POINTS TO CONSIDER* REGARDING SAFETY ASSESSMENT OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS IN NON-CLINICAL STUDIES (ENGLISH TRANSLATION)

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(Received September 2, 2004, Accepted September 22, 2004)

ABSTRACT — Regulatory and industrial scientists collaborated to publish a points to consider document regarding the safety assessment of biotechnology-derived pharmaceuticals in non-clinical studies in 2002 (Pharmaceutical Non-clinical Investigation Group, 2002) The collaboration team intended to clarify the interpretation of ICH-S6 guideline and furthermore share recent Japanese practices on this matter However, the document was written in Japanese Thus, we share here an English translation of the document so that non-native Japanese correctly understand the contents

KEY WORDS: English translation, Points to consider, Non-clinical, Biotechnology-derived pharmaceuticals, ICH-S6 guideline

INTRODUCTION

Scientists from National Institute of Health Sciences, Pharmaceuticals and Medical Devices Evaluation Center (currently, Pharmaceuticals and Medical Devices Agency) and Japan Pharmaceutical Manufacturers Association collaborated to publish a "points to consider" document regarding the safety assessment of biotechnology-derived pharmaceuticals, or biopharmaceuticals, in non-clinical studies in 2002 (Pharmaceutical Non-clinical Investigation Group, 2002) The collaboration team intended to clarify the interpretation of ICH-S6 guideline and furthermore share recent Japanese practices on this matter However, it was written in Japanese Thus, the follow-up team (the authors of this review and almost the same as the initial collaboration team members) made an English translation of the document and collected comments on it from experts in the US and EU The experts were generally very supportive of the ideas shown in the "points to consider" document They also suggested more clarification on some other ideas Considering those comments, the follow-up team has revised the Japanese "points to consider" document to be published in the near future and shares here the English translation of the revised document so that non-native Japanese correctly understand the contents The following sections 1 to 15 are the English translation

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Background

Biotechnology-derived pharmaceuticals (biopharmaceuticals) were initially developed in the 1980s. In recent years, various kinds of new biopharmaceuticals suitable for clinical trials and marketing are on the increase.

A primary objective of the development of biopharmaceuticals derived from animal or plant tissue is to have proteins consisting of primary amino acid sequence which are identical to endogenous human proteins via DNA recombinant technology. Human proteins are expected to have low or no antigenicity and the potential for long-term use in humans. On the other hand, it is recognized that human protein biopharmaceuticals may sometimes be immunogenic in animals due to differences in the primary amino acid sequence of the protein between humans and animals, however, this is not always the case. There are many examples of human proteins produced by recombinant DNA technology that are not immunogenic in animals. In cases where a human protein is highly immunogenic in animals, the safety evaluation of human proteins in animals sometimes has technical limitations.

In addition, differences in approaches for safety evaluation of biopharmaceuticals among the European Union, the United States, and Japan have been identified, pointing out the need for harmonization between the three regions. In 1997 the three regions reached an agreement concerning “Preclinical safety evaluation of biotechnology-derived pharmaceuticals” (“ICH S6 guideline”). Based on this ICH-S6 guideline, the Notification No. 326 was issued, as ICH Step 5, by the Ministry of Health and Welfare (MHW) in 2000. The interpretation described here is related to this notification, and was developed in conformity with the ICH guideline, serving as a reference for the data gathered after issuance of the notification.

The guideline employs the principle that preclinical safety evaluation of biopharmaceuticals should be addressed on a case-by-case basis. The term “case-by-case” refers to the understanding that (1) as biopharmaceuticals intended as human-specific products are developed, safety evaluation in animals has limitations and cannot be addressed by routine nonclinical safety study methods adapted to chemically synthesized non-protein/peptide compounds (CSC), and (2) not only human-type protein and peptides but also various modified proteins and monoclonal antibody biopharmaceuticals are being developed and therefore study design optimized to each type of biopharmaceutical is needed.

