Comments and suggestions from reviewer

Title: WHO Guidelines on the Quality, Safety, and Efficacy of Biological Medicinal Products Prepared by Recombinant DNA Technology: WHO/rDNA_DRAFT/12 March 2013

Reviewer (name, position, full contact details): **Andrew W. Womack, Ph.D.**
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)
1201 Maryland Avenue SW, Suite 900
Washington, DC 20024
USA
202.962.9200
awomack@bio.org

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
GENERAL COMMENT The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the "WHO Guidelines on the Quality, Safety, and Efficacy of Biological Medicinal Products Prepared by Recombinant DNA Technology." BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. BIO is generally supportive of the World Health Organization (WHO) Draft Guidelines and has limited the scope of specific comments to the Nonclinical Evaluation section (Part B). BIO believes that there are several topics in Part B for which additional clarification is warranted, including aspects of the current language that could result in additional animal use beyond that currently specified in International Conference on Harmonization (ICH) guidance or that is standard practice in biological medicinal product development. We would be pleased to provide further input or clarification of our comments, as needed.				
INTRODUCTION				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
BACKGROUND				
SCOPE				
GLOSSARY				
PART A. Manufacturing and quality control				
A.1 Definitions				
A.1.1 International name and proper name				
A.1.2 Descriptive definition				
A.1.3 International standards and reference materials				
A.2 General manufacturing guidelines				
A.3 Control of starting/source materials				
A.3.1 Expression vector and host				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
cell				
A.3.2 Cell bank system				
A.3.3 Cell culture medium/other materials				
A.4 Control manufacturing process				
A.4.1 Cell culture				
A.4.2 Purification				
A.5 Control of drug substance and drug product				
A.5.1 Characterization				
A.5.2 Routine control				
A.6 Filling and container				
A.7 Records, retained samples, labeling, distribution and transport				
A.8 Stability, storage and expiry date				
A.8.1 Stability studies				
A.8.2 Drug product requirements				
A.9 Manufacturing				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
process changes				
PART B. Nonclinical evaluation				
B.1 Introduction	Page 35, Lines 1-7: *Further guidance can be found in for example the ICH guideline preclinical safety evaluation of biotechnology-derived pharmaceutical and other relevant guidelines (e.g., 31).*	BIO is in agreement with the principles in ICH Guideline S6(R1) on development of biotechnology-derived pharmaceuticals. BIO suggests that the WHO guideline should not just indicate the availability of the ICH guidances, but clarify that WHO guidelines are consistent with those in ICH guidelines, as it appears that the ICH guidances were the primary source for the information in the nonclinical sections of the draft guidance.	At the end of the paragraph, BIO suggests WHO consider inserting: These ICH guidance documents form the primary basis of the scientific recommendations that follow. As such, development programs that conform to ICH guidance would also conform to the scientific expectations provided in this WHO guideline.	
	Page 34, Lines 4-19.	BIO supports the case-by-case approach described in the introduction; however, lines 4-19 could lead reviewers not familiar with biologic development to conclude that animal studies do not provide value.	BIO suggests WHO consider deleting, or significantly condensing, the first paragraph (lines 4-19) and begin this section with the statements in line 20 that focus on the need for a case-by-case evaluation.	
B.1.1 Objectives of the nonclinical evaluation	Page 35, Lines 22-24: *rDNA-derived BMPs that are structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive nonclinical testing*	BIO believes the intent of this sentence is not clear. If this is in reference to a biosimilar, this should be explicitly stated as such. For an innovative product, BIO believes such a statement is not appropriate.	BIO requests that WHO clarify that this statement is made in reference to biosimilar biological products only.	
B.1.2 Product development and				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
characterization				
B.1.3 Good laboratory practice				
B.2 Pharmacodynamics				
B.2.1 Primary and secondary pharmacodynamics/biological activities	Page 36, Lines 24-25: *Due to the species specificity of many rDNA-derived BMP, it is important to select relevant animal species for testing (see Appendix 6).*	BIO believes it should be stated in this section that non-human primates (NHPs) are usually the only pharmacologically or toxicologically relevant species, and that rodents (*e.g.*, rats and mice) should also be evaluated for relevant biological activity.	BIO suggests WHO revise to: ". . . to select relevant animal species for testing (see Appendix 6). Non-human primates (NHPs) are usually the only pharmacologically or toxicologically relevant species; however, rodents (e.g., rats and mice) should also be evaluated for relevant biological activity."	
	Page 37, Lines 3-4: *When feasible, in vivo pharmacology can be incorporated into general toxicity studies.*	Use of the term "*in vivo* pharmacology" in this sentence could imply endpoints from animal models of human disease. In general, toxicity studies will be conducted in "normal animals." BIO recommends replacing "*in vivo* pharmacology" with "pharmacodynamic endpoints".	BIO recommends WHO revise to: "When feasible, ~~*in vivo* pharmacology~~ pharmacodynamic endpoints can be incorporated into general toxicity studies."	
B.2.2 Safety pharmacology	Page 37, Lines 7-8: *It is important to investigate the potential for undesirable pharmacological activity in appropriate animal models.*	BIO suggests adding the rationale for conducting Safety Pharmacology studies for biological medicinal products (BMPs).	BIO suggests WHO revise to: Based on the target or mechanism of action of the product, it ~~It~~ is important to investigate the potential for undesirable	

