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By Electronic Mail

Emmanuelle Charton, Ph. D.
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European Directorate for the Quality of Medicines and HealthCare
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Re: Pharmeuropa Vol. 21, No.1, January 2009, proposed revisions to,
Chapter XXXX:2031, "Monoclonal Antibodies for Human Use"

Dear Dr. Charton,

On behalf of PDA, I am writing to submit our comments and recommendations on the proposed revisions to Chapter XXXX:2031, "Monoclonal Antibodies for Human Use." Our comments are based on review by a group of PDA members with expertise in this subject matter, and approved in accordance with PDA's internal governance procedures. It is PDA practice to focus our comments on scientific and technical issues that affect the utility and value of regulatory standards.

Regarding the revised monograph, we have highlighted three primary areas of concern, and have additional commented on several other points.

Areas of Concern

A.Visible Particles: We believe there is potential for confusion by users of the chapter based on differing descriptions for particles under the sections CHARACTERS and TESTS. We offer recommended wording, below, to remedy this issue. But we preface our recommendations with three points:

First, it is a requirement in the manufacturing of biopharmaceuticals to inspect all containers for particles during production. Like many other quality attributes, product quality with respect to particles is determined by application of production process controls and testing or inspection at a relevant time. For particle testing, this is a 100% control for each container of drug product immediately after filling. Inspection is performed at this stage because only then is it assured that the entire contents of every product container can be visually inspected.

Second, many biological products, including some monoclonal antibody medicinal products, may contain visible and sub-visible proteinaceous particles that are intrinsic to the product. For such products manufacturers strive to develop formulations that minimize this effect. With some products this is difficult, if not impossible, to achieve over a long term product shelf life. This intrinsic tendency is identified during the product development. During nonclinical and clinical studies such intrinsic proteinaceous particles can be demonstrated not to affect product quality or safety.

Third, there is no clear rationale that distinguishes the appearance of monoclonal antibody preparations from those parenteral preparations described more generally in monograph *Ph. Eur.* 0520. To aide in this discussion, please find attached our 18 June

2008 statement to the EMEA Biologics Working Party in support of scientific discussion on MAb issues[1]. Specifically, see pages 10–13 which discuss issues related to particles in parenteral preparations including MAb preparations.

In the context of these three points, we would like to make the following recommendations:

1. Section CHARACTERS: We recommend inserting the phrase, "practically free from particles" in replacement of the existing phrase, "without particles."
2. Section TESTS, Appearance: As above, we recommend inserting the phrase, "practically free from particles" in replacement of the existing phrase, "without visible particles, unless otherwise justified and authorized," and,
3. Section TESTS, Appearance. We suggest the sentence on particles with the recommended wording, "They are practically free from particles," may more appropriately be relocated in the section PRODUCTION since, as noted above, production process controls include 100% inspection of containers during production.

B.Solubility. The monograph states that "Freeze-dried preparations dissolve completely in the prescribed volume of reconstituting liquid, within a defined time, as approved for the particular product." We believe that defining this time is not needed or practical for readily dissolving lyophilisates, only for specific products, i.e. those that need substantial time because of their formulation. We recommend the removal of the test for solubility as it does not provide a benefit to delivery of monoclonal antibodies to patients.

C.Consistency with ICH Guidance and accepted practice: On page 106 there are several inconsistencies with ICH guidance. As a general comment we recommend referencing ICH Q5A & ICH Q5D where appropriate including for cell line and cell bank requirements. This will avoid potential inconsistencies or interpretational issues.

1. It is accepted practice to perform genetic stability studies using Master Cell Bank (MCB) cells. An interpretational issue arises when it is recommended to perform these studies on the "cell line", which could be a number of passages before or after the MCB.
2. Adventitious agent testing may be interpreted to be optional after the first few harvests (page 106 in 2nd to last paragraph). This is inconsistent with ICH guidance and accepted industry practice.
3. Some language in "Cell banks", specifically the requirement for "absence of bioburden," may cause an interpretational issue as it implies that cell banks are tested using a bioburden test, not a sterility test.
4. As written, the monograph indicates that nucleic testing is always required as part of the genetic stability program. ICH guidance allows product analysis in place of nucleic acid testing, and nucleic acid testing is not a requirement (ICH Q5D, section 2.3.3, paragraph 3). We recommend deleting the following text in the 5th bullet, "for recombinant DNA products, stability of the host/vector genetic and phenotypic characteristics up to or beyond the population doubling level or generation number used for routing production". The replacement text should reference ICH Q5D, "consistency of the coding sequence of the expression construct should be verified in cells cultivated to the limit of *in vitro* cell age for production use or beyond by either nucleic acid testing or product analysis."
5. For PRODUCTION: CELL LINE PRODUCING THE MONOCLONAL ANTIBODY, the industry practice defined in ICH Q5D does not specify evaluating the cell substrate stability using either level of expression or glycosylation. In section 2.3.3 of the ICH guidance, paragraph 4, it is actually mentioned that productivity of the desired product can be evaluated as another specific trait only "where the product cannot be analyzed…" As such, we recommend changing the 4th bullet by deletion of the following text, "stability of antibody secretion with respect to the characteristics of the antibody and level of expression and glycosylation up to and or beyond the population

