Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

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1. Introduction

There has been significant interest in developing drug delivery technologies to achieve improved delivery of poorly soluble, highly-toxic and/or unstable drugs, to increase tissue targeting and/or to improve the efficiency of cytosolic delivery of macromolecular drugs. One of the strategies under development uses block copolymer micelles. Block copolymer micelles are self-assembled micelles, and they are typically prepared from AB block copolymers. Other more complex compositions have been proposed. An active substance can be incorporated into the inner core of the block copolymer micelle product by chemical conjugation or by physical entrapment. Block copolymers with amphiphilic character spontaneously assemble into polymeric micelles in aqueous media, hydrophobic interactions typically drive this self-association. However, other driving forces may be used to promote micelle formation and enhance micelle stability. For example, electrostatic interactions between charged block copolymers and oppositely charged active substances, polymer–metal complex formation, and hydrogen bonding. In specific cases functional features may also be added to the system, for example, by targeting molecule conjugation to the block copolymer, or by the addition of another homopolymer or an additional stabilizer to stabilize the micelle, to modify the release rate and/or to increase the loading of the active substance. In any given product, a proportion of the active substance could be free in the bulk solution (i.e., not incorporated into the micelle).

It should be emphasised that such block copolymer micelle products (as described above) have a carefully designed structure in which the inner core typically serves as a container for active substance and this is surrounded by an outer shell of hydrophilic polymers. Additionally the chemistry of such block copolymer micelles may be designed to ensure high stability after dilution on administration due to a low critical association concentration (cac), to optimize the pharmacokinetics (PK) (targeting), and to control the drug release, etc. Thus the dissociation of such block copolymer micelles may be kinetically slow. These properties are different from traditional surfactant micelles used to entrap/solubilise/aid the transport of drugs. Moreover, a block copolymer micelle product can contain multiple components within the core including chemically bound active substance, which in certain cases may be covalently bound.

Furthermore, it has been shown in non-clinical studies that block copolymer micelles may have the potential to preferentially accumulate in solid tumors due to microvascular hyperpermeability and impaired lymphatic drainage (known as the enhanced permeability and retention (EPR) effect). The specific physicochemical properties of block copolymer micelles, such as size, surface-charge, composition, and stability can be important determinants of safety and efficacy in all proposed applications.

Several block copolymer micelle products are currently in pre-clinical or in clinical development, for example, products containing anti-tumor agents and proteins

As block copolymer micelle products are of nano-scale size, contain more than one component, and are purposely designed for specific clinical applications they may be considered as nanomedicines.

This reflection paper discusses the general principles for assessing block copolymer micelle products but does not aim to prescribe any particular quality, non-clinical or clinical strategy.

ICH Guidelines

Where applicable, it should be read in connection with the following ICH guidelines:

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and

products Q1A(R2)

- ICH Quality of biotechnological/biological products Q5A(R1)-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process)
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B
- ICH Pharmaceutical Development Q8(R2)
- ICH Development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) Q11
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9

2. Scope

This paper provides basic information for the pharmaceutical development, and non-clinical and early clinical studies of block-copolymer micelle drug products created to affect PK, stability and distribution of incorporated or conjugated active substances in vivo. Although the focus is on products designed for intravenous administration, the principles outlined in this reflection paper might also be considered to be applicable to block copolymer micelle products designed for other routes of administration. The active substance could be a low molecular weight chemical entity, a nucleic acid or a biological or biotechnologically derived entity, including, for example, peptides and proteins.

Due to the complexity of the system, i.e. whether or not the active substance is chemically bound, and/or additional stabilizers are used, it is recommended that an early dialogue with the regulators takes place to discuss the likely critical product attributes of each particular block copolymer micelle product. During this dialogue the sponsors are encouraged to discuss emerging methods that might be applied to define quality and non-clinical properties relevant to the proposed clinical application.