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
			pharmacological activity in appropriate animal models.	
	Page 37, Lines 8-10: *The aim of the safety pharmacology studies is to reveal any functional effects on the major physiological systems (e.g. cardiovascular, respiratory, renal, and central nervous systems).*	Current text includes the renal system, which is no longer part of the core battery as per ICH S7. While renal studies can be added on an as-needed basis, renal pharmacology (*i.e.*, glomerular filtration rate [GFR], electrolyte excretion, *etc.*) are not warranted as a default.	BIO requests WHO revise to: "…systems (e.g. cardiovascular, respiratory, ~~renal,~~ and central nervous systems)."	
B.3 Pharmacokinetics/ Toxicokinetics				
B.3.1 General principles	Page 38, Lines 5-7: *When using radiolabeled proteins, it is important to show that the radiolabeled test material maintains activity and biological properties equivalent to that of the unlabeled material.*	BIO believes this statement should be placed in the *Studies with radiolabelled products* section on page 39.	BIO suggests WHO move the statement, "When using radiolabeled proteins, it is important to show that the radiolabeled test material maintains activity and biological properties equivalent to that of the unlabeled material." to the *Studies with radiolabelled products* section on page 39.	
B.3.2 Assay				
B.3.3 Distribution	Page 38, Line 24 – Page 39, Line 20: Subsection entitled: *Tissue cross-reactivity studies*	The section on tissue cross-reactivity studies was derived from ICH S6; however, it should not be listed in the Distribution studies. These studies are not designed to inform regarding the distribution of the molecule.	BIO suggests WHO move all reference to tissue cross-reactivity to a new section under B.4.8	

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
B.3.4 Metabolism				
B.4 Toxicity studies				
B.4.1 General principles	Page 40, Lines 8-12: *A small sample size may lead to failure to observe toxic events due to observed frequency alone regardless of severity. The limitations that are imposed by sample size, as often is the case for non-human primate studies, may be in part compensated by increasing the frequency and duration of monitoring. Both genders should generally be used or justification given for specific omissions.*	Although the guideline points out that too small a sample size may not detect potential toxicity, BIO believes guidance be provided on the minimum number of animals required in a study, especially for non-human primate (NHP) toxicity studies.	BIO recommends WHO revise to: "…used or justification given for specific omissions. As an example, the minimum sample size for a pivotal Good Laboratory Practice (GLP) toxicity study in non-human primates (NHPs) is considered to be 3 animals per sex, and, if a recovery group is included in the study, an additional minimum of 2 animals per sex would be included."	
	Page 42, Lines 14-17: *Many rDNA-derived BMP intended for human use are immunogenic in animals. Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies (for details, see B.4.8.1).*	As written, this section specifies the measurement of anti-drug antibodies should be conducted in each study, which is not consistent with the approach described later in the document or in ICH S6(R1).	BIO suggests WHO delete immunogenicity from this section and leave immunogenicity discussion to B.4.8.1	
B.4.2 Single dose toxicity studies	Page 42, Lines 25-27: *In general, single dose toxicity*	BIO suggests this sentence to the front of the section to reflect standard practice. In general,	BIO requests WHO move the sentence, "*In general, single dose toxicity studies should only be*	