Difficulty in conducting safety evaluation of biopharmaceuticals by routine studies

A major consideration for safety testing of biopharmaceuticals is that they can possess highly selective pharmacological actions and/or species selectivity as opposed to CSC, and therefore safety evaluation of biopharmaceuticals in animals is difficult. Some biopharmaceuticals are active only in humans. Therefore, testing these molecules in irrelevant animals is of no predictive value with respect to human safety. If the proteins are highly immunogenic and if the immune response is “neutralizing,” then the conduct of repeat-dose studies beyond 2-3 weeks duration is problematic, especially if dose schedule is episodic compared to the daily dosing regimen.

Type of biologics and scope of the guideline

1. Biopharmaceuticals: protein/peptide based biologics

Biopharmaceuticals covered by the guideline include protein/peptide products consisting of amino acids. The upper column of Table 1 shows the subcategories of biopharmaceuticals. Antibodies are originally classified by protein subclass, but a separate category was provided for antibodies because the biological action differs from general protein products. In recent years, the development of human protein analogs has sporadically been observed with improvement in efficacy expected, and therefore approaches to these analogs are also described here. The guideline should cover safety evaluation of biopharmaceuticals by taking into account the type and clinical application of individual biopharmaceuticals. The considerations for each type of biopharmaceutical are shown below. The safety of impurities and degradation products in biopharmaceuticals need to be comprehensively assessed, according to their quality and bioactivity.

1) Proteins

When a human-type protein is used at a blood concentration exceeding the physiological level, studies for safety evaluation should be designed with reference to many of the considerations mentioned in the guideline. Moreover, consideration should be given to entirely different physiological secretion patterns in humans. Changes in blood concentration are known to be more significant than the concentration level itself for some classes of proteins. Biopharmaceuticals intended for sustained-release profile show changes in blood concentration level further diverging from the physiological secretion pattern. Therefore, when the changes in blood concentration of exogenous human
protein differ from the physiological secretory patterns of endogenous proteins, attention should be paid to the potential changes in physiological action.

For animal proteins or human-type protein analogs consisting of natural amino acids (i.e., human-type protein analogs with original human protein amino acids being substituted with other natural amino acids, added natural amino acids to or deleted amino acids), consideration should be given to the potential difference in potency and quality of biological activity from those of original human protein. For example, in a human-type protein analog where the substituted site is involved in receptor recognition sites, its biological activity would be enhanced/diminished or new biological activity may occur. Moreover, depending on the type and site of amino acid replaced, a new antigen determinant (epitope) may express and result in changes of antigenicity.

For human-type protein analogs with non-natural amino acids, in addition to the above considerations, attention should be paid to the potential biological activity and its pharmacokinetic behavior in the fragment containing the site where this protein has been metabolized. For example, no genotoxicity studies are needed for proteins not passing through cell membranes, while applicability of this theory should be discussed on a case-by-case basis for fragments containing non-natural amino acids. No metabolism studies are needed for proteins just degraded into amino acids, while metabolism studies may provide useful information for proteins containing non-natural amino acids.

Two types of bioconjugates may exist. Bioconjugates of human-type protein with other protein may have the combined biological activity of both proteins and their effects on the body may be altered due to the interaction between these proteins. Therefore, consideration should be given to the conducting of safety evaluation in pharmacological studies. On the other hand, bioconjugates of human-type protein with

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organic linker can be handled in a manner similar to human-type protein analogs containing non-natural amino acid.

2) Peptides
Peptides, like proteins, consist of amino acids, although their molecular weights are smaller than those of proteins. Therefore, the above considerations for proteins are also applicable to peptides. Antibody formation, which is a key issue in animal experiments for human-type proteins, is generally dependent on molecular weight (i.e., probability of antibody formation is lower if molecular weight is lower). The guideline covers not only biotechnologically produced peptides but also chemically synthesized peptides.

3) Antibodies
Antibodies are usually targeted to specific receptors, especially in the cases of monoclonal antibodies. Many of these antibodies are inherently species-specific. It is important for the sponsor to verify species specificity in order to justify the use (or non-use) of a particular animal species for safety studies. In the cases where an appropriate animal model is not available, then the use of homologous antibodies for animals or the use of relevant transgenic animals expressing the human antigen should be considered. In addition, when an IgG antibody is used in possibly pregnant or lactating women and based upon the intended indication, reproductive toxicity needs to be investigated because of its potential for antibody being transferred to placenta or the milk. Immunoconjugates of antibodies, conjugated either with other proteins or with organic linker, should be handled the same way as bioconjugates as described above.