[1] PDA Consensus Scientific Views On Selected Topics Relating to:
Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances (draft)
EMEA/CHMP/BWP/157653/2007 (5 April 2007)
EMEA / Biologics Working Party, Scientific Discussion, London, 18 June 2008

doubling level or generation number used for routine production". The text should be replaced by reference to the ICH Q5D text, "consistency of critical quality attributes for the antibody up to and beyond the population doubling level of generation number used for routine production"

6. In CULTURE AND HARVEST, the bottom sentence seems to imply that endogenous retroviruses are problematic. Process validation approaches for purification schemes of monoclonal antibody products are sufficiently robust and well understood to achieve reductions in retroviral load well in excess of the amounts of retrovirus that may be present in the unpurified bulk material.

Additional comments.

Definitions, pages 106 & 107: We recommend replacing "Active substance" with "drug substance", consistent with ICH terminology. Accordingly, we also recommend replacing "reference preparation" with "reference material," and "final lot" with "drug product".

TESTS, page 107:

a. "Identity" should stipulate the ability to distinguish the medicinal product from others manufactured at same facility. This is important from a regulatory standpoint to avoid product mix-ups.
b. "Purity" should allow validation-based approaches (vs., batch testing) for assuring absence of process-related impurities. It is an accepted practice to validate removal for certain process-related impurities like DNA, host cell proteins or media components and then waive batch testing of final drug product or drug substance.
c. "Total protein" references monograph 2.5.33, which describes the use of comparative UV as a method to determine total protein. However, it is common practice in the industry to determine total protein content by UV using a defined extinction coefficient.
d. In practice, "Molecular integrity and structural integrity" are commonly performed on the drug substance rather than the "final lot" (drug product). This is the case where it can be justified that these quality attributes are determined by the drug substance process, and the drug product process does not alter these quality attributes.
e. In "Assay" the reference to 5.3 suggests that this is a biological assay. However, monoclonal antibodies are commonly dosed based upon total protein (i.e., as measured by UV assay) rather than a biological assay. Therefore we recommend removal of the reference to 5.3 and to remove the following text from the first sentence 'against the reference preparation.'

LABEL, page 108:

We suggest deleting "the quantity of monoclonal antibody in the container" from the "Label" because dosing for monoclonal antibodies is typically based upon protein content.

Thank you again for the opportunity to support your activities. Please contact me, or James Lyda (lyda@pda.org) of my staff, if you have any questions.

Very best regards,

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cc: RAQC, BioAB, Biotech Interest Group

Enclosure

Connecting People, Science and Regulation

PDA Consensus Scientific Views On Selected Topics Relating to:

Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances, draft

EMEA/CHMP/BWP/157653/2007 (5 April 2007)

EMEA / Biologics Working Party Scientific Discussion London | 18 June 2008

The attached information is submitted by PDA to the Biologics Working Party in support of the scientific discussion to be held on 18 June 2008, and in support of the PDA slide presentation submitted to the BWP for the same purpose. The information represents input from numerous experts involved in the PDA review and was assembled into a final document by the PDA staff. Due to the speed with which the information was developed and assembled, there may be style or format differences between the different topic discussions.

PDA Consensus Scientific Views on Selected Topics Relating to: Guideline on Production and Quality Control of Monoclonal Antibodies and Related Substances

The following information is submitted by PDA to the Biologics Working Party in support of the scientific discussion to be held on 18 June 2008, and in support of the PDA slide presentation submitted to the BWP for the same purpose. The information represents input from several experts involved in the PDA review and was assembled into a final document by the PDA staff. Due to the speed with which the information was developed and assembled, there may be occasional style or organizational differences between the different topic discussions.