This document, being a reflection paper, should be read in connection with relevant ICH guidelines (listed above) and regional guidelines (Annexes I and II)[1].

[1] Post-marketing issues are not discussed. Drug products that use block copolymers as coating materials for nanoparticles of other materials such as homopolymers or metals are also not covered in this paper.

3. Discussion

3.1 Chemistry, manufacturing and controls

3.1.1 Pharmaceutical Quality

It is important to identify the critical quality attributes of block copolymer micelle products that will have a major impact on the in vivo PK and pharmacodynamic (PD) properties that may impact on safety and efficacy. Correctly identifying the parameters that define relevant physicochemical properties of the block copolymer micelle product is critical to ensure its quality.

The following subsections will discuss additional parameters that can be considered critical to quality attributes of block copolymers.

3.1.2 Description and composition

The typical components of block copolymer micelle products are, the active substance, the block copolymer, and in certain cases, other components such as stabilizing agents.

The critical quality attributes of block copolymer micelle product should be carefully considered on a product specific basis. Of particular importance may be:

- The content of the block copolymer and active substance in the block copolymer micelle product. These should be expressed both as the molar ratio and the percentage of each by weight;
- The composition, mean molecular weight and polydispersity of the polymers (homopolymers, copolymers etc.) used to synthesise the block copolymers (or block copolymer-active substance conjugates);
- The composition, mean molecular weight and polydispersity of the block copolymers used to create the block copolymer micelle.

Any acceptable ranges given should be fully justified.

3.1.3 Quality characterisation

The following are typical examples of properties, related to:

A. Components containing block copolymers

The chemical composition of block copolymers greatly impacts the driving force behind polymer self-association, and therefore, size and physicochemical characteristics and in vitro and in vivo stability of the resultant micelles. Crucial properties include:

- Chemical structure of the block copolymers
- Chemical nature and stability of chemical linkage in the case of block copolymer-active substance conjugate
- Impurity profile (e.g., macromolecular impurities).

B. Block copolymer micelle products

Properties relevant for the quality characterisation of the finished product are of different types and include:

<u>Properties related to the block copolymer micelle</u>

- Block copolymer micelle size (mean and distribution profile)
- Morphology
- Zeta potential

- Other surface properties (e.g. targeting ligand)
- Association number
- Concentration dependency of the nano-structure (In some cases, this may be expressed as critical micelle concentration (cmc), or critical association concentration (cac). It should be noted that these parameters of some block copolymers are too low to be measured using the current analytical techniques.)
- Drug loading
- Chemical structure
- Physical state of the active substance
- Viscosity
- In vitro stability of the block copolymer micelle in plasma and/or relevant media
- In vitro release of the active substance from the block copolymer micelle product in plasma and/or relevant media
- In vitro degradation of the block copolymer in plasma and/or relevant media.

Properties related to the manufacturing process

- Validated process for reconstitution
- Validated process for ensuring sterility.

Properties related to the *in vivo* behaviour

- Osmolarity
- Fraction of active substance that is surface associated
- Release rate and place of active substance release
- Block copolymer degradation rate and place of degradation.

Reliable and discriminating validated in-vitro release methods should be developed to monitor the simulated release of the active substance from the block copolymer micelle in physiologically/clinically relevant media in order to predict in vivo stability. The value of such in vitro drug release as a quality control test should be adequately demonstrated. However, it is acknowledged that it may not always be possible to establish in vitro-in vivo correlations.

Where the block copolymer component itself (not the active substance) has a biological activity which would have an impact on clinical efficacy and/or safety, its potency and physicochemical properties that are critical for its biological activity should be evaluated as part of characterisation.

A list of validated tests to be applied routinely to the block copolymer micelle product should be defined by the applicant and should be based on the parameters chosen to characterise the drug product including those described above, as appropriate.

