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EXPERT OPINION

Thirty years of preclinical safety evaluation of biopharmaceuticals: did scientific progress lead to appropriate regulatory guidance?

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Introduction: The first biopharmaceuticals were developed 30 years ago. Biopharmaceuticals differ significantly from small molecule therapeutics (SMTs). Because of such differences, it was expected that classical preclinical safety evaluation procedures applied to SMTs would not predict the adverse effects of biopharmaceuticals. Therefore, until sufficient experience was gained, the preclinical safety evaluation of biopharmaceuticals was carried out on a case-by-case basis. 30 years of experience has since expanded the knowledge base in this area, in the hope to design a preclinical safety evaluation procedure suited to biopharmaceuticals.

Areas covered: This review describes how the preclinical safety evaluation of biopharmaceuticals has evolved. It shows that, as result of the risk-averse behavior of regulators and industry, classical procedures were taken as starting point although state-of-the-art knowledge on biopharmaceuticals was directed towards creating a new procedure, driven by the specific properties of biopharmaceuticals.

Expert opinion: Current preclinical safety evaluation guidance of biopharmaceuticals is criticized because it employs a checkbox approach. The adverse effects induced by biopharmaceuticals are on-target or immune system–induced, therefore, the preclinical safety evaluation should not be standardized, but rather driven by product specific safety concerns.

Keywords: biopharmaceuticals, case-by-case approach, checkbox approach, preclinical safety evaluation, regulation

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1. Introduction

30 years ago the first biopharmaceuticals produced by recombinant DNA technology and other biotechnological methods were introduced. At that time it was already known that the classical preclinical safety evaluation procedure applied to small molecule therapeutics (SMTs) would not predict adverse effects of biopharmaceuticals [1]. The checkbox approaches used in the classical procedure were considered not appropriate [2,3]. It was suggested, "*when developing a biotechnology product, attention should be focused on the unique characteristics of the products itself, rather than on existing testing guidelines*" ([2], p 170).

It was clear that new safety evaluation procedures needed to be developed. However, more knowledge and experience was necessary to design a scientific and rational preclinical safety evaluation procedure for biopharmaceuticals [3,4]. To gain that experience, the safety evaluation of biopharmaceuticals should be done on a case-by-case basis [4,5].

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Article highlights.

- 30 years of experience with preclinical safety evaluation of biopharmaceuticals did not result in a science-based rational design of the preclinical safety evaluation procedure for biopharmaceuticals.
- Even though the classical SMTs procedure was considered as not appropriate for the preclinical safety evaluation of biopharmaceuticals, this procedure was taken as starting point when there was not yet a guideline, due to risk-averse regulators and pharmaceutical companies.
- Despite the fact that from the start of modern biotechnology in drug development experts have recommended a case-by-case approach, a standardized checkbox approach with some case-by-case decisions is dominant in ICH S6(R1) because of the experience gained with this standardized checkbox approach.
- Regulation got behind scientific progress due to risk aversion
- When developing preclinical safety procedures of innovative drugs, regulators and industry should step out of their comfort zones and design a relevant preclinical safety evaluation procedure based on the characteristics and the safety concerns of the specific product under study and not on the procedures that have been successfully applied to incomparable products in the past.

This box summarizes key points contained in the article.

Since then the knowledge base has expanded, experience has been gained, and several preclinical safety guidelines for biopharmaceuticals have been implemented, replaced, and updated. But did these advancements in science enable regulators to design a preclinical safety evaluation procedure suited to biopharmaceuticals?

2. The evolution of the preclinical safety guideline

Analysis of the evolution of the preclinical safety evaluation procedures of the last 30 years shows how the current guideline, ICH S6(R1), came about. When the first biopharmaceuticals received market approval many experts concluded that biopharmaceuticals have different safety concerns than SMTs and so the classical preclinical safety evaluation procedure would not provide useful results concerning the safety of biopharmaceuticals [1,2,4,5]. Due to the novelty and different safety concerns, scientific progress was necessary to enable the design of a scientific and rational preclinical safety evaluation procedure for biopharmaceuticals [3,4]. To gain experience, the preclinical safety evaluation would be conducted on a case-by-case basis focused on the unique characteristics of these biotechnology-derived products [4,5].