Topic 2.1:
Terminology to be used in the guideline to refer to products "affiliated" to monoclonal antibodies

PDA has not prepared a written statement for this topic. Please refer to the PPT presentation.

Topic 2.2:
Need to describe in the guideline the differences for IgG, IgM, IgE, fragments and fusion proteins.

PDA has not prepared a written statement for this topic. Please refer to the PPT presentation.

Topic 2.3
Flexibility of requirements and aspects related to the "platform manufacturing" approach, including viral safety data
Pages 7-8- Section 4.3.2. "Platform Manufacturing"

Proposal: The guideline should
1. More clearly and fully reflect how "platform" technology can be used during serial development of processes for related products such as monoclonal antibodies.

2. Communicate, in general terms, how "platform" knowledge may be scientifically justified to support the validation of product-specific processes developed from the same "platform" technology, including the assurance of viral safety.

3. Communicate, in general terms, how "platform" knowledge may be scientifically justified to support changes (Variations to MAs) proposed for multiple products whose development was based on and contributed to the pool of "platform" knowledge.

These recommendations are consistent with the knowledge and risk-based concepts in ICH Q8, Q9 and Q10.

Additionally, PDA offers a procedural suggestion beyond the scope of the Guideline is that a process be developed to ensure the most efficient mechanism for submitting and reviewing multi-product Variations.

Rationale:
Pg7, Lines 19-22 defines "Platform Manufacturing" as a concept whereby different monoclonal antibodies are manufactured using an identical- pre-defined purification process, and further states that these processes are not identical throughout industry, but describe each manufacturer's own purification process.

The suggested change to the document allows the term "platform manufacturing" to extend to the entire manufacturing process, rather than only the purification operation. Further, it substitutes the word "similar" for the word "identical". This is critically important because while each new monoclonal may be initially fit into a standard set of platform conditions, the process for each molecule will evolve to some extent to meet the needs of that particular product. "Platform knowledge" therefore represents the collective development, characterization and validation knowledge across multiple processes that are related, but not identical.

The applicability of platform knowledge to a process for a new molecule or a post-market process change must be assessed on a case-by-case basis and scientifically justified.

In an effort to provide more clarity around the process a manufacturer would use to assess the similarity, and therefore the applicability of platform knowledge, the following example criteria are provided:

Same type of molecule (e.g., IgG)
Same type of host cell (e.g., CHO)
Same type of unit operation (e.g., Protein A)
Same raw material (e.g., specific affinity chromatography material)
Similar operating parameters
identical
better case
bracketed within a design space

Platform information may also provide justification for which operating parameters are most relevant to consider in assessing similarity.

For example, for virus inactivation by low pH at the protein A pool step, platform knowledge generated across a spectrum of related processes derived from a single manufacturer's platform could demonstrate that differences in (a) column load, (b) host cell protein, (3) DNA composition or (d) product aggregate levels in the protein A pool, do not alter the effectiveness of virus inactivation in product specific validation studies for multiple MAb's. However, the effects of pH, inactivation time and temperature are reproducibly critical. Therefore, selection of data used to support viral safety of new products would need to reflect identical or 'better case' operating parameters in terms of time, temperature and pH, but may not need to be similar in terms of protein A pool impurity composition, as long as levels are justifiably representative of the previously tested ranges. Such platform knowledge may reduce or eliminate the need for process specific validation for subsequent processes to a streamlined confirmatory exercise. Any confirmatory data collected would be added to the overall set of platform knowledge available to assess new processes, including post-market process changes.

Where a proposed post-market change reaches across products, these are considered "multi-product changes" rather than changes to the whole "manufacturing platform." A scientifically justified rationale would need to be supplied by the manufacturer for each product involved to support validation of multi-product changes using platform knowledge.

Proposed rewording of Sections 4.3.2
Note: Line numbers refer to placement in original document. Text in italics & bold is new or changed from original.