Development of discriminating, bio-relevant in-vitro release methods is important for the purpose of:

- Defining the release of the active substance or block copolymer-active substance conjugate from the block copolymer micelle when in the circulation;
- Defining the release of the active substance or block copolymer-active substance conjugate from the block copolymer micelle at the targeted site of action. The proposed media should reflect the physiological environment of the block

copolymer micelle when in use;

- Defining the stability on storage.

The methods used must be sensitive enough to ensure batch to batch consistency.

This is particularly important to monitor in the case that a block copolymer-active substance conjugate is involved.

3.1.4 Manufacturing process and process control

A well-defined manufacturing process with its associated process controls is needed to ensure that acceptable product is produced on a consistent basis. It is known that small changes to block copolymer micelle products may significantly influence their performance.

The manufacturing process should be controlled to ensure consistency in the product's performance in terms of safety and efficacy. Data showing consistency in quality, and controls for critical steps and intermediates should be provided. In addition to the information recommended by the ICH Q8(R2) – pharmaceutical development, recommendations specific to block copolymer micelle products are provided below.

Components containing block copolymers and/or block copolymer active substance conjugates

Detailed descriptions of the synthetic process, extraction, and purification procedures should be provided as applicable.

The source and specifications for any starting materials should be provided. In particular, for polymeric starting materials, molecular weight and molecular weight distribution should be clearly described. Impurities such as manufacturing impurities, and macromolecular reaction by-products should be clearly specified.

Key intermediates in the manufacturing process should be identified and controlled.

Biotechnologically derived and/or entities of biological origin that are used as starting materials or active substance should follow the requirement for medical use contained in the ICH quality guidelines for biotechnological/biological products.

To identify the impact of a manufacturing process change, e.g. change in scale, a careful evaluation of all foreseeable consequences for the product including process validation/evaluation should be performed.

Block copolymer micelle products

In the manufacturing process of block copolymer micelle products, micelle formation process is critical. When micelle formation occurs spontaneously, the process of micelle formation would be equal to the dispersion process of block copolymer. When other methods are required for micelle formation, critical quality attributes associated with the process (e.g. micelle size and solution transparency) should be controlled.

Block copolymer micelle products contain highly-functional polymers, and the end product testing alone is insufficient to define quality. Therefore, it is highly recommended that appropriate quality control of intermediates (i.e. the block copolymer) and/or the process, is undertaken based on the Quality by Design (QbD) concept as outlined in ICH Q8(R2) and Q11.

3.1.5 Product Specification

Regarding definition of an acceptable specification for a block copolymer micelle product (see guidelines ICH Q6A or Q6B), it is recommended that the applicant

engages in an *early dialogue with the regulators*. Additional testing specific to block copolymer micelle products may be needed.

Components containing block copolymers

A detailed description of the tests, procedures, and acceptance criteria for block copolymers and/or block copolymer-active conjugates should be provided. Evaluation of the polymer, such as mean molecular weight and its distribution should be obtained. The composition of each component should also be obtained.

Block copolymers micelle products

Because drug products based on block copolymers are functional polymeric structures, the critical quality attributes should be defined in respect of the functions for the intended use. These attributes will include particle size, release rate of the active substance from the micelle, and potency if the active substance is a biotechnological/biological entity. Where present, the composition regarding average number of targeting-molecules conjugated to the polymeric micelle to promote active targeting should be justified.

- It should be noted that block copolymer micelle products may be a mixture of block copolymer micelles and block copolymer unimers (with or without bound active substance), depending on the individual characteristics of the block copolymers, the active substance and the test conditions used. Therefore, analytical tests should be performed considering the product's form under appropriate test conditions and procedures. The test concentration should be carefully considered, because dilution of block copolymer micelle products may cause disassociation of micelles and result in an increased proportion of unimers.
- Considerations relating to identity and purity should take into account both the active substance and the block copolymers. Impurities, including possible synthetic macromolecular by-products, should be evaluated. Undesirable aggregates, precipitates, and degradation products will be also considered as impurities.
- Potency, if the active substance is a biotechnological/biological entity.