2. Related biopharmaceuticals: non-protein/peptide based biologics
The middle section of Table 1 shows the pharmaceuticals not classified as biopharmaceuticals, although having selective pharmacological action similar to biopharmaceuticals. Their safety evaluation in animals is sometimes difficult. The guideline does not cover these pharmaceuticals but its basic principles can be used as reference.

1) Peptide mimics
Peptide mimics are CSC with a selective affinity to peptide receptors. When a peptide mimic to be tested has an action specific to human peptide receptors, sufficient response may not be obtained in those animal species that have been commonly used in toxicity studies. In such cases, appropriate safety evaluation may be feasible by designing the study, using the basic principles of the guideline for biopharmaceuticals as a reference.

2) Antisense compounds and ribozymes
Antisense compounds and ribozymes used for gene therapy need to be examined separately from biopharmaceuticals. They selectively modify (generally suppress) expression of a certain kind of gene, for example, suppressed production of endogenous molecules by a certain kind of gene, thereby exerting their efficacy. Therefore, as in the case of antibodies, if the antisense compound or ribozyme does not recognize or interact with a gene in the test animal, then such studies would not predict human safety concerns. In such cases, the safety evaluation would be incorporated into primary pharmacodynamic studies in relevant animal models. One should know the limitation of nonclinical evaluation for antisense compounds and ribozymes.

3. Other biologics
The conventional biologics shown in the bottom section of Table 1 are not covered by this guideline. Non-clinical safety evaluation based on relevant standards is necessary for them.

Selection of animal species
Studies conducted with animals that do not respond pharmacologically to a test biopharmaceutical do not provide useful safety information. Similarly, in the case that a biopharmaceutical produces significant neutralizing antibodies in an animal, it may be difficult to evaluate the safety of the compound in the animal study. If no relevant animal species are available, animal models mimicking the human disease, transgenic animals expressing human proteins (e.g., receptors) or homologous proteins (animal) may be useful. If neither of them is available, the necessity of toxicity studies including cardiovascular and respiratory function tests in a single animal species (e.g., 14-day repeated-dose toxicity study) should be justified on a case-by-case basis.

Setting of the maximum dose
In many cases, no toxicity is observed in safety studies with biopharmaceuticals, which have aroused much discussion concerning a maximum dose for toxicology studies. ICH-S6 Expert Working Group suggested that the maximum dose of a biopharmaceutical could be about 5 times higher than the intended maxi-
Points to consider for non-clinical safety assessment of biopharmaceuticals

The maximum clinical dose of the biopharmaceutical based on its AUC. Another thought is that the maximum dose may be taken as the dose in which the pharmacodynamic response has reached the plateau (pharmacodynamic maximum dose). There is generally no need to investigate biopharmaceuticals at doses much higher than the intended clinical dose, unlike CSC.

In cases of effects at higher doses of biopharmaceuticals, one must note the potential association of protein molecules as a result of the high protein concentration. The difference of the dosing formulation between associated molecules and monomers in biopharmaceuticals might affect the pharmacokinetics and pharmacodynamics. Some biopharmaceuticals are not absorbed from subcutaneous regions to the blood in associated form and can be absorbed only after being dissociated to a monomer or dimer.

**Toxicological effects and pharmacological action**

In many cases, only exaggerated pharmacological effects are observed in toxicology studies with biopharmaceuticals. Sometimes these effects are difficult to distinguish from compound-related toxicity. However, if the effect is related to mechanism (predictable) and reversible, it should not be considered as an adverse effect.

In the case that lethality is observed, it should still be prudent to assess whether the death is due to toxicity or an exaggerated pharmacological effect, considering the clinical application. For example, death due to hemorrhage is sometimes observed in healthy animals after administration of biopharmaceuticals with an anti-coagulative activity. In addition, death due to hypoglycemia can occur in healthy animals after administration of insulin. To attribute these death cases to toxicity has little value for determining human safety in clinical practice. Because these changes are observed only in healthy animals, and because biopharmaceuticals are prescribed for the normalization of abnormal functions in patients (e.g., hypercoagulability or hyperglycemia) through their pharmacological actions, one can easily assume that hemorrhage or hypoglycemia due to excessive expression of the pharmacological actions may occur.

