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The Impact of Preclinical Planning and Study Outcome on the Risk Management of Biologicals

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Introduction

Background

This chapter discusses how early preclinical assessment of potential toxicology liabilities, combined with exploratory toxicology evaluations, can benefit the final toxicology assessment for a candidate biotherapeutic molecule. This early effort at hazard identification can facilitate the following steps of risk assessment and risk management. Rather than choosing a minimal set of standard toxicology studies that may meet the regulatory review requirements, sponsors and patients alike are better served by a drug development plan incorporating information obtained from exploratory toxicology investigations. Exploratory, or early discovery toxicology as it also may be called, generally involves mechanistic or hypothesis-driven studies during the lead optimization or drug-selection phase. In other cases, it simply means characterizing drug effects on receptors, pathways, and potential target organs at exposures that tend to be higher than those typically used in animal models seeking to demonstrate efficacy. But by taking either approach, the design of standard toxicology studies can be customized based on the findings and interpretations derived from actual pilot data, including drug-related pharmacology and pharmacokinetics, with the candidate molecule itself.

The topic of exploratory toxicology and where it fits into drug development schemes is the subject of several reviews.[1–5] This chapter highlights how the melding of early toxicity studies with the pharmacology-profiling phase of drug development provides a strong scientific base for dose selection and specific study design considerations during preclinical development. An overall driver for implementing this approach is to facilitate the preclinical to clinical transition by identifying potential toxicology liabilities as early as possible, then mitigating these through the inclusion of toxicology studies that have been optimally designed to address these concerns.

Using Discovery Pharmacology and Exploratory Toxicology for Risk Minimization

Discovery in pharmaceutical development involves the selection of the best candidate drug molecule. This endeavor relies on the evaluation of preclinical pharmacokinetics and dose-response pharmacology endpoints in animals to choose the molecule with the best efficacy,

specificity, and pharmaceutical properties. Traditionally, relatively low doses are used at this phase, with the singular focus being on profiling the molecule's primary pharmacological effects. Exploratory toxicology, on the other hand, refers to the practice of using an expanded dose range of a candidate molecule in studies to look for potential target organ toxicities during the lead optimization and discovery phases of development. Typically limited to acute or single-dose exposure, the studies are intended to identify any overt on- or off-target toxicities in relevant animal species. The information then is used to justify species selection, and to aid in dose setting, inclusion of appropriate endpoints, and analyses for subsequent preclinical toxicity studies. Many sponsors today combine both aspects of pharmacological profiling and exploratory toxicology during the drug-discovery phase due to the cost, both in time and money, of unexpected or unmanageable toxicity. What advantages are realized by executing an exploratory toxicology strategy? Foremost is the identification of liabilities for the biotherapeutic before making large resource and time commitments. Much information can be obtained in the exploratory phase of development with experiments using minimal animal numbers and are specifically designed to identify toxicity liabilities. Once determined, a judgment can be made whether the toxicity can be monitored and/or managed. A decision also can be made to attempt preclinical experiments at this phase that may clarify hypothetical liabilities or perhaps explore using toxicity biomarkers. The information then is evaluated considering what is known about the mechanism of drug action, what preclinical and clinical pharmacology or safety data are already available, and whether there are pharmaceutical precedents (class effects) known for similar therapeutic molecules. For a new biotherapeutic molecule, the conclusions reached about the preceding can be documented in a summary fashion in an early toxicology liability assessment (ETLA) with the information organized by headings as suggested in **Table 6-1**.

The ETLA document itself becomes a component of the formalized drug project plan and a record for the development team on the early decision and planning process for the drug candidate. In addition to identifying toxicology liabilities, other relevant information can be captured, including:

- Reasons for dose and species selection for GLP toxicology studies that will support first-in-human (FIH) dosing,
- Explanation of the drug candidate's mechanism of action that also may lead to the identification of clinically useful biomarkers, and
- Supporting data and criteria for selection of the drug candidate based perhaps on early screening of multiple molecules.