Other attributes are as follows:

- Physicochemical properties of block copolymer micelle products determined to be critical to product quality. However, not all the characterization tests need to be included in the specifications. (See section 3.1.3 on Physicochemical characteristics of block copolymer micelles).
- Assay of incorporated (or conjugated) and unincorporated (or unconjugated) active substance.
- Assay of block copolymers or weight fraction to active substance

Stability should be considered in the context of the proposed clinical use and justified in the specification.

3.1.6 Stability

The concepts in ICH Q1A(R2) apply to the design of stability studies for block copolymer micelle products. Those in ICH Q5C also apply to biotechnological/biological entities.

In general, stability studies should address the physical and chemical stability of the active substance, the block copolymers (and if present block copolymer-active substance conjugates), and the resultant micelles. Typical attributes that may be

evaluated include, but are not limited to:

Physical stability:

- Mean block copolymer micelle size
- Release of the incorporated or conjugated active substance
- Secondary aggregation.

Chemical stability:

- Stability of active substance
- Stability of block copolymer components (e.g. degradation of polymers)
- If present, stability of block copolymer-active substance conjugates.

In vitro methods, using conditions relevant to the proposed use, should be used to determine

- The release rate of the active substance entrapped in the block copolymer micelles
- The rate of release of active substance chemically bound to block copolymer micelles.

3.1.7 Changes in manufacturing during development

If there are changes in manufacturing critical process parameters or equipment used for manufacture, complete characterization of the block copolymer micelle product may be warranted on a case-by-case basis. Approaches to determining the impact of any process change will vary with respect to the specific manufacturing process, the product, the extent of the manufacturer's knowledge and experience with the process and development data provided.

It is important to also consider applying the principles for assessing the comparability studies of products before and after changes made in the manufacturing process, as those developed for Biological Medicinal Products. The principles of comparability studies are outlined in section 1.4 of ICH Q5E (Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process).

3.2 Non-clinical studies

3.2.1 General Considerations

Significant changes in pharmacokinetic characteristics can occur when an active substance is administered as a block copolymer micelle product, i.e. volume of distribution and clearance may be changed, half-life prolonged and tissue distribution changed. Significant changes not only in the PK characteristics but also in the PD and safety of the active substance can also occur when it is administered as a block copolymer micelle product. Moreover, it has been noted that certain block copolymers (not containing an active substance) can display inherent biological activity, which would have an impact on clinical efficacy and/or safety. Cellular uptake of block copolymer micelle entrapped active substance may be limited to the endocytic route.

The PK characteristics of the block copolymer micelle product could be dependent on:

- The rate of clearance of the block copolymer micelle containing entrapped or chemically bound active substance
- The rate of dissociation of the block copolymer micelle. This may lead to release

of block copolymer unimers (with or without bound active substance) that would have lower molecular weight (smaller size characteristics) and may display different clearance characteristics

- The rate of release of entrapped active substance from the block copolymer micelle
- The rate of release of active substance chemically bound to the block copolymer unimer
- The rate of degradation of the block copolymer
- Clearance and metabolism of free active substance
- The distribution of the block copolymer micelle
- Interaction of the block copolymer micelle with plasma or serum proteins or blood cells.

The rate and location of in vivo active substance release is a crucial parameter which often determines the toxicity and efficacy. An attempt should be made to develop the necessary methodology to define active substance release.

All non-clinical studies should be conducted using well-characterised block copolymer micelle product and the rate of micelle dissociation and product stability should be known under the chosen test conditions.

3.2.2 Non-clinical Pharmacokinetics

Analytical Methods

Validated analytical techniques should be developed, that are capable of measuring the concentrations of active substance both in total and in free form in blood, plasma or serum, and the total concentration of active substance in organs and/or tissues.

