Safety assessment of biopharmaceuticals: Japanese perspective on ICH S6 guideline maintenance

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ABSTRACT — Safety assessment of biopharmaceuticals in preclinical studies is guided by the ICH S6 guideline issued in 1997. Along with enormous experiences and knowledge on safety assessment of some classes of biopharmaceuticals over the last decade, the necessity and feasibility of updating the guideline has been discussed. According to a recommendation by safety experts at the ICH meeting in Chicago in 2006, regional discussions of ICH S6 were held in the USA, EU and Japan. The meeting to clarify the values, challenges and recommendations for ICH S6 from Japanese perspective was held as a part of the first Drug Evaluation Forum in Tokyo on August 10, 2007. Of utmost importance, the “case-by-case” approach must be preserved as the basic principle of the ICH S6 guideline. It is our opinion that oligonucleotides, siRNA, aptamers and related molecules should be excluded from ICH S6 and may be more appropriate for separate guidance. However, based on experiences and accumulated knowledge, there are a number of issues that can be updated including new types of biopharmaceuticals such as bioconjugates, use of homologous proteins and transgenic animals, reproductive/developmental toxicity studies in non-human primates, in vitro cardiac ion channel assay and alternative approaches for carcinogenicity assessment. Preliminary recommendations for some of these topics were outlined at the meeting. The overall Japanese recommendation is that the ICH S6 guideline should be updated to address these topics.

Key words: ICH S6 guideline, Biopharmaceutical, Safety assessment, Preclinical

INTRODUCTION

Biotechnology-derived pharmaceuticals (biopharmaceuticals) appeared for the first time in the 1980s, and the numbers of biopharmaceuticals in the market and in development have increased dramatically over the last two decades. A number of concerns/questions were raised in the early 1990s about the scientific justifications for the safety assessment of biopharmaceuticals in preclinical studies, since preclinical safety guidelines for small molecular new chemical entities (NCEs) are usually not appropriate for biopharmaceuticals. To answer some of those questions, the ICH S6 guideline was issued in 1997. The ICH S6 guideline stresses the principle that preclin-
ical safety evaluation of biopharmaceuticals should be addressed on a “case-by-case” basis. The “case-by-case” approach means that the design and evaluation of safety studies is justified based on an appropriately understanding: (1) of the pharmacology across species, (2) that differences between biopharmaceuticals and NCEs require different endpoints and studies, and (3) that the class of biopharmaceutical influences the endpoints and studies. These principles are still valid and must continue to be preserved. However, enormous experience and knowledge on safety assessment of some classes of biopharmaceuticals has been accumulated while novel types of biopharmaceuticals continue to be developed. Furthermore, to help clarify the regional interpretations of ICH S6, local documents on the safety assessment of biopharmaceuticals have been written in the USA (FDA, 1997; FDA, 2000; Hastings, 2007), EU (CPMP/372/01, 2001; CPMP/SWP/2600/01, 2002; EMEA/CHMP/SWP/294648, 2007) and Japan (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa et al., 2004). It was agreed at the ICH Chicago meeting in 2006 that regional meetings in the EU, USA and Japan would be convened to address the potential need for updating the ICH S6 guideline. Future discussions were to be guided by the following key questions: 1) What can be learned from case studies and experience? 2) What is the predictive value of preclinical studies?; and 3) Where does the ICH S6 guideline “work” and/or “not work”? In addressing these questions, topics considered to be important were: new types of biopharmaceuticals, such as bioconjugates and oligonucleotide medicines, initial dose for first in human study (FIH) selected from preclinical data, non-human primate developmental toxicity studies, in vitro cardiac testing, genotoxicity tests, carcinogenicity studies and the use of transgenic models and homologous products. The Japanese regional meeting was held at the first Drug Evaluation Forum in Tokyo on August 10, 2007. Experts from industry, regulatory bodies and academia participated in the meeting. This paper summarizes the Japanese perspective on values, challenges and recommendations for ICH S6 guidelines that emerged from the meeting.