However, case-by-case approaches are difficult to apply in practice, because case-by-case approaches require a high level of expertise from pharmaceutical companies and regulators. The absence of standardized rules also contradicted the "safety-first principle" which is a basic principle of drug regulation. Driven by risk-averse behavior, national regulatory authorities requested, and industry used, the classical preclinical safety evaluation procedure to assess the safety of biopharmaceuticals. However, deviating from this standard procedure was possible if the company developing the biopharmaceutical could justify that a different approach was required [4,6,7].

In 1997, the national procedures were replaced by a harmonized guideline, S6 [8]. The S6 was designed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with the aim to harmonize the practice of the preclinical safety evaluation of biopharmaceuticals. But while there are differences, as for example that the use of one species can be sufficient and that genotoxicity is not required as a standard, in general this guideline resembled the classical safety evaluation program as this had become the common practice of the regulators and industry [7]. Although S6 provides opportunities for case-by-case flexibility, the checkbox approach remains dominant in S6. This is understandable because harmonization of guidelines is perpendicular to the flexibility needed for a case-by-case approach. The aim of harmonizing guidelines is to create a basic framework, recognized by all parties, that streamlines the regulatory assessment process and reduces the development times and resources for drug development. Flexibility (e.g., case-by-case approaches) may lead to differing interpretations and inconsistent opinions between regulatory agencies [9] and it therefore does not reduce the development time and does not contribute to a streamlined regulatory assessment process [9], which is the opposite of what ICH tries to achieve.

3. Status quo

Revision of the S6 was considered to be necessary by the ICH because *"clarification (and sometimes amplification) of this guidance (S6) is needed as substantial experience and new information has been gained since Step 4 (the adoption of the guideline) (1997)"* ([10], p 1). According to the ICH preclinical safety experts clarification was required with regard to species selection, study design, reproductive and developmental toxicity, carcinogenicity and immunogenicity [8]. In June 2011 the revised guideline S6(R1) concerning the preclinical safety evaluation of biotechnology-derived pharmaceuticals (biopharmaceuticals), was approved by the ICH steering committee [8]. Did the ICH design this revised guideline making use of the state-of-the-art knowledge.

4. State of the art knowledge on biopharmaceuticals

Experience with biopharmaceuticals has shown safety concerns of biopharmaceuticals to be different from SMTs. The adverse effects of biopharmaceuticals are either caused by

exaggerated pharmacology, unintentional tissue cross-reactivity, or by immune system-mediated adverse effects [11-14]. These insights validate the proposed approach to design the preclinical safety evaluation procedure on a case-by-case basis, driven by product specific questions, such as the cause, mechanisms, and reversibility of adverse effects. Despite the fact that from the start of modern biotechnology in drug development experts have recommended a case-by-case approach [5], this approach was not used as basis for the preclinical safety evaluation guidelines. Instead a standardized checkbox approach with some case-by-case decisions has been dominant in the preclinical safety evaluation guidelines.

The recent update of the ICH S6 guideline was an opportunity to catch up with scientific progress and introduce preclinical safety testing driven by the specific properties of biopharmaceuticals. Instead this update only clarified and complemented the S6, thus still closely resembles the classical preclinical safety evaluation procedure and checkbox approach. S6(R1) is only an update of S6, whereas a total reform of S6 would have been more appropriate. Unfortunately, regulators missed the opportunity to catch up with scientific progress into the toxicity of biopharmaceuticals and design a new preclinical safety evaluation procedure suited to biopharmaceuticals.

5. The risk of risk aversion

30 years of experience with preclinical safety evaluation of biopharmaceuticals did not result in a science-based rational design of the preclinical safety evaluation procedure for biopharmaceuticals, but in outdated guidelines driven by risk-averse behavior. Risk aversion induces behavior that prefers elaborating on the successful approaches of the past over new approaches. In other words, risk aversion leads to path dependency. Path dependency is the routine whereby the set of solutions is limited by knowledge and experiences gained in the past, even though past circumstances may no longer be relevant [15]. Consequently, suboptimal solutions for problems are adopted. This can be exemplified by the role of animal experimentation in the preclinical safety evaluation procedure of biopharmaceuticals.