Pharmacokinetics

As the PK behaviour of block copolymer micelle products can be very different from that of the active substance administered without the block copolymer micelle carrier and this can impact significantly on efficacy and safety, in vivo PK should be determined. The choice of appropriate species and models to investigate in vivo PK, and release of the active substance should be justified in respect of proposed clinical use and the composition of the block copolymer micelle.

As physicochemical parameters such as size, surface-charge and morphology may impact on the distribution of block copolymer micelle product, the effect of variability in such parameters on distribution should be shown to justify the product specification. Therefore, in addition to the information recommended in the ICH S3 (S3A and S3B), S6(R1) and M3 (R2), the following parameters specific to block copolymer micelle products should be assessed:

- PK parameters such as Cmax, half-life, and AUC, of the block copolymer micelle product both for total active substance and for free active substance in blood, plasma, or serum.
- PK parameters should be measured at different dose levels and at appropriate time points.
- Distribution of the block copolymer micelle products in organs and/or tissues relevant to proposed clinical use and route of administration. Specifically total amounts of active substance may be required - see analytical methods. A distribution time profile should be obtained using multiple time points with

justification of the time course of the study.

- Sampling time points and sampling duration should be carefully selected so as to accurately quantify the time course of the concentrations of active substance both in total and in free form and metabolites in blood, plasma or serum, and the total concentration of active substance and metabolites in organs and/or tissues. Some factors should be considered for the sampling schedules, for example, the block copolymer micelle stability after administration, and the profile of localization to specific organs and/or tissues. In particular, samples taken in the initial distribution phase (e.g. <15 min) are considered very informative for calculating the distribution volume to estimate the stability of block copolymer micelles in blood circulation.
- Measurement of active substance metabolites in blood, plasma or serum and maybe organs and/or tissues is especially important when the metabolite is acknowledged to be the primary active compound. If one or more metabolites have substantial clinical activity then it might be necessary to compare their kinetics, and where necessary, toxicokinetics, to determine accumulation following multiple doses.
- Comparing the PK of the block copolymer micelle product and the active substance administered by itself is recommended. Such comparative studies are also considered useful to demonstrate a claimed pharmacokinetic advantage of the block copolymer product against the active substance administered by itself.
- It may also be important to consider the protein and cellular interaction of block copolymer micelles administered intravenously as these factors are known to have potential to influence the distribution, stability and safety of nanomedicines.

The metabolic and excretion pathways of the active substance should be determined and fully characterized after administration of the block copolymer micelle product. Furthermore, the metabolic and excretion pathways of the micelle constituents are by themselves of interest. Their detailed characterization is needed unless otherwise justified.

If there is concern that components of the block copolymer micelle drug products may cause drug-drug interactions, for example by modulating membrane transporters such as p-glycoprotein, an appropriate evaluation should be carefully undertaken.

3.2.3 Non-clinical pharmacodynamics

The non-clinical pharmacodynamic studies should include demonstration of pharmacodynamic response in appropriately justified in vitro (where possible) and in vivo models. In vivo evaluation should involve an appropriate route of administration, justified dose levels and a justified dosing regimen depending on proposed clinical application. Appropriateness of the pharmacological model should be discussed in respect of the PK of the block copolymer micelle product, and of the PD and PK of the active substance when administered by itself.

The chemical composition and physicochemical properties (including size and surface-charge, and the rate of release of the active substance) of a block copolymer micelle product affect pharmacodynamic properties. Some important factors to consider when designing studies to discuss the mechanisms of action include:

- The fate of active substance (the location and rate of in vivo active substance release)
- The fate of the micelles (block copolymers or other stabilizing components) following administration and/or cellular entry by endocytosis or other

mechanisms.

The PD effect of the micelles should be assessed using in vitro and in-vivo pharmacodynamic models. Failure to use both in vitro and in vivo models to assess the PD effects of the micelles should be extensively justified by the Applicant.

