Scientific Advice on Quality Aspects for Biologicals

Highlights from recent Scientific advice and Protocol assistance on Quality issues "

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Presentation outlook

- ✓ BWP brief presentation
- ✓ BWP experience in Scientific advice and protocol assistance
  - Number of dossiers covered
  - Type of products and biological origins
  - Examples of typical questions put
- ✓ Recommendations for the best use of the Sc Ad procedure

Biologics Working Party (BWP)

- ✓ Composition
- ✓ Functioning
- ✓ Main activities
  - Dossier evaluation
  - Scientific advice
  - Preparation of guidelines
  - General questions and recommendations

Biologics Working Party (BWP)

- ✓27 members appointed by their National Authorities + Chairperson
- ✓Experts (permanent or ad hoc)
- ✓European Pharmacopea (Observer)
- ✓Commission representative
- ✓EMEA technical secretariat and staff

Biologics Working Party (BWP)

- ✓ 11 meetings per year (1 week before the CHMP)
- ✓ Two-day meeting organized in
  - a plenary session
  - break-out sessions
  - drafting groups
- ✓ All documents (reports, opinions, position papers) are approved by the plenary session before being transmitted to the CHMP

BWP - CHMP interaction

- ✓ BWP is mandated by the CHMP
  - to provide them with scientific opinion
    - dossier evaluation
    - scientific advice
    - general questions
  - to prepare guideline
- ✓ All documents prepared by BWP have to be approved by the CHMP before being released
- ✓ BWP can propose to deal with a topic:
  - concept paper and action plan
  - approval by the CHMP
  - Preparation of a guideline, QnA document, etc.

Dossier evaluation

- ✓ First evaluation made by Rapporteur and Co-rapporteur (quality and biological aspects)
- ✓ Before discussion at the CHMP assessment reports and list of questions are discussed at the BWP:
  - to harmonize divergent opinions
  - to clarify a question
  - to consolidate the list of question and confirm the major objections
  - to initiate a discussion on general question(s) raised during evaluation of the dossier

Scientific Advice

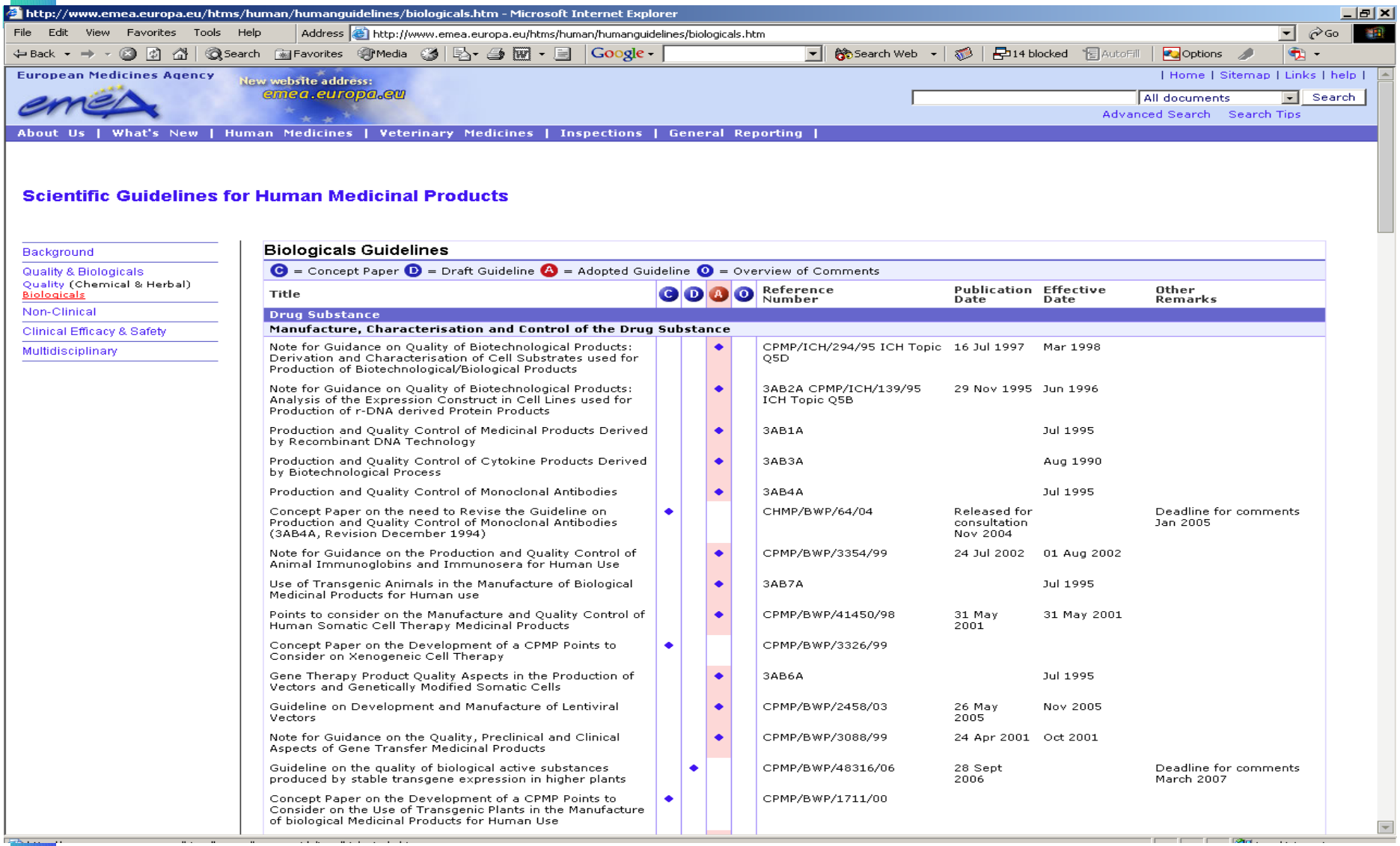
- ✓ On request of the Scientific advice working party
- ✓ Two Co-ordinators are appointed and prepare a report submitted to the BWP
- ✓ Discussion of the reports and proposed answers in BWP plenary session
- ✓ Preparation of a report to the CHMP
- ✓ Possible hearing with the Company if needed