17. The structural and physiochemical characteristics of monoclonal antibodies are now well understood and together with many years of antibody process development and production experience in industry, a concept whereby different monoclonal antibodies are manufactured using a ***similar,*** pre-defined process has evolved. This concept is termed "platform manufacturing." However, this term does not represent similar processes throughout industry; it is rather used to describe each manufacturer's own unique "platform manufacturing" ***knowledge.***

23. From the viewpoint of process development, a "platform manufacturing" approach can be accepted, because it is not necessary to develop each new manufacturing process from scratch, instead it is based on previously developed in-house knowledge and may also be appropriate to make efficient use of available or shared equipment *[No change recommended for this paragraph]*

27. However, each ***product and*** producer cell line (even if it is derived from the same parent cell line and a similar genetic construct is used) ***may*** have different properties. Therefore, any product-specific process should be duly validated in its own right. ***The manufacturer may rely on process characterization or validation data obtained with other similar products manufactured using similar processes (i.e., platform knowledge) if the data relevance is justified. This applies to both new processes and process changes, and includes application to the ability of process to remove virus.***

30. The platform-derived manufacturing processes may also vary for each monoclonal antibody in the choice of unit operations and the operational controls. Platform knowledge may be considered supportive of the performance of individual

unit operations, but the manufacturer will need to justify the relevance of the data used. Data to support each product submission should be provided on a product by product basis whether a platform manufacturing or a product-specific approach is used.

39. ***If a change is made that will be implemented globally on several marketed products that were validated using a combination of platform knowledge and product specific confirmatory data, revalidation of the process performance related to the proposed change should be reconfirmed for each product unless it can be justified that data supporting the change can be extrapolated across the platform. Use of streamlined approaches to validation is encouraged.***

Page 8

1. Platform assays" are equally acceptable; however, for each product at least a partial revalidation to demonstrate suitability for the intended purpose should be performed (for example a platform assay for HCP might be feasible, especially if the parent cell line is identical for several products, but it should have the ***appropriate*** sensitivity and specificity for HCPs from different producer cell lines.

Recommendation outside the scope of the Guideline:
It is the recommendation of this PDA review group that EMEA consider a consolidated approach to the review of similar Variations affecting multiple products, perhaps through the appointment of a lead Rapporteur whose assessment could be leveraged by other agency reviewers and applied to filing of similar future changes.

Topic 3.1
Need to describe specific analytical methods in the guideline
Pages 8-11, Section 4.4. "Characterization of Monoclonal Antibodies" and Section 4.5 "Specifications"

Proposal:
1. Inclusion of specific analytical methods in the guideline is acceptable provided that referenced techniques are suitable for the quality attributes and flexibility is maintained to allow use of appropriate alternative technologies.

2. Flexibility can be achieved by including the additional text "or other appropriate analytical technologies" immediately following any referenced methods used as examples in the guideline.

Rationale:
Section 4.4 lines 25 to 26 indicate that "A state-of-the-art characterization should be performed in line with the ICH Q6B Guideline, which addresses the primary and higher-order structure and the physicochemical properties of the product." Reference to ICH Q6B is most appropriate as this guideline provides the necessary framework for characterization and specification testing applicable to monoclonal antibodies. However, there are several instances throughout the text of Sections 4.4 and 4.5 where analytical methods are specified.

Such use of pre-specified analytical methods in the guideline may remove the incentive for sponsors to apply improved or innovative technologies. More importantly, analytical technologies should be selected with the objective of maximizing the information on identified quality attributes as determined and justified by the sponsor. Advances in the field of analytical chemistry will continue to yield improvements to existing methodology and creation of innovative technologies. To encourage application of these improved or innovative analytical technologies, maintain flexibility for use of alternative methods, and prevent misinterpretation that certain techniques are required; reference to specific analytical methods in the guideline should include additional text indicating "other appropriate analytical technologies" may be utilized.

Section 4.5.6. Other release tests for the drug substance and drug product lines 29 to 33 include a discussion on analytical determination of particulate matter mentioning that SEC methods may not be suitable for visible particulates, but analytical ultracentrifugation (AUC) may be more suitable to isolate and characterize particulates. Neither method is appropriate for characterization of visible particulates and only should be applied for analysis of soluble aggregates. Furthermore, the current state-of-the-art of AUC precludes use of this technology as a specification test. This example demonstrates a case where the referenced techniques are inappropriately applied.

Proposed rewording of Sections 4.4 and 4.5
27. *"The primary sequence should be deduced by DNA sequencing and confirmed experimentally by peptide mapping* ***or other appropriate analytical technologies****."*

39*. "Monoclonal antibodies therefore display considerable heterogeneity that can be characterized by several orthogonal methods for example isoelectric focusing (IEF), ion exchange chromatography (IEC) or capillary electrophoresis (CE)* ***or other appropriate analytical technologies****".*

Proposed rewording for Section 4.5.6 lines 29 to 33 is provided in the text for Topic 3.3.