3.2.4 Safety Pharmacology

When applicable (e.g. for block copolymer micelle drugs out of the scope of ICH S9) the core battery of safety pharmacology studies should be conducted, in accordance with ICH M3 (R2), ICH S7A and ICH S7B.

3.2.5 Toxicology

For the non-clinical evaluation of toxicities of block copolymer micelle products, the recommendations in the ICH safety guidelines especially of S4, S6(R1) and S9 and M3 (R2) should be followed.

Relevant toxicity studies of the block copolymer micelle product should be conducted to assess both the toxicological profile and exposure-response relations according to the ICH safety guidelines.

Toxicokinetics

In addition to blood, plasma, or serum concentration, the active substance should be measured in the target tissue(s) and toxicologically relevant organs related to proposed clinical use.

Additional studies

Depending on the physicochemical and/or pharmacokinetic characteristics of the block copolymer micelle product and/or the block copolymer used for its manufacture, target organ function evaluation may be necessary.

Certain nanomedicines have the potential to induce infusion reactions. Studies designed to investigate complement activation, hematotoxicity, antigenicity, and/or immunotoxicity (ICH S8) should be considered depending on the characteristics of the block copolymer micelle product.

3.3 Considerations for first-in-human studies

Block copolymer micelle products are often designed to change the distribution of active substance. Therefore, in addition to the information recommended in the ICH S3 (S3A and S3B), S6(R1), M3 (R2) and PMFS/ELD Notification NO. 0402-1, April2, 2012 or EMEA/CHMP/SWP/28367/2007 (as appropriate), when considering first-in-human studies it will be essential to consider non-clinical pharmacokinetic data specific to the block copolymer micelle product e.g. the block copolymer micelle, the active substance, the proposed clinical use and the route of administration, using sampling time points and sampling duration that is carefully selected so as to accurately quantify the time course of block copolymer micelle products for total active substance and for free active substance and metabolites, as follows:

- PK parameters such as Cmax, half-life, and AUC, of block copolymer micelle products both for total active substance and for free active substance in blood, plasma or serum.
- A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected. Frequent sampling at early time points are considered useful for providing reliable information about the initial distribution process. Generally the sampling schedule should also cover the plasma

concentration time curve long enough to provide a reliable estimate of the total extent of exposure.

- Distribution of the block copolymer micelle products in target lesion and major organs; specifically total amounts of active substance in target lesion and major organs and their time profiles at multiple time points over an adequate period of time.

The starting dose for first-in-human studies should be chosen in compliance with ICH M3(R2), and regional guidelines, and following careful consideration of all related non-clinical data, including critical product attributes, pharmacological dose-response, PK, and pharmacological/toxicological profile as discussed in sections 3.1 and 3.2 above.

Dose-limiting toxicity in humans can be determined in a similar way to that of conventional drugs, except for hypersensitivity reactions because these reactions are not always dose-dependent.

Potential critical quality attributes for each block copolymer micelle product should be identified and used to evaluate consistency as discussed in section 3.1. Consistency of the quality attributes should be confirmed between the products used for non-clinical studies and those for first-in-human studies, and test procedures should be established before commencement of first-in-human studies. If the manufacturing process used to prepare block copolymer micelle product for non-clinical studies is changed before first-in-human studies comparability should be demonstrated or otherwise justified.

Stability data that ensure the block copolymer micelle stability throughout the first-in-human studies are required.

4. Conclusions

Given the complexity of block copolymer micelle products and the fact that experience with such products is limited companies are advised to seek product-specific scientific advice regarding specific questions on the data requirements.

5. Glossary

The purpose of this glossary is to describe terms as they are used in this reflection paper.

1) Active substance: Molecule which shows the main therapeutic effect.

2) Block copolymer: More than two kinds of polymer connected in series e.g. an AB block copolymer or an ABA block copolymer (or others).

The block copolymer is also called a unimer: the minimum unit from which the block copolymer micelle is prepared. The active substance may be chemically bound to the unimer.