VALUES, CHALLENGES AND RECOMMENDATIONS FOR ICH S6 GUIDELINE

General principle

1. Scope

The ICH S6 guideline was developed for pharmaceuticals derived from biotechnology, i.e. medical products of proteins/peptides and their analogues. It can also be applied to chemically synthesized peptides, most of which have properties similar to biopharmaceuticals as well as to bioconjugates (a protein combined with chemical molecule or a part or full molecule of other protein), although some special considerations are needed, as discussed in the sections of genotoxicity testing, human ether-a-go-go related gene (hERG) assay and carcinogenicity studies. In the event that there is a safety concern about a chemical fragment derived from a bioconjugate through degradation and/or metabolism, the concern should be addressed as a NCE. Such considerations for bioconjugates would be shared for protein/peptide analogs with non-natural amino acids. On the other hand, oligonucleotide medicines including antisense, RNAi and aptamers have very different physiochemical and biological properties from biopharmaceuticals, and therefore may need a new guideline for preclinical safety assessment.

2. Basic principle

The most important concept established by the ICH S6 guideline is the “case-by-case” approach. The underlying principle is that an appropriate safety test should be used for each biopharmaceutical considering the available information and the unique nature of each entity. Thus, it allows flexibility in designing the best safety assessment possible and discourages uniformed application of a standard list of studies designed for NCEs. The overwhelming consensus of the meeting was that the “case-by-case” concept must be preserved.

3. Species selection

It is very important to select relevant species for the safety assessment of a biopharmaceutical based on its pharmacological and/or biological activities. However, no relevant animal species are available in some cases. No clear advice is written in the ICH S6 guideline on when and how to use transgenic animals or homologous proteins, although the guideline recommends that these alternatives may assist in the safety assessment of biopharmaceuticals.

The use of homologous proteins to address species difference is more common than transgenic animals. However, it is important to consider that it takes months to years to make and characterize a homologue, and thus the sponsor needs to make a decision as early as possible whether or not a homologue is needed for safety assessment. As described in the ICH S6 guideline, the production process, range of impurities/contaminants, pharmaco-kinetics, and exact pharmacological mechanism(s) may differ between the homologous form and the product intended for clinical use. The comparability of the homologue with
The clinical candidate is critical for the interpretation of the toxicity results obtained with the homologue. Therefore, the sponsor should pay particular attentions to characterizing the pharmacology and pharmacokinetics of the homologue. For monoclonal antibodies, literature information, in vitro binding, function assays, tissue cross-reactivity and Fc activity are useful for the characterization.

Another important consideration when interpreting results using a homologue is the margin of safety. Even if negative findings are obtained with a homologue, the sponsor should still be cautious in the risk assessment of the clinical candidate. Conversely, if a homologue produces more severe toxicity in a rodent study compared to data using the clinical candidate in a monkey toxicity study, it is not a foregone conclusion that the results from rodent homologue studies take precedence over those with the clinical candidate. Additional factors need to be considered including that the homologue may have different pharmacokinetics and/or pharmacodynamics from the clinical candidate. Furthermore, the physiology of the target organ in a rodent can differ significantly from human. Finally, physiological similarity between the monkey and human may make the interpretation of the nonhuman primate studies more relevant to risk assessment of man. Thus, a sponsor should interpret the results from studies using a homologue using case-by-case considerations of all available scientific information, including comparability data between a homologue and clinical candidate, physiology across species and literature data with similar products. If a relevant animal species is available for the clinical candidate, a rodent study with a homologue usually is not needed.

4. Dose selection

The ICH S6 guideline recommends the dose selection for toxicity studies should take pharmacokinetics, pharmacodynamics and the expected clinical dose into consideration. The need for observable toxicity at the highest dose remains controversial for biopharmaceuticals. In some cases, only exaggerated pharmacological effects may be observed in toxicological studies of biopharmaceuticals. It is advised in the Japanese “Points to consider” document (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa et al., 2004) that the highest dose may be justified based on the observed plateau for the pharmacodynamic response without respect to toxicological changes (i.e., the maximum pharmacological dose). Other justifications for the highest dose include the emergence of a toxicological change, a multiple of anticipated clinical dose, or a maximum feasible dose. Because multiple different approaches are currently being used, additional scientific discussion may be necessary to establish the best method for setting the highest dose in a preclinical safety assessment study.

The use of select animal data to determine a starting dose for FIH has had little predictive value in some cases (Expert Scientific Group, 2006). For example, no toxicological changes were observed at the highest dose of TGN1412 in monkeys, which was determined to be the maximum feasible dose (Investigator’s Brochure, 2005). Many reasons including species differences, insufficient preclinical data and lack of consideration for pharmacology information may have been involved in the failure to predict a safe starting dose TGN1412. The minimum anticipated biological effect level (MABEL) approach, recently proposed in a EMEA guideline (EMEA/CHMP/ SWP/294648/2007, 2007), has been proposed as a better method to predict a safe starting dose for FIH from preclinical information. However, Ozaki et al. (2006) have argued that for FIH studies in Japan, such a conservative approach would slow down the development of biopharmaceuticals and that the conventional no observed adverse effect level (NOAEL) approach is more appropriate. Therefore, a balance between regulatory control and innovation is needed to deliver safe and effective new medicines to patients. Learning from implementation of the MABEL approach in the EMEA guideline and its effect on the safety and/or duration of clinical development should be considered during future ICH S6 discussions.