Guidelines

- ✓ Mandate from the CHMP, after approval of a concept paper
- ✓ BWP appoints a rapporteur and set up a drafting group
- ✓ At regular interval, drafting group meets and the rapporteur reports progress to the BWP
- ✓ Liaison with interested parties (CHMP working parties, EFPIA)
- ✓ Release for consultation
- ✓ Implementation of the comments, finalisation
- ✓ Adoption by CHMP and publication on the EMEA website

Guidelines

http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm



http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm - Microsoft Internet Explorer

European Medicines Agency

New website address: emea.europa.eu

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Scientific Guidelines for Human Medicinal Products

- Background
- Quality & Biologicals
  - Quality (Chemical & Herbal)
  - Biologicals
- Non-Clinical
- Clinical Efficacy & Safety
- Multidisciplinary

Biologicals Guidelines

C = Concept Paper D = Draft Guideline A = Adopted Guideline O = Overview of Comments

Title	C	D	A	O	Reference Number	Publication Date	Effective Date	Other Remarks
Drug Substance								
Manufacture, Characterisation and Control of the Drug Substance								
Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products			◆		CPMP/ICH/294/95 ICH Topic Q5D	16 Jul 1997	Mar 1998	
Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products			◆		3AB2A CPMP/ICH/139/95 ICH Topic Q5B	29 Nov 1995	Jun 1996	
Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology			◆		3AB1A		Jul 1995	
Production and Quality Control of Cytokine Products Derived by Biotechnological Process			◆		3AB3A		Aug 1990	
Production and Quality Control of Monoclonal Antibodies			◆		3AB4A		Jul 1995	
Concept Paper on the need to Revise the Guideline on Production and Quality Control of Monoclonal Antibodies (3AB4A, Revision December 1994)	◆				CHMP/BWP/64/04	Released for consultation Nov 2004		Deadline for comments Jan 2005
Note for Guidance on the Production and Quality Control of Animal Immunoglobins and Immunosera for Human Use			◆		CPMP/BWP/3354/99	24 Jul 2002	01 Aug 2002	
Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human use			◆		3AB7A		Jul 1995	
Points to consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products			◆		CPMP/BWP/41450/98	31 May 2001	31 May 2001	
Concept Paper on the Development of a CPMP Points to Consider on Xenogeneic Cell Therapy	◆				CPMP/BWP/3326/99			
Gene Therapy Product Quality Aspects in the Production of Vectors and Genetically Modified Somatic Cells			◆		3AB6A		Jul 1995	
Guideline on Development and Manufacture of Lentiviral Vectors			◆		CPMP/BWP/2458/03	26 May 2005	Nov 2005	
Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products			◆		CPMP/BWP/3088/99	24 Apr 2001	Oct 2001	
Guideline on the quality of biological active substances produced by stable transgene expression in higher plants		◆			CPMP/BWP/48316/06	28 Sept 2006		Deadline for comments March 2007
Concept Paper on the Development of a CPMP Points to Consider on the Use of Transgenic Plants in the Manufacture of biological Medicinal Products for Human Use	◆				CPMP/BWP/1711/00			