When the first biopharmaceuticals entered the market, it was already clear that the value of animal experimentation in the preclinical safety evaluation of biopharmaceuticals was limited due to species specificity and immunogenicity [1,3,5,16]. At the same time, the European Union expressed its ambition to reduce animal experimentation in Directive 86/609/EEC. The recognized limited value of animal studies for the preclinical safety evaluation of biopharmaceuticals in combination with the implementation of Directive 86/609/EEC provided a window of opportunity to design a preclinical safety evaluation procedure whereby the role of animal experimentation could be limited. However, instead of actively exploring possibilities to use radically different techniques in the preclinical safety evaluation procedure, the regulatory authorities used the classical procedure, with animal studies playing a leading role. Using this classical procedure, studies in species wherein the biopharmaceutical is pharmacologically active were shown to provide insight in the potential adverse effects [9,17-19]. As a result, studies in Non-Human Primates (NHPs) became increasingly popular in preclinical safety evaluation testing of biopharmaceuticals [13]. Nevertheless, using NHPs only partly solved the problem; some biopharmaceuticals are human specific [20,21] and in addition, reproductive and developmental toxicity and carcinogenicity are not easily studied in NHPs [13]. Two new animal-based approaches were introduced to conduct studies for human specific biopharmaceuticals and reproductive and developmental toxicity and carcinogenicity studies: i.e., (1) adapting the animals to the human product by using transgenic animals, and (2) adapting the product to animals by the development of animal homologues. However the value of the results of safety evaluation studies using transgenic animal or animal homologues is uncertain [22], because "*the ultimate validation (of transgenic animals) will not occur until there are clinical data to compare with...*" ([20], p 233) and "until the clinical candidate has been evaluated in humans, the extent to which the surrogate molecule (homologue) is truly homologous or analogues cannot be completely understood" ([20], p 234).

The window of opportunity to realize the long-desired break with the classical animal testing paradigm was not effectively exploited. To overcome problems as species specificity and immunogenicity, the regulatory authorities and pharmaceuticals companies did not choose to develop new approaches, but they developed and adopted suboptimal new animal-based approaches. Despite the public and political pressure to reduce animal testing and the scientific discussion concerning the predictive value of animal testing, rigidity and risk-averse behavior of regulators and pharmaceutical companies alike have made it impossible to break through the path dependency.

The role of animal experimentation in the preclinical safety evaluation procedure of biopharmaceuticals is a perfect analogy for the evolution of this preclinical safety evaluation procedure in general. Instead of creating a new procedure that takes into account the differences in safety concerns between SMTs and biopharmaceuticals, the classical procedure was taken as starting point. So the result is a flawed preclinical safety evaluation procedure for biopharmaceuticals.

6. Concluding remarks

Although scientific evidence has accumulated, regulators only used this knowledge to complement and clarify the preclinical safety evaluation guidance instead of using these insights to revise the procedure to a more flexible procedure driven by product specific questions. Regulation got behind scientific progress due to risk aversion.

Today, the regulatory authorities are confronted with comparable challenges. For instance, preclinical safety evaluation

procedures have to be developed for innovative medicines, such as nanomedicines and advance therapies. To prevent the development of suboptimal preclinical safety evaluation procedures for innovative medicines, lessons should be learned from the development of the preclinical safety evaluation procedure for biopharmaceuticals. Pharmaceutical companies in collaboration with regulatory authorities need to explore the window of opportunity, when innovative medicines enter drug development, to design state-of-the-art procedures to guarantee goal-oriented preclinical safety procedures and patient safety. They should step out of their comfort zones and design a relevant preclinical safety evaluation procedure based on the characteristics and the safety concerns of the specific product under study and not on the procedures that have been successfully applied to incomparable products in the past, because past performance of a procedure does not guarantee that this procedure will also be efficient in predicting the toxicity of incomparable products in the future.

7. Expert opinion

The main critique on the ICH S6 is that it is a guidance inspired by standard procedures that are somehow adapted to be useful for the evaluation of biopharmaceuticals and that it does not operate a full case-by-case approach that is only driven by product specific concerns. That a case-by-case approach should be leading in the design of the preclinical safety evaluation of biopharmaceuticals was already suggested at the time of the introduction of the first biopharmaceuticals. The scientific evidence showing that adverse effects are target-induced or immune system-mediated also supports a case-by-case approach.

In practice a full case-by-case approach would mean that the preclinical safety evaluation should not be standardized but should be designed for every product in dialog with the regulators. Studies with homologues and transgenic animals should be discouraged, because studies should only be done when they provide insights that do not have to be confirmed in the first-in-human studies. When confirmation of results of animal studies is necessary then microdosing in humans would be appropriate.