INDIVIDUAL STUDIES

1. Repeat dose toxicity studies

There seems to be disharmony among three regions regarding the regulatory requirement on the duration of non-rodent repeat dose toxicity studies (i.e., 6 months vs. 9 months vs. 12 months). Six-month studies are acceptable in Japan and the EU unless there is a specific concern for the investigational biopharmaceutical. Available data from approvals supports the position (Clarke et al., 2007). Further scientific discussion is needed.

It is recommended in the ICH S6 guideline that immunogenicity should be measured and characterized in a repeat dose toxicity study. This information is helpful for the interpretation of toxicity study results, but it has little predictive value for immunogenicity in humans, as discussed in the ICH S6 guideline. Although the recommendation for immunogenicity testing is still useful, there does not appear to be a clear need for immunogenicity in all studies. It may be more efficient and informative
to conduct immunogenicity testing only when changes in biopharmaceutical plasma levels or toxicity potentially related to immunogenicity are important to the overall risk assessment.

2. Reproductive/developmental toxicity studies

Because the ICH S6 guideline allows flexibility in designing toxicity studies, a sponsor may consider conducting a modified reproductive/developmental toxicity study in rodents or rabbits even with mild immunogenicity. However, these conventional animal species may not be applicable if severe neutralizing antibody production occurs or if there is a lack of pharmacological response. In these cases, non-human primates (NHP) studies with the human product, studies in rodents with a homologue or studies in transgenic animals may be useful alternatives (JPMA and PMDA collaboration group, 2003; Nishimura, 2004; Evaluation Report). Among these alternate choices, NHP should be the first choice due to difficulties in interpreting data from homologues or transgenic animal as noted above. However, there are difficulties in using NHP for reproductive/developmental toxicity studies including low fertility, single fetus, relatively high abortion rate, long life cycle and seasonal reproduction with Rhesus monkeys. Furthermore, practical and ethical concerns impact the use of large number of NHPs per group (i.e., more than 12 females per group for Embryo Fetal Development Study). Therefore, historical data on NHP results from the testing facility is critical for the interpretation of results from these studies.

3. Safety Pharmacology

The ICH S7A guideline (2000) applies to both biopharmaceuticals and NCEs, but it is unclear from the scope in the ICH S7B guideline (2005) whether or not an in vitro cardiac channel assay, such as hERG and action potential duration (APD) assays, is required for biopharmaceuticals. Therefore, there seems to be some confusion among countries on the regulatory requirement. The Japanese “Points to consider” document (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa et al., 2004) suggests that such an in vitro study should not be applied for biopharmaceuticals because in contrast to NCEs, biopharmaceuticals are unlikely to interact with this cellular channel (Tristani-Firouz et al., 2001; Recanatini et al., 2005).

Some new findings reported after the publication of Japanese “Points to consider” document suggest that the ion current through the hERG channel can be modified by agents that do not block the channel. It has been reported that some toxins have high affinity for and block the hERG channel (Zhang et al., 2003; Zhang et al., 2007). The toxin binding site is located external to the channel and consists of a specific amino acid sequence. Although most biopharmaceuticals are unlikely to bind to such a specific toxin-binding site or produce a secondary blockade of hERG channel, this possibility cannot be ruled out. However, it is likely that these effects would be detected by in vivo electrocardiogram (ECG) evaluations. Therefore, it is recommended that if there is a signal indicating QTc effects in an in vivo study, the mechanism should be discussed in context with relevant scientific information and/or in vitro study data including the hERG assay. Furthermore, bioconjugates with an organic linker may have properties of both biopharmaceutical and NCE. If small fragments derived from a bioconjugate are of concern, they may have to be dealt with like a NCE. However, it may be difficult to identify, synthesize and examine all possible chemical fragments of a bioconjugate using in vitro studies. Therefore, the decision to conduct or not conduct an in vitro study should be based on the results of an in vivo study in which both a parent bioconjugate and all fragments are tested as a whole for the potential of QTc prolongation. If a scientific explanation from existing information is possible for QTc prolongation observed in an in vivo study, additional in vitro study may not always be needed.