Scientific Advice activities at the BWP Overview -1-

- ✓ 34 Scientific advice procedures, in the past 12 months

- ✓ Type of (biological) products covered
  - Recombinant proteins including (50%)
    - Monoclonal antibodies,
    - chimeric proteins,
    - Biosimilars
    - Chemically modified proteins (PEG)
  - Other macromolecules
  - Vaccine antigen (live, attenuated, inactivated, purified, combined, conjugated)
  - Plasmid DNA
  - Recombinant virus for Gene Transfer medicinal products
  - Cell Therapy products

Scientific Advice activities at the BWP Overview -2-

- ✓ Biological origin of the medicinal products
  - Animal or Human tissues or fluids (urine, blood)
  - Cell substrates (from *E.coli* to mammalian cells, insect cells or plant cells)
  - Cell cultures
  - Transgenic plants
  - Transgenic animals
- ✓ Number of question(s) put in a request for scientific advice
  - From one very specific question, up to 12 detailed questions, covering almost all the pharmaceutical/quality/biology dossier (not mentioning sometime the "sub-questions")
- ✓ Type of questions put
  - Comparability after a change is made in a process
    - During the development phase
    - During the commercialisation phase
  - Comparability for a biosimilar
  - Guidelines say nothing on a technical point raised during the development
  - New product or new approach or new technology for which no guideline have yet been drafted

Acceptability of the cell banking system

- ✓ Is the strategy proposed for testing of the Master and Working Cell Banks acceptable?
- ✓ Regarding the Cell bank system does the CHMP agree on
  - The acceptability of the approach for developing a cell bank system during development,
  - The introduction of a working cell bank only at the stage of phase III clinical studies,
  - The comparability testing of material produced from the initial cell bank and the now derived working cell bank

Comparability after a change in the process during the development phase -1-

- ✓ Very early change:
  - The company intents to switch from cell line xxx to cell line xxy. In the opinion of the company a comparability study (with thorough analytical testing of the drug substance) is adequate to document this switch. As this switch will take place before the initiation of any phase 3 clinical studies and the initiation of the non-clinical studies, the company finds that no further documentation is needed. Does the SAWP agree?
- ✓ Change between phase II and III :
  - Does the SAWP agree that the proposed plan to assess comparability between the Drug Substance manufactured by the Phase II and Phase III processes is sufficient to support the use of product manufactured by the Phase III process in future clinical studies?
- ✓ Change during the phase III
  - The Company proposes to use drug substance material manufactured at the yyy L scale process in phase III clinical studies 1 and 2 whereas the drug substance to be used in phase III clinical studies 3 and 4 will be manufactured at the zzz L scale. Does the SAWP agree with the approach for integrating drug substance material manufactured from two processes into the Phase III program?

Comparability after a change in the process during the development phase -2-

- ✓ Comparisons of characterization data from one batch of drug substance manufactured by the Process 1 and Process 2 to data from one batch of drug substance manufactured by the Process 3. Is the strategy sufficient.
- ✓ Does CHMP consider the assays used to assess biochemical/biophysical comparability of the API produced in cell line XX and cell line YY to be adequate and represent state-of–the-art techniques? Could CHMP suggest additional assays that should be considered?
- ✓ We consider the API comparability as demonstrated by the comparability protocol and the proposed comparability stability study to be sufficient demonstration of comparability. Nothing more is necessary. Does the Agency agree?

Comparability for biosimilars

- ✓ Due to the use of different expression and purification systems, the purity and impurity profiles of the biosimilar API will not be identical to the reference product. Does the CHMP agree that the proposed strategy for characterisation and comparison of the purity and impurity profiles is acceptable
- ✓ Applicant seeks the Agency's concurrence on the proposed comparability study designed to assess the biosimilarity of the Investigational product with the Reference product. Applicant seeks advice on the adequacy of the proposed study
- ✓ Does the proposed quality strategy to characterise substance xx, as biosimilar to the chosen reference product meet the quality requirements for biosimilarity

Characterisation – quality attribute

- ✓ The company believes that the proposed process validation program encompasses an evaluation of all the major production steps and on product quality attributes in support of a MAA. Does EMEA agree or are there any specific concerns with the proposed approach to process validation
- ✓ Given that the product
  - is an Orphan Medicinal Product
  - only a small quantity of material needs to be produced because the dose administered is less than 1mg,

  the company believes that a concurrent validation strategy, without the manufacture of unneeded lots, will support a MAA. Does the EMEA agree?

impurity

✓ Process Related Impurities:

- After satisfactory removal of these process-related impurities has been demonstrated, the company proposes to remove Host Cell Protein and Total DNA as release assays. Does the EMEA agree with this strategy?

✓ Comparisons of purity and impurity:

- release data from 3 batches of drug substance manufactured by Process 1 and process 2 to be compared with purity and impurity release data from 3 batches of drug substance manufactured by Process 3 (Other release attributes will be compared to release specifications). Is the strategy satisfactory?