However, microdosing is not popular because many companies and regulators do not feel comfortable about testing biopharmaceuticals in humans without having the product tested in animals. Even though companies and regulators know that the findings of animal studies only confirm what they already knew or are irrelevant, they feel more secure when they have done animal tests to verify whether the biopharmaceutical does not induce any unexpected toxicity. This extra sense of safety that the results of animal tests provide to regulators and companies is thus false but also exposes participants of standard first-in-human studies to a higher risk than participants in microdosing studies because results of animal tests often make it possible to start at higher doses than is allowed in microdosing studies. To reduce the use of irrelevant studies in the preclinical safety evaluation of biopharmaceuticals the misperception that animal testing provides more safety to clinical trial participant than the lower starting dose in microdosing should be cleared up.

Furthermore the authors would like to signal to regulators now working on guidance for the preclinical evaluation of advanced therapies, nanotechnology and other innovative drugs to take the product or class specific concerns and not the standard approaches as point of departure. Taking standard approaches as basis results in adaptations of these procedures and guidance documents including many studies often not relevant.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Teelmann K, Hohbach C, Lehmann H. Preclinical safety testing of species-specific proteins produced with recombinant DNA-techniques. An attempt to transfer current experience into future testing strategies. Arch Toxicol 1986;59:195–200
2. Stoll RE. The preclinical development of biotechnology-derived pharmaceuticals: the PMA perspective. Pharmaceutical manufacturers association. Prog Clin Biol Res 1987;235:169–71
3. Dayan AD. Rationality and regulatory requirements - a view from Britain. Prog Clin Biol Res 1987;235:89–106
4. Zbinden G. Biotechnology products intended for human use, toxicological targets and research strategies. Prog Clin Biol Res 1987;235:143–59
5. Finkle BS. Genetically engineered drugs: toxicology with a difference. Prog Clin Biol Res 1987;235:161–7
6. European Economic Community. Pre-clinical biological safety testing on medicinal products derived from biotechnology (3BS13a), 1988
7. Hohbach C. Safety in biotechnology progress & problems, industrial point of view. In: D'Arcy PF, Harron DWG, editors. Proceedings of The First International Conference on Harmonisation: Brussels 1991. The Queen's University of Belfast, Belfast, Northern Ireland; 1992. p. 307–16
8. ICH. S6(R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, 2011
9. Cavagnaro JA. Preclinical safety evaluation of biotechnology-derived pharmaceuticals. Nat Rev Drug Discov 2002;1:469–75
10. ICH. Addendum to ICH S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6 (R1), 2009
11. Giezen TJ, Mantel-Teeuwisse AK, Meyboom RHB, et al. Mapping the safety profile of biologicals: a disproportionality analysis using the who adverse drug reaction database, vigibase. Drug Saf 2010;33:865–78
12. Haller CA, Cosenza ME, Sullivan JT. Safety issues specific to clinical development of protein therapeutics. Clin Pharmacol Ther 2008;84:624–7
13. Baumann A. Nonclinical development of biopharmaceuticals. Drug Discov Today 2009;14:1112–22
14. Baldrick P. Safety evaluation of biological drugs: what are toxicology studies in primates telling us? Regul Toxicol Pharmacol 2011;59:227–36

• **A very informative article regarding the safety evaluation of biopharmaceuticals in primates.**

15. Arthur WB. Competing technologies, increasing returns, and lock-in by historical events. Econ J 1989;99:116–31
16. Hobson WC, Fuller GB. Species selection for safety evaluation of biotechnology products. Prog Clin Biol Res 1987;235:55–71
17. Dayan AD. Safety evaluation of biological and biotechnology-derived medicines. Toxicology 1995;105:59–68
18. Serabian MA, Pilaro AM. Safety assessment of biotechnology-derived pharmaceuticals: ICH and beyond. Toxicol Pathol 1999;27:27–31
19. Baumann A. Early development of therapeutic biologics-pharmacokinetics. Curr Drug Metab 2006;7:15–21
20. Bussiere JL, Martin P, Horner M, et al. Alternative strategies for toxicity testing of species-specific biopharmaceuticals. Int J Toxicol 2009;28:230–53
21. Dixit R, Iciek LA, McKeever K, et al. Challenges of general safety evaluations of biologics compared to small molecule pharmaceuticals in animal models. Expert Opin Drug Discov 2010;5:79–94

• **Broad overview of the challenges of the preclinical safety evaluation of biopharmaceuiticals.**

22. Bornstein GG, Klakamp SL, Andrews L, et al. Surrogate approaches in development of monoclonal antibodies. Drug Discov Today 2009;14:1159–65

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