It has also been reported that tumor necrosis factor-α (TNF-α) consistently and reversibly decreased hERG current by stimulating superoxide anion (Wang et al., 2004). This is a secondary effect but not direct blockade of the hERG channel. Testing for these potential secondary effects of biopharmaceuticals is not expected.

4. Genotoxicity studies

Genotoxicity studies routinely conducted for NCEs are not needed for most biopharmaceuticals because of the failure of transmembrane penetration of biopharmaceuticals, due to their high molecular weight. As described in the previous section, genotoxicity studies with some bioconjugates may provide scientific value for the assessment of their genotoxicity risk (Gocke et al., 1999). The decision to conduct genotoxicity studies and the experimental design should be scientifically justified. For example, if no degradation of a bioconjugate occurs or if there is a precedent for using a particular linker, genotoxicity studies may not be needed.

5. Carcinogenicity studies

According to ICH S6 guideline, a standard carcinogenicity assessment is not needed for most biopharmaceuticals. However, there may be a cause for concern.
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for some biopharmaceuticals when the clinical treatment duration, patient population and biological activities of biopharmaceuticals (e.g., growth factors and immunosuppressants) are considered. Nevertheless, the necessity of carcinogenicity assessment for growth factors and immunosuppressants has not yet been fully scientifically justified. For instance, it was recently reported that negative results with mouse and rat growth hormones were obtained in 2-year bioassays (Farris et al., 2007). The rodent findings are consistent with existing clinical data suggesting no risk for tumors following human growth hormone treatment in patients (Allen et al., 1997). Thus, the animal findings provide little additional value for the carcinogenicity risk assessment of biopharmaceuticals if there is enough human data with similar molecules. Besides human growth hormone, carcinogenicity assessments were conducted for insulin and its analogues, basic fibroblast growth factor, FSH and PTH (Advisory Committee Briefing Document, 2001; Hodsman, 2005; Barbehenn et al., 2001; FDA Draft Guidance, 2000). The relevance of these studies to human risk has not been determined.

The concern associated with these growth factors or hormones is mitogenicity but not mutagenicity. Furthermore, in many cases, rodents are generally inappropriate for assessing biopharmaceuticals due to a lack of pharmacological response or neutralizing antibody production. Thus, a 2-year rodent bioassay should not be a regulatory expectation. Proliferative lesions noted by histopathological examination in a chronic toxicity study using a relevant animal could be an early indicator of potential carcinogenicity. For histopathological evaluation, techniques such as proliferative cell nuclear antigen (PCNA) or replicative DNA synthesis (RDS) is recommended in the chronic toxicity study. However, proliferative changes are clearly not sufficient to fully characterize the human risk, which can only be determined by clinical data. Two-step carcinogenicity testing may be an option if rodents are relevant species, while rodent studies using homologous proteins or surrogate antibodies, or the use of humanized mice (Bugelskil et al., 2000), may be other choices. Besides those in vivo data, results of in vitro proliferation assay using a target cells may be useful for the risk assessment carcinogenicity. It is important to consider all options and to select an approach on a case-by-case basis using scientific justification for the selected evaluation.

CONCLUSION

Japanese experts from industry, regulatory bodies and academia recommend updating the ICH S6 guideline to reflect experience and knowledge accumulated over the last decade, although the “case-by-case” approach must be preserved as a basic principle. The major areas for the update are as follows: 1) Transgenic animals and homologous proteins could be an alternative in the case of no available relevant animal species; however, there are limitations with regard to the safety margin, validation, historical data, and physicochemical and pharmacological differences from the clinical candidate. Therefore, if a relevant animal species is available for the clinical candidate, a rodent study with a homologue usually is not needed. 2) Monkey reproductive development toxicity studies are feasible and meet regulatory requirement, although there are some technical difficulties. 3) Most biopharmaceuticals cannot block potassium channels because they cannot penetrate inside the cell to block the channel. However, if QTc prolongation is observed in an in vivo study, an in vitro study including hERG should be considered. 4) Alternative approaches for the risk assessment of carcinogenicity (e.g., a chronic toxicity study with proliferative markers in a relevant animal) are useful and justified in many cases, since the concern for biopharmaceuticals is mitogenicity rather than mutagenicity. 5) Bioconjugates are a new category of ICH S6 and need specific considerations, while oligonucleotides should be out of scope.

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