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
	studies should only be pursued in cases where significant toxicity is anticipated and the information is needed to select doses for repeated dose studies.	stand-alone acute toxicity studies of BMPs are not warranted and clarity here may prevent undue animal usage.	*pursued in cases where significant toxicity is anticipated and the information is needed to select doses for repeated dose studies.*" to the beginning of paragraph.	
B.4.3 Repeat dose toxicity studies	Page 43, Lines 26-29: *Since antibody formation to human proteins in animal studies is usually not predictive for the clinical situation, concerns regarding antibody formation to the endogenous hormone, e.g. in case of erythropoietin orsomatropin, will have to be addressed on a clinical safety level.*	Issues related to the predictability of anti-drug antibodies (ADAs) are covered in other sections. BIO supports the ICH language referred to above, which indicates that recovery groups solely to investigate immunogenicity are not warranted.	BIO requests WHO delete this sentence: ~~Since antibody formation to human proteins in animal studies is usually not predictive for the clinical situation, concerns regarding antibody formation to the endogenous hormone, e.g. in case of erythropoietin orsomatropin, will have to be addressed on a clinical safety level.~~	
B.4.4 Genotoxicity studies				
B.4.5 Carcinogenicity studies	Page 44, Line 18 – Page 46, Line 14. Section entitled, *B.4.5 Carcinogenicity studies*	The draft guideline has inter-mixed the language in the original ICH S6 document and the addendum. As such, there are certain types of studies [*e.g.*, receptor expression (line 19)] that appear to be firmly recommended, rather than potential studies to consider in a weight of evidence assessment. BIO suggests that relying on the R1 language and not attempting to inter-mix these sections would be more appropriate.	BIO suggests WHO modify the section to reflect the intact carcinogenicity section present in the R1 addendum of ICH S6**.**	
B.4.6 Reproductive				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
performance and developmental toxicity studies				
B.4.7 Local tolerance studies	Page 50, Lines 25-27: *In some cases, the potential adverse effects of the product can be evaluated in single or repeated dose toxicity studies, thus obviating the need for separate local tolerance studies.*	BIO believes the current language suggests that in some cases, local tolerance can be evaluated in the repeat-dose studies. In reality, repeat-dose toxicity studies are the most common, and most appropriate, experiment to assess local tolerance. This approach is consistent with reduction and refinement of animal use.	BIO requests WHO revise to: "In ~~some~~ most cases, the potential adverse effects of the product can be evaluated in single or repeated dose toxicity studies, thus obviating the need for separate local tolerance studies."	
B.4.8 Other toxicity studies	Page 52, Lines 6-9: *In this regard, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive for reactions in humans. Therefore, such studies are considered of little value for the routine evaluation of these types of products.*	BIO believes the guinea pig anaphylaxis test is not relevant to humans and therefore, to be consistent with the 3Rs (reduce/refine/replace)[1], should not be conducted. The current draft wording, therefore, is not strong enough.	BIO requests WHO revise to: "In this regard, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive for reactions in humans and should not be conducted. ~~Therefore, such studies are considered of little value for the routine evaluation of these types of products.~~"	
	Page 52, Lines 16-17: *However, such reaction may cause or contribute to by injection trauma and/or specific toxic effects caused by the formulation vehicle.*	This statement appears to be a modification of the original sentence in ICH S6, but it does not convey the original statement with complete fidelity.	BIO requests that WHO revert to the original sentence in ICH S6 by revising to: "~~However, such reaction may cause or contribute to by injection trauma and/or specific toxic effects caused by the formulation~~	

[1] S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals,

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
			~~vehicle.~~ It is important, however, to recognize that simple injection trauma and/or specific toxic effects caused by the formulation vehicle may result in toxic changes at the injection site."	
B.5 Selection of dose for exploratory clinical trials (first in human use)	Page 53, Lines 5-9.	The rationale for selection of dosage for first-in-human use is a complex topic, and this section does not provide adequate information on the subject. BIO, therefore, believes this topic is outside the scope of these guidelines.	BIO suggests WHO consider either deleting entirely or cross-referencing a more complete discussion of this topic.	
PART C. Clinical evaluation				
C.1 Good clinical practice				
C.2 1Clinical pharmacology (Phase I)				
C.2.2 Pharmacogenomics				
C.2.3 Pharmacokinetics				
C.2.4 Pharmacodynamics				
C.2.5 Pharmacokinetics/ Pharmacodynamics relationship				
C.2.6 Modifications of				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
PK and PD profiles of therapeutic proteins				
C.3 Efficacy				
C.3.1 Phase II				
C.3.2 Confirmatory phase III				
C.3.3 Biomarkers				
C.3.4 Manufacturing and formulation changes				
C.3.5 Special populations				
C.3.6 Post-marketing: Phase VI				
C.4 Statistical considerations				
C.4.1 General considerations				
C.4.2 Special considerations for rDNA-derived BMPs				
C.5 Safety				
C.5.1 Special populations				
C.6 Immunogenicity				
C.7 Pharmacovigilanc				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
e and risk management planning				
C.8 Additional guidance				
Appendix 1. Manufacturing process validation				
Appendix 2. Characterization of rDNA-derived BMP				
Appendix 3. Technical approaches to analytical characterization				
Appendix 4. Routine control of rDNA-derived BMP				
Appendix 5. Product specific guidance in nonclinical evaluation (examples)				
Appendix 6. Animal species/model selection				
Appendix 7. Explanatory notes				

Sections	Page No/Text	Comment	Suggested Amendment	Internal Use Only [blank]
OTHER SECTIONS				