Topic 3.2
Setting of Specifications Including Glycosylation, C-terminal heterogeneity and process-related impurities
Pages 10-11- Section 4.5 "Specifications"

Proposal:
1. The document sets regional requirements for specifications beyond what is established in ICH Q6B and generally does not incorporate the principles of QbD set forth in ICH Q8, Q9 and Q10.

2. The requirement for setting specifications on glycosylation should be linked to the demonstrated biological relevance (or lack of) of the glycoforms of the specific product.

3. Regarding process-related impurities, a provision should be made in the document to allow for an appropriate validation approach combined with development history and platform knowledge to replace the need for testing as part of specifications.

Rationale:
General Comments: Consistent with ICH Q6B guidelines on "Specifications…for Biotechnological/Biological Products", specifications are considered only "one part of a total control strategy…and are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular characteristics found to be useful in ensuring the safety and efficacy of the product". The selection of those quality attributes relevant to specifications is typically based on a detailed understanding of the structure-function relationship specific to a given product and entails a careful consideration of several key factors:

1) chemical and biological product characterization studies
2) process development, characterization and validation studies
3) pre-clinical and clinical experience
4) manufacturing history including demonstrated experience and consistency

The in-depth knowledge derived from the above listed factors provides a scientific determination of the quality attributes that are deemed critical for control and establishment of specifications, and will equally aid in the determination of the remaining quality attributes that do not warrant additional controls or whereby controls can be readily established through mechanisms other than specifications. Such mechanisms include appropriately justified internal action limits used in conjunction with continuous data monitoring and trending. This scientific rigorous approach is also consistent with the spirit of ICH guidelines Q8, Q9, Q10 that in sum advocate an enhanced product and process knowledge and effective utilization of risk tools integrated with a total quality system.

While we acknowledge that monoclonal antibodies as a class exhibit various similarities that facilitate the establishment of common platform technologies and shared knowledge, nonetheless the determination of the quality attributes that are relevant for the proper function should be determined or at a minimum be confirmed for the specific product at hand. Various monoclonal antibodies exhibit widely differing mechanisms of actions that can be at times solely limited to the binding domain of the molecule or alternatively involve various down-modulation/regulation pathways or reliant on critical properties of the Fc domain for cell killing such as CDC or ADCC. It is thus imperative that the selection of these relevant attributes be performed in relation to the intended mechanism of action of a given product.

While the document generally provides relevant details on the types of attributes that should be considered for specifications, it is too prescriptive in requiring such detailed list of parameters to be included in specifications for a class of molecule without a proper link to the specific mechanism of action, clinical indication and special CMC issues relevant to a given product. Such pre-specified requirements may remove the incentive for sponsors to perform the scientific rigorous studies required to justify the inclusion or exclusion of a "Quality Parameter" from specifications, may lead to reduced product understanding and is inconsistent with the spirit and principles being advocated in recent ICH guidelines (8-10) regarding enhanced product and process knowledge as described above.

It also appears that one of the main reasons for inclusion of certain parameters in the required specification list is the desire to ensure "manufacturing consistency" (line 47, page 10 and line 12 page 11). We do acknowledge that this is an important consideration, and would like to offer alternate suitable mechanisms. The desire to ensure control of the manufacturing process and achieve manufacturing consistency is best achieved through the use of an integrated Quality System that includes control on raw materials, internal process controls and associated limits, process development and validation history, adherence to cGMP's and specifications. The document overemphasizes the role of specifications in ensuring manufacturing consistency, especially for attributes deemed non-critical. Such attributes are best managed through the use of internal action limits tied to an appropriate Quality risk management system.

Specific Comments:

Specifications on glycosylation—section 4.5.3, lines 45-47

We do agree that glycan structures present on monoclonal antibodies must be well characterized and their distribution included in comparability exercises in support of relevant manufacturing changes. We also agree that in several instances, glycan structure can play an important role in the biological function of a given monoclonal antibody thus potentially impacting product safety and efficacy. However, the latter statement is not inclusive of the entire class of molecule and a significant number of monoclonal antibodies (both licensed and in clinical development) achieve their desired biological properties independent of the structure and distribution of the glycoforms present in the Fc domain. To that end, several scientific studies have been recently performed and published in peer reviewed journals to address the role that Fc glycans in IgG molecules on clearance (references provided in the appendix to the slide deck). These studies have confirmed that IgG oligosaccharides do not play a significant role in clearance rates consistent with the understanding that they are sequestered in the interior of the Fc region, making direct mannose or galactose receptor-mediated binding unlikely. In addition, 4 different studies have shown no change in oligosaccharide distribution over the course of the molecule clearance demonstrating that Fc oligosaccharides do not influence clearance by either the direct (terminal saccharide) or the non-specific (FcRn) mechanisms. In these studies, actual antibody samples were recovered from sera samples (human and animal) at several time points following administration, purified using tandem affinity/reversed phase HPLC, and the actual glycans on the antibody samples released by enzymatic treatment and analyzed using mass spectrometry.