**Safety pharmacological studies**

Safety pharmacological studies of biopharmaceuticals are performed as a separate study or incorporated in the design of toxicity studies in order to examine the effects on vital functions. Normally, follow-up or supplementary studies are performed to provide a greater depth of understanding than that provided by the "core battery" (central nervous system, circulatory system, and respiratory system) and renal system. In vitro electrophysiological studies are not applicable for biopharmaceuticals. Thus, because CSC acts on each cellular channel after passing through the cell membranes, while biopharmaceuticals are not expected to act in the same manner because they cannot pass through cell membranes. A part of or all of the safety pharmacological studies can be obviated in the case of biopharmaceuticals whose mechanism of actions is highly selective.

The safety pharmacological studies should be designed under the same considerations as the toxicity studies as regards selection of animal species, dose, and species specificity.

**ADME studies (absorption, distribution, metabolism and excretion)**

As stated in the guideline, it is difficult to establish uniform guidelines for ADME studies for the various types of biopharmaceuticals. ADME study should be designed on a case-by-case basis, with the following considerations:

The patterns of drug absorption may be influenced by formulation, concentration, administration site, and/or volume. ADME studies should, whenever possible, utilize preparations that are representative of those actually intended for toxicological studies and clinical use and employ a route of administration that is relevant to the anticipated clinical trials. In addition, an assessment of systemic exposure should be performed together with toxicity studies.

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, and to consider the stoichiometric radiolabeling, the loss of radiolabel, recycling of radiolabeled amino acid into non-drug related protein and aggravation of stability. However, biopharmaceuticals not meeting the satisfactory radiolabeling should inevitably be evaluated using unlabeled proteins in many cases. Degradation of protein to peptides and amino acid moieties is commonly expected as a representative metabolic pattern. Therefore, conventional biotransformation studies are not needed for biopharmaceuticals consisting of natural amino acid. However, metabolism studies of biopharmaceuticals containing non-natural amino acid may provide useful information. In such cases, radiolabeled proteins should be prepared in order to trace the pharmacokinetic behav-
ror of the non-natural amino acid fragments. When using $^{125}$I-labeled proteins in distribution studies, consideration should be given to the formation of inorganic iodine by deiodination in vivo. For example, free $^{125}$I thus produced is accumulated in the thyroid gland, and thereby the biopharmaceutical seems to be distributed mainly in the thyroid gland.

For biopharmaceuticals, particular attention should be paid to expression of neutralizing antibodies. However, neutralizing antibodies may appear as a result of not only repeated administration but also by single administration depending on the pharmacokinetic properties of the biopharmaceuticals, and therefore particular attention should be paid to the antibodies or to the PK.

**Single-dose toxicity studies**

An objective of single-dose studies is to define the relationship of dose to systemic and/or local toxicity. For biopharmaceuticals repeatedly administered clinically, the data from single-dose toxicity studies can be used to select doses for repeated-dose toxicity studies. For biopharmaceuticals with a weak toxicity, repeated-dose toxicity studies can be performed without conducting single-dose toxicity studies under the GLP condition, and therefore single-dose toxicity studies in two animal species is not considered to be as necessary for these biopharmaceuticals than it is for CSC.

When necessary, single-dose toxicity can be evaluated as a component of safety pharmacology or primary pharmacodynamic studies using animal models. When provided doses set for the repeated-dose toxicity study are reasonable, the initial administration data in the repeated-dose toxicity study can be used as data for single-dose toxicity.

Since biopharmaceuticals need not be examined at high doses such as the approximate lethal dose, conducting single-dose toxicity studies merely to obtain information on the potential of toxic substances, etc would be meaningless. Single-dose toxicity studies in non-rats should in general only be considered in cases where rodents are not considered a relevant species.

**Repeated-dose toxicity study**

The duration of repeated-dose toxicity studies should be based on the intended duration of clinical exposure and disease indication as follows:

1) In cases of biopharmaceuticals intended for short-term use ($e g \leq 7$ days) and/or acutely life-threatening diseases, repeated-dose toxicity studies up to two weeks have been considered adequate to support clinical studies as well as obtaining marketing authorization.