As aptly stated by JL Stevens[6] regarding the implementation of exploratory toxicology:

Table 6-1. Summary Elements of an ETLA

Target	Drug name, therapeutic indication, description of the target, and mechanism
On Target Risks	Listing and brief explanation of potential target related toxicities
Off Target Risks	Listing and brief explanation of potential off target toxicities related to secondary pharmacology
Previous Target Experience	Drug class information, clinical trial experience, and competitive intelligence
Summary	Overview of the intended mechanism of action of the drug molecule and the potential liabilities or adverse effects gleaned from the toxicology assessment
Recommendations	Toxicologist's recommendations on specific studies or concerns to be addressed during preclinical development and on a possible risk mitigation strategy
Timeline	Stage in development at which major liabilities should be addressed
Impact	Risk to program development if potential toxicology issues are not mitigated

"Proactive safety assessment at this stage is largely an *in cerebro* and/or *in silico* exercise. Safety issues inherent in modulating a target can be anticipated from existing drug precedent; for example, agonists for peroxisome proliferator-activator receptors (PPAR) might be anticipated to be tumorigenic, increase heart weight, and produce plasma-volume expansion in preclinical studies. For novel targets, safety concerns must be inferred from literature on genetic studies in humans and lower organisms, or by mining pathways involved in a disease process."

An example of an ETLA summary for a hypothetical GLP-1 analog is provided as **Appendix 6-1.**

Safety Pharmacology and Exploratory Toxicology

An ETLA also complements the required regulatory safety pharmacology assessments. These latter studies are conducted per the International Conference on Harmonisation (ICH) S7A guideline[7] and consist of a base set of studies designed to characterize drug effects on the cardiovascular, respiratory, and central nervous system. The overall purpose is to investigate a new drug candidate's potential undesirable pharmacological effects on critical organ system functions.[8–10] However, the guideline indicates flexibility in the design of such studies and suggests supplemental studies on different organ systems may be required (such as renal, GI, immune, and autonomic nervous system). A recently published Q&A from the E14 and S7A guidelines provides more detailed discussion on the use of nonclinical data to address risk for QTc prolongation.[11] This may be particularly important for biotherapeutics, since most of these entities have been exempted from routine safety pharmacology testing. On the other hand, most biotherapeutics have pharmacology that is highly specific for a particular system, such as the immune system. Several novel bio-immunotherapeutics have been developed for the treatment of autoimmune disorders, such as asthma, rheumatoid arthritis, psoriasis, and others. Many of these agents produce no toxicity and often no pharmacological effects in normal or diseased animals in preclinical studies. In the latter case, conducting directed preclinical experiments in normal animals or in animal disease models specific for the drug's indication, for the purpose of identifying potential pharmacology biomarkers, would seem appropriate. Identifying such markers offers significant advantages in the drug's clinical development if such markers can be monitored clinically. These studies can be conducted either separately in early discovery, or they can be conducted in the context of a safety pharmacology paradigm where both pharmacological and toxicological exposures are characterized.

Combining a safety pharmacology approach with the pharmacology-profiling phase offers a chance to clarify hypothetical liabilities identified during the ETLA. If done with forethought, these investigations can contribute to defining, in relation to pharmacology and toxicology, a dose-response effect, time-course of action, dose for maximum effect, metabolism, and pharmacokinetics, biomarkers of pharmacology and/or toxicology, and identification of safety issues. At the least, such information adds to a more complete mechanistic understanding of a drug's overall action that is important, especially in early development, before experience is gained with the drug in the actual clinical setting. Further, high-dose pharmacological profiling may disclose unintended effects that are a direct result of drug-receptor interactions, or via nonselective or off-target effects. Understanding whether unintended toxicity is related to the mechanism of action is essential in clinical safety interpretation.[12] Ideally, these studies would be done prior to planning the standard toxicology screening studies to aid in defining the maximum tolerated dose.

Designing Risk-Mitigating GLP Toxicology Studies

The overarching reasons for conducting preclinical toxicology studies are because they are required by regulation and because of the need to define the initial FIH dose selection. But rather than using a template approach, there is an opportunity to design these screening studies in a manner providing support for clinical trials in the way of biomarker characterization and

information for risk mitigation purposes through additional target organ function analyses or pathology characterization to address anticipated toxicities. The dose range, as well as the number of dose groups, should anticipate a pharmacological or no observable adverse effect level (NOAEL), as well as a maximum feasible dose for a biotherapeutic drug candidate. In some cases, it may be strategically advantageous to include four or five dose groups rather than the standard three dose levels, especially when it is important to have a NOAEL or no observed effect level (NOEL), and the *in vivo* pharmacology data in the toxicology species are lacking or weak. This must be balanced by consideration of the