As such and consistent with the general comments made above, the requirement for setting specifications on the observed glycan structures should be directly linked to the understanding and demonstrated relevance of the glycoforms on the biological properties and pharmacokinetics of the product. While it is expected to set a specification for relevant glycan structures such as degree of fucosylation and or bisecting GlcNAc for antibodies

with significant ADCC activity, galactosylation for antibodies with known CDC activity or potential immunogenic structures, setting of specifications should not be a default for the entire class of molecules solely for the aim of ensuring manufacturing consistency.

In addition, the type of glycan that require specification can vary from one molecule to another; for instance in the case of antibodies that elicit significant effector function, core fucosylation (rather than G0 or G1) levels is a more important parameter for specification setting.

We would like to propose that page 10, lines 45-47 be rewritten as follows:
"Therefore, if specific glycoforms are necessary for the proper function of the antibody, a specification for glycosylation….should be set…"

Specifications on process-related impurities, page 11, lines 10-17

The proposal for required specifications on process-related impurities (e.g., protein A) disagrees with ICH Q6B section 2.3.1 (Process Controls):

> "For certain impurities, testing of either the drug substance or drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies"

Provision should be made in the document to allow for an appropriate validation approach combined with development history and platform knowledge to replace the need to include testing for process-related impurities as part of specifications. The validation approach has been successfully utilized in several marketing applications and approval was obtained without the need for inclusion for HCP, protein A, DNA and other process related-impurities such as insulin and small molecules as part of the specifications.

We would like to propose the following addition to the text after the first and second sentences in section 4.5.5:
"An appropriate validation approach may be used in lieu of a specification"

Topic 3.3
Requirements regarding the presence of sub-visible and visible particulates in drug product

Proposal:
1. Section 4.4.4 "Formulation" [under 4.4 "Characterization"] requires revision to (1) differentiate between soluble aggregates, intrinsic sub-visible/visible proteinaceous particles and foreign particulate matter; (2) emphasize the need for development of optimal formulations to minimize the formation of soluble aggregates and intrinsic proteinaceous particles at release and during storage; and (3) remove reference to *Ph. Eur. 2.9.19* monograph.
2. Section 4.5.6 Lines 29 – 33 [under 4.5 "Specifications"] requires revision to (1) eliminate references to SEC and AUC and (2) include reference to *Ph. Eur. 2.9.19 "Particulate Contamination: sub-visible particles"* and other pharmacopoeia requirements for foreign visible particles specification testing of drug product only.
3. The guideline should acknowledge that intrinsic proteinaceous particles may be an inherent property of some monoclonal antibody formulations and clarify conflicting compendia expectations for drug product appearance.

Page 9 - Section 4.4.4 "Formulation" under the heading "4.4 Characterization"

Rationale:
To improve clarity in sections of the guideline addressing aggregation and particulate formation, it would be beneficial to use definitions to distinguish between these different physical phenomena. The term **soluble aggregates** should be specifically applied when referring to intrinsic and dynamic assemblies of proteins. The resulting proteinaceous assemblies are soluble. Solution formulations of proteins, including monoclonal antibodies, can also produce sub-visible or visible proteinaceous particles induced by various factors (e.g., temperature, agitation, etc.). These intrinsic proteinaceous sub-visible or visible particles are distinct from extraneous foreign particulate matter that can be inadvertently introduced during manufacturing. The term **intrinsic sub-visible/visible proteinaceous particles** should be applied to distinguish proteinaceous particles from foreign particulate matter.