2) In the case those biopharmaceuticals are intended for chronic indications, studies of 6 months have generally been accepted as regulatory agreement, although in some cases shorter or longer durations have been adequate to support marketing authorizations. The duration of long-term toxicity studies should be scientifically justified.

3) In cases of biopharmaceuticals not covered by 1) or 2), the duration for animal dosing should be determined based on the intended clinical duration, i.e., generally 1-3 months.

Typically, toxicity studies are performed in two animal species. However, for toxicity studies where there is only one relevant animal species, the studies may be performed in a single animal species. When two animal species show the same toxicity profile in short-term studies, long-term studies may employ one animal species. Comparison of toxicity profiles means comparing the type and severity of any toxicity observed. However, biopharmaceuticals with a weak toxicity may display no toxicity at high doses in some cases. Therefore, even if no toxicity is observed in any animal species, the same toxicity profile can be determined based on the justified rationale for determining the maximum dose.

The basic concepts of inclusion of toxicokinetics and setting of recovery period are identical to the concepts for designing usual repeated-dose toxicity studies. For biopharmaceuticals that induce prolonged pharmacological/toxicological effects, recovery group animals should be monitored until reversibility is demonstrated. However, for mechanisms of change whose toxic action is clear and whose reversibility is predictable, recovery studies are not needed. Specifically, for biopharmaceuticals, alteration may be observed due to the excessive expression of pharmacological actions, therefore, the pharmacological assessment should be made for potential reversibility of the alteration observed. In addition, whether the alteration accompanies organic changes or not may be useful for assessing potential reversibility. When the mechanism of the toxic effect is unknown or a unique mechanism obviously different from the pharmacological actions is involved, recovery studies should be performed.

Particular attention should be paid to appearance of neutralizing antibodies, but the detection of neutralizing antibodies should not be the sole criterion for early termination, or not conducting studies. In some
cases, useful studies can be achieved by prudently performing them. The early termination of studies should be considered when pharmacological actions are masked and no biological response is observed due to the occurrence of unexpected adverse toxicity attributable to antibody formation or marked decrease in plasma concentrations of test materials during the study period. When the results from short-term studies or preliminary studies suggest the potential of any such situation in longer-term repeated dose toxicity studies, to conduct longer-term studies should prudently be considered for assuring the significance of safety evaluation.

Antigenicity and immunotoxicity studies

These are important assessment because the objective of antigenicity studies is the prediction of anaphylactic shock. For biopharmaceuticals, however, there are no appropriate animal models that are considered to be predictive of human allergic responses. Although technical progress would be achieved in the future, antigenicity should be evaluated carefully in clinical practice at present.

Many biopharmaceuticals are intended to either stimulate or suppress the immune system of the host. When biopharmaceuticals with no expected immunopharmacological action affect the immune system, immunotoxicity studies should be performed. However, standard immunotoxicity assessments as currently being discussed for CSCs are not appropriate. In such cases, repeated-dose toxicity studies in relevant animal species may clarify the effects on the immune system.

Reproductive and developmental toxicity studies

Reproductive and developmental toxicity studies are needed when 1) relevant animal species exist, 2) application for pregnant or women of childbearing potential (WOCBP) is intended, and 3) natural biopharmaceuticals do not exist or structurally differ from the biopharmaceuticals.

When standard reproductive and developmental toxicity studies are unfeasible due to neutralizing antibody formation, etc., although it is deemed necessary, the study design and dosing schedule may be modified based on issues related to species specificity, antigenicity, biological activity and/or a long elimination half-life. For example, a reproductive and developmental toxicity study with shorter periodic dosing than the whole period dosing shown in the toxicology guideline for CSC can be meaningful. In addition, alternative studies using relevant transgenic animals, or homologous proteins, should be considered. However, as reproductive performance in transgenic animals has not yet been clarified, careful selection is therefore needed for the study system.

The need for reproductive and developmental toxicity studies is dependent upon the clinical indication and intended patient population. For example, when 1) no relevant animal species exist and the biopharmaceutical is not indicated for pregnant or WOCBP, 2) structurally comparable to a natural biopharmaceutical for which there is wide experience in clinical practice and 3) the biopharmaceutical is indicated for patients without childbearing potential and indicated for those with serious diseases, reproductive and developmental toxicity studies can be obviated.

