dosage forms (ICH Q1C) CPMP/ICH/280/95
- Bracketing and matrixing designs for stability testing of drug substances and drug products (ICH Q1D) CPMP/ICH/4104/00
- Note for guidance on in-use stability testing of human medicinal products CPMP/QWP/2934/99
- Guideline on stability testing: Stability testing of existing active substances and related finished products CPMP/QWP/122/02, rev1 corr
- Maximum shelf-life for sterile products for human use after first opening or following reconstitution CPMP/QWP/159/96 corr

**Analytical Validation**

- ICH Q4B Annex 1: Residue on ignition/sulphated ash CHMP/ICH/222063/06
- ICH Q4B Annex 2: Test for extractable volume in parenteral preparations CHMP/ICH/559409/2007
- ICH Q4B Annex 3: Test for particulate contamination: Sub-visible particles CHMP/ICH/561176/2007
- ICH Q4B Annex 4A: Microbiological examination of non-sterile products: Microbial enumeration tests CHMP/ICH/308671/07
- ICH Q4B Annex 4B: Test for microbiological examination of non-sterile products: Tests for specified microorganisms CHMP/ICH/308817/07
- ICH Q4B Annex 4C: Test for microbiological examination of non-sterile products: Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use CHMP/ICH/308867/08
- ICH Q4B Annex 5: Disintegration test CHMP/ICH/308895/08
- ICH Q4B Annex 6: Uniformity of dosage units EMA/CHMP/ICH/645408/2008
- ICH Q4B Annex 7: Dissolution test CHMP/ICH/645469/08
- ICH Q4B Annex 8: Sterility test CHMP/ICH/645592/08
- ICH 4 QB Annex 9: Tablet friability CHMP/ICH/379801/09
- ICH Q4B Annex 10: Polyacrylamide gel electrophoresis CHMP/ICH/381133/09
- ICH Q4B Annex 11: Capillary electrophoresis CHMP/ICH/730028/09
- ICH Q4B Annex 12: Analytical sieving CHMP/ICH/730028/09
- ICH Q4B Annex 13: Bulk density and tapped density of powders CHMP/ICH/405290/10
- ICH Q4B Annex 14: Bacterial endotoxins tests CHMP/ICH/529785/10

**Adventitious Agents**

- Guideline on the adventitious agent safety of urine-derived medicinal products EMA/CHMP/BWP/126802/2012