High concentrations of monoclonal antibody solutions do exhibit the tendency to form soluble aggregates as well as intrinsic sub-visible/visible proteinaceous particles. Soluble aggregates can be characterized using SEC, light scattering and/or AUC. While light scattering and AUC are not suitable for release purposes, these methods can and should be employed during product development and characterization to assess the effects of formulation and environmental factors on monoclonal antibody aggregation. Other techniques (e.g., light scattering or microscopy) can likewise be employed during development and characterization to understand factors potentially influencing formation of intrinsic proteinaceous particles and whether there is any relationship to the presence of soluble aggregates. However, **the presence of soluble aggregates may or may not lead to the formation of intrinsic sub-visible/visible proteinaceous particles.**

Reference to *Ph. Eur. Monograph 2.9.19* "*Particulate Contamination: sub-visible particles*" test during the characterization and formulation stages of product development raises concern because the monograph test methodology is designed only for counting visible insoluble particulates based on the principle of light blockage and enumeration of undissolved foreign extraneous particles providing light obscuration and magnification of sub-visible particles retained by a membrane filter. The physical properties of intrinsic sub-visible/visible proteinaceous particles are commonly found to be loosely and dynamically

associated, irregularly shaped and translucent with poor to no light obscuration capability and are not generally retained on membrane filters used in the test. In addition, the statement "The presence of such visible particulates is unwanted" can be interpreted as a specification requirement of **"Zero"** which is inconsistent with *Ph. Eur. 0520*.

By utilizing the principles of ICH Q8, experimental approaches are applied to define the drug product and understand its physicochemical properties. The resulting product development and characterization data supports identification of optimized and well understood formulations whereby formation of soluble aggregates and/or intrinsic sub-visible/visible proteinaceous particles are minimized. As a consequence, the requirements for testing of the final drug product to determine insoluble foreign extraneous particulate matter per *Ph. Eur. 2.9.19 Monograph* should be specified only on page 11 in section 4.5.6 "Other release tests…" and not in the characterization section 4.4.4 of the proposed guideline.

Section 4.4.4 should be revised with the following considerations:
Add consideration to the need for characterization and differentiation between soluble aggregates, intrinsic sub-visible/visible proteinaceous particles and foreign insoluble particulate matter. Emphasize the need for development of optimal formulations to minimize the formation of soluble aggregates and intrinsic proteinaceous particles at release and during storage. Remove reference to *Ph. Eur. 2.9.19* in this section and allow usage of alternative test methodologies during characterization.

Proposed rewording of lines 36 to 46 are as follows:
"High doses of monoclonal antibody are often necessary to obtain a therapeutic effect, and therefore the concentration of monoclonal antibody in the final formulation is typically higher than for other biotechnological products. Because of their high concentrations and tendency to form soluble aggregates and intrinsic sub-visible or visible proteinaceous particles in the final formulation, appropriate studies should be performed to find an optimal formulation that minimizes the formation of soluble aggregates and intrinsic proteinaceous particles at release and during storage. Soluble aggregates can be characterized for example using SEC and other orthogonal methods such as AUC and light scattering and intrinsic proteinaceous particles can be characterized by light scattering or microscopy. Other appropriate analytical technologies may also be applied. Such methodologies should be employed during product development and characterization to assess the effects of formulation and environmental factors on protein aggregation and the relationship between formation of soluble aggregates and potential intrinsic proteinaceous particles."

Page 11 - Section 4.5.6 "Other release tests for drug substance and drug product" under the heading "4.5 Specifications"

Rationale:
Formulation characterization as described in the proposed wording for Section 4.4.4 provides sufficient guidance and assurance that appropriate methods are utilized to minimize formation of soluble proteinaceous aggregates and potential intrinsic proteinaceous sub-visible/visible particulates at release and during storage. Therefore, for properly designed formulations whose properties are appropriately understood, compendia specification testing with *Ph Eur 2.9.19* should be sufficient for the control of foreign extraneous matter only, as the monograph is intended.

The draft text of the guideline identifies SEC and AUC as methodology suitable for particulate analysis. These methods are suitable for analysis of soluble aggregates not

particulates. Additionally, AUC is only suitable for characterization purposes since the current state-of-the-art of this technology precludes its use as a release test.

The draft text of the guideline in Section 4.5.6 Line 18 has the heading "Other release tests for the drug substance and drug product." However, appropriate characterization at a stage downstream from the drug substance but upstream from drug product would obviate the requirement for *Ph. Eur. 2.9.19* compendia specification testing of drug substance.

Section 4.5.6 Lines 29 – 33 should be revised with the following considerations:
The proposed use of AUC should be discussed in the context of characterization and not as a specification test. See the proposed rewording and inclusion of AUC as an alternative methodology during formulation characterization in Section 4.4.4. Particulate testing should utilize *Ph. Eur. 2.9.19* and only apply to drug product specification testing of foreign extraneous particulate matter as the monograph is intended.