Points to consider on the need for assessment of reproduction toxicity of human insulin analogues have been published (CPMP, 2002).

Genotoxicity studies

This is generally not applicable for biopharmaceuticals to routinely implement the genotoxicity studies required for CSC. Proteins and peptides are not expected to interact directly with DNA or other chromosomal material by passing through the cell membrane. On the other hand, as the guideline describes “With some biopharmaceuticals there is a potential concern about accumulation of spontaneously mutated cells (e.g., via selectively facilitating a predominating factor of proliferation) leading to carcinogenicity, alternative in vivo or in vitro models to address such concerns may have to be developed and evaluated.” When in vitro or in vivo data suggest the potential biopharmaceuticals’ ability to strongly stimulate cell proliferation, conducting carcinogenicity studies should be considered. In the case of human-type proteins or peptides, it would be helpful for assessing the necessity of further studies to compare the physiological concentration of the biopharmaceutical in blood or tissue with the concentration at which the enhancement activity of the biopharmaceutical on cell proliferation is observed. Human protein analogs should be evaluated for potential difference in activity from human protein.

Genotoxicity studies should be performed for biopharmaceuticals with bioconjugates having an organic linker molecule or biopharmaceuticals with non-natural amino acid. The need for genotoxicity studies depends on whether a biopharmaceutical is a natural human protein or an analog such as a bioconjugate. Genotoxicity studies are not needed for natural
proteins, because it is not expected that they would interact directly with DNA or other chromosomal material after passing through the membrane and then just degraded into natural amino acid. In the case of analogs, it may be necessary to assess their genotoxicity under metabolic activation conditions, since there might be a possibility that unknown compounds can potentially be formed. However, genotoxicity studies can be obviated even for analogs by demonstrating no penetration into cells using radiolabeled materials.

Carcinogenicity studies
The guideline requires flexible approaches to evaluate the carcinogenic risk of biopharmaceuticals under the description that “Standard carcinogenicity studies are generally inappropriate for biopharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.) When there is a concern about carcinogenic potential, a variety of approaches should be considered to evaluate the risk.”

If the following are confirmed, generally, carcinogenicity studies are not necessary even when a biopharmaceutical is used for a long period of time:
1) It is used for substitution therapies at the physiological level
2) It has no physiological activity differing from that of endogenous substances
3) Its biological action is not significantly stronger than that of endogenous substances
4) It has no potential to induce tumor cell division (in case of growth promoter)
5) It neither locally retains nor accumulates at a high concentration for a long period of time
6) It does not have sustained pharmacological action
7) In repeated-dose toxicity studies when a dosing duration adequate for evaluation is attained, no preneoplastic lesions are observed
8) The results of genotoxicity studies were negative in the case that the studies had been conducted (e.g., bioconjugate with organ linker).

Conducting carcinogenicity studies should be considered in some cases due to the dosing duration, relationship of target diseases with cancer, biological activity of a product, presence or absence of immunosuppressive action, in vitro data, etc. In those cases where the product is biologically active and non-immunogenic in rodents and other studies have not provided sufficient information to allow an assessment of carcinogenic potential, then the utility of a single rodent species should be considered. Careful consideration should be given to the selection of doses. The use of a combination of pharmacokinetic and pharmacodynamic endpoints with consideration of comparative receptor characteristics and intended human exposures represents the most scientifically based approach for defining the appropriate doses. The rationale for the selection of doses should be provided.

Points to consider on the non-clinical assessment of the carcinogenic potential of insulin analogues have been published (CPMP, 2001)

Local tolerance studies
Local tolerance should be evaluated using the dosage form to be clinically used or similar dosage form if appropriate. As described in the guideline, local tolerance does not mean eye- or skin-irritation safety studies for personnel engaged in manufacturing of CSC. It means there is irritable response at the injection site. 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.

ACKNOWLEDGMENT

Authors very much acknowledge useful comments on the “points to consider” document from Drs. Joy A Cavagnaro, Jim Green, Mary Ellen Cosenza, Jay Stoudemire, Corine Klingbeil, Dale Johnson and Jan Willem van der Laan.

REFERENCES