3) Block copolymer micelle: A micelle which consists of block copolymers. Active substances can be incorporated into the inner core of the block copolymer micelle by chemical conjugation (including covalent conjugation) or by physical entrapment.

4) Block copolymer micelle product: "Medicinal product", a drug product which contains active substance, block copolymers and in certain cases, other ingredients.

5) Free active substance: Active substance present in the drug product that is not incorporated within the block copolymer micelle by chemical conjugation or by physical entrapment.

Free active substance may be released from the block copolymer micelle product after administration. In this reflection paper, the term “free” does not suggest the disassociation of active substances from plasma or serum proteins.

6) Biological activity: The specific ability or capacity of a product to achieve a defined biological effect.

7) Potency (expressed in units): In the case that the active substance is a protein, the quantitative measure of biological activity based on the attribute of the product which is linked to the relevant biological properties, whereas, quantity (expressed in mass) is a physicochemical measure of protein content.

Regional guidelines

Annex I: MHLW

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and products Q1A(R2)[June 3, 2003, PMSB/ELD Notification No.0603001]
- ICH Quality of biotechnological/biological products Q5A(R1)-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process) [February 22, 2000, PMSB/ELD Notification No.329 (Q5A(R1)), January 6, 1998, PMSB/ELD Notification No.3 (Q5B), January 6, 1998, PMSB/ELD Notification No.6 (Q5C), July 14, 2000, PMSB/ELD Notification No.873 (Q5D) and April 26, 2005, PFSB/ELD Notification No.0426001 (Q5E)]
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A [May 1, 2001, PMSB/ELD Notification No.568]
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B [May 1, 2001, PMSB/ELD Notification No.571]
- ICH Pharmaceutical Development Q8(R2) [June 28, 2010, PFSB/ELD Notification No.0628-1]
- ICH Development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) Q11, Step4
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2) [February 19, 2010, PFSB/ELD Notification No.0219-4]
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B [July 2, 1996, PMSB/ELD Notification No.443 and PMSB/ELD Notification No.442]
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4 [April 5, 1999, PMSB/ELD Notification No.655]
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) [March 23, 2012, PFSB/ELD Notification No.0323-1]
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A [June 21, 2001, PMSB/ELD Notification No.902]
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B [October 23, 2009, PFSB/ELD Notification No.1023-4]
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8 [April 18, 2006, PFSB/ELD Notification No.0418001]
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9 [June 4, 2010, PFSB/ELD Notification No.0604-1]
- Guidelines for Non-clinical Pharmacokinetic Studies [June 26, 1998, PMSB/ELD Notification No. 496]
- Guidance for Establishing Safety in First-in-Human Studies during Drug Development [April 2, 2012, PFSB/ELD Notification No. 0402-1]

Annex II:**EMA**

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and products Q1A(R2) [CPMP/ICH/2736/99]
- ICH Quality of biotechnological/biological products Q5A-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process) [CPMP/ICH/295/95 (Q5A(R1)), CPMP/ICH/139/95 (Q5B), CPMP/ICH/138/95 (Q5C), CPMP/ICH/294/95 (Q5D) and CPMP/ICH/5721/03 (Q5E)]
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A [CPMP/ICH/367/96]
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B [CPMP/ICH/365/96]
- ICH Pharmaceutical Development Q8(R2) [EMEA/CHMP/167068/2004]
- ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) [EMA/CHMP/ICH/425213/2011]
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2) [CPMP/ICH/286/95]
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B [CPMP/ICH/384/95 and CPMP/ICH/385/95]
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4 [CPMP/ICH/300/95]
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) [EMA/CHMP/ICH/731268/1998]
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A [CPMP/ICH/539/00]
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B [CPMP/ICH/423/02]
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8 [CHMP/167235/2004]
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9 [EMEA/CHMP/ICH/646107/2008]
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