Proposed rewording of lines 29 to 33 is as follows:
"Sub-visible and visible insoluble foreign extraneous particulate matter in drug product only should comply with the requirements set forth in the Ph. Eur. Monograph on "Parenteral preparations" (07/2005:0520): 2.9.19. Particulate contamination: sub-visible particles (01/2005:20919) and other pharmacopoeia requirements on visible particles".

Need for additional guidance on appearance requirements

Rationale:
Despite significant efforts by manufacturers, it may not be possible to identify formulations of proteins including monoclonal antibodies that completely avoid formation of intrinsic sub-visible/visible proteinaceous particles. Indeed, the presence of intrinsic proteinaceous particles may be inherent to the formulation and their presence not necessarily a significant issue provided that the proteinaceous particles are appropriately identified, characterized, quantified, and the kinetics of formation well understood. Intrinsic sub-visible/visible proteinaceous particles often form transiently and are reversible, and they may or may not increase over time. The acceptability of monoclonal antibody formations containing intrinsic sub-visible/visible proteinaceous particles needs to consider other important factors such as stability, safety, efficacy and clinical experience.

There are examples of authorized protein products including monoclonal antibodies that do contain proteinaceous particles. Product administered to patients through in-line filters is an accepted practice to address this situation provided it is justified with appropriate characterization of the filtered solution. The monograph *Ph. Eur. 0275 "Human Coagulation Factor VIII (plasma derived)* provides a specific example of a product that contains particles upon reconstitution and use of a filter is accepted prior to dose administration:

> **"*Products that show flakes or particles after reconstitution for use*.** If a few small flakes or particles remain when the preparation is reconstituted, it shall be demonstrated during validation studies that the potency is not significantly affected after passage of the preparation through the micro aggregate filter provided."

In another example, the product information literature for the monoclonal antibody Erbitux (2 mg/ml solution for infusion) indicates that the drug product may contain intrinsic proteinaceous particles and requires use of a filter during dose administration:

> "Erbitux 2 mg/ml is a colourless solution that **may contain product-related whitish and amorphous visible particles**. These particles do not affect the quality of the

> product. Nevertheless, the solution must be **filtered with an in-line filter** of 0.2 micrometer or 0.22 micrometer nominal pore size during administration."

Similarly, the product information literature for the monoclonal antibody Remicade (Infliximab) 10 mg/ml solution acknowledges that intrinsic proteinaceous particles may form following reconstitution of the product and further requires use of an in-line filter:

> "Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colourless to light yellow and opalescent. **The solution may develop a few fine translucent particles, as infliximab is a protein**."
>
> "Use only an infusion set with an **in-line, sterile, non-pyrogenic, low protein-binding filter** (pore size 1.2 micrometer or less)".

For these reasons, the guideline needs to include text acknowledging that some monoclonal antibody formulations may contain the presence of sub-visible/visible proteinaceous particles. In addition, the guideline should clarify conflicting requirements for **Appearance** testing included in the draft text and between the monographs *Ph. Eur. 0520 "Parenteral Preparations* and *Ph. Eur. 2031 "Monoclonal Antibodies for Human Use."* The draft text of the guideline states that "The presence of such visible particles is unwanted," while *Ph. Eur. 2031* indicates that "Liquid or reconstituted freeze-dried preparations are clear or slightly opalescent and colorless or slightly yellow, **without visible particles**". Both descriptions are inconsistent with *Ph. Eur. 0520 "Parenteral Preparations"* which requires "Solutions for injection, examined under suitable conditions of visibility, are clear and **practically free from particles**." Furthermore, the requirements in the draft guideline and *Ph. Eur. 2031* do not adequately provide for monoclonal antibody formulations containing acceptable amounts of intrinsic proteinaceous particles.

The guideline should support the overarching monograph *Ph. Eur. 0520,* and the accepted appearance specification for monoclonal antibody products should include **"practically free from particles."** There are numerous examples of monographs for other protein products that comply with *Ph. Eur. 0520*:

- alteplase
- human albumin
- erythropoietin
- human coagulation F VIII (rDNA), IX, VII, and XI
- human IgG for IV
- recombinant human insulins for injection, including aspart and lispro
- interferon alfa-2
- molgramastin
- somatropin
- somatropin concentrated solution
- somatropin for injection
- Anti-T lymphocyte immunoglobulin for human use, animal origin

Appearance expectations for monoclonal antibodies should not be any different than those required of other protein products.