Setting specifications

- ✓ Does the agency agree that the proposed panels of tests for the drug substances and drug products are appropriate and acceptable for presentation in the dossier for the Marketing Authorisation Application?
- ✓ Does the Agency consider that the company strategy for quality control (QC) testing performed on the Master Virus Seed, on the Drug Substance and on the Drug Product as described in the quality section is appropriate for Phase III and for supporting a Marketing Application Authorization?
- ✓ Applicant seeks the Agency's advice that all essential tests are covered and the limits are adequate for the proposed Specifications for routine testing of Active Substance and Drug Product

Validation

- ✓ After process validation is completed, does the EMEA agree with the company proposal to discontinue in-process monitoring with both WB and ELISA and to utilise ELISA only in the panel of release tests
- ✓ Does the Working Party concur with the proposed validation bracketing strategy and scale for demonstrating drug product process validation and plans to provide only the drug product process validation protocols in the MAA?

Demonstration of consistency

- ✓ The company plans to study the “lot to lot” consistency by conducting on three lots of Drug Substance as well as three lots of Drug Product analytical and in vivo testing according to the release specification but does not intend to assess “lot to lot consistency” by using and comparing several lots during the pivotal clinical studies. Does the Agency agree

Stability program

- ✓ The following ICH stability strategies for drug substance and drug product are being proposed. Does the Working Party agree with these strategies, pending the outcome of the data?
  - Six months of drug product and twelve months of drug substance ICH stability data, supported by at least 24 months of drug substance and drug product stability (at all strengths) from the Phase 3 studies (same processes and formulations as ICH and commercial),.
  - Three drug substance ICH production batches will be produced at the commercial site, at commercial scale and with the commercial process and placed on stability. Drug product ICH production batches will be produced with the commercial process and at no less than one-third the commercial scale and in the commercial formulation and placed on stability.
- ✓ Based on the drug substance and drug product ICH stability data that will be provided in the MAA filing, it is believed that there is no need for a post-approval commitment to place the first 3 commercial lots of drug substance and drug product on stability. Does the Working Party agree?

Stability program

- ✓ Does the Agency consider that the company strategy regarding the stability studies conducted to validate the storage at -70°C of the Drug Substance as well as the storage at -20°C +/- 5°C of the Drug Product is appropriate for the Phase III study and the future registration in Europe

miscellaneuous

- ✓ For recombinant vectors – GMO
  - Does the SAWP agree that the presence of an ampicillin resistance gene as a selection marker in the construct is scientifically acceptable and is adequately justified in the Company's position?
  - Does the SAWP agree that a kanamycin resistance gene is a scientifically acceptable selection marker (if ampicillin resistance gene is not considered to be acceptable)?
  - Does the SAWP agree that the results of animal experiments with the current version of the plasmid construct (containing ampicillin resistance gene as selection marker) can be extrapolated to a newer version of the plasmid containing kanamycin resistance gene instead?
- ✓ Is it acceptable to retain the kanamycin resistance gene in the plasmid for production of material for market supply?
- ✓ Is it acceptable to retain the lacZ gene in the construct used to produce material for market supply?

The "comparability" question

- ✓ Distinction should be made on the use of the term “comparability”
  - During the development → the comparison exercise is
    - to identify the differences generated by the change
    - To keep record (filiation) of the evolution of the product(s) tested at different stages of the (non) clinical development
  - After the Marketing authorisation → to determine to what extent additional clinical data (or PMS studies) would be warranted
  - For biosimilar products → concept of head to head comparison in an attempt to detect any "differences" (structure, purity, potency, …) between the originator product and the biosimilar counterpart

Recommendations

- ✓ The Sc Ad procedure is NOT :
  - a pre-evaluation of the dossier to be submitted and get an opinion on the completeness of the data package
  - a bargaining with the CHMP and its scientific groups in an attempt to waive some tests or reduce the development plan
  - a consultation with a consultant to get further input or suggestions on the development of the product → developer responsibilities
  - For getting an approval or assessment of the quality of a product for clinical trials → National competences
- ✓ The Sc Ad procedure is aimed at
  - Providing advice and recommendations on difficult technical issues where guidelines may be differently interpreted
  - Providing an opportunity to raise questions which are not covered in the Quality guidelines
- ✓ Quality of the responses provided is largely dependent upon
  - the relevance and quality of the question(s) put
  - and the documentation provided to support the Company position

Conclusion

- ✓ Scientific advice:
  - a good and valuable tool to open debate and get advice
    - on emerging issues – topics
    - where nothing or little is said in the existing guidelines and requirement (new technologies, new concepts such as Quality by Design, Process analytical technology…)
  - To stimulate debate and reflection ahead of the MA submission when decision have to be made in a constrained time frame
  - To trigger development of new guideline or update or clarification of the existing ones
  - Should be used in a proactive approach by both companies and regulators

BWP is at your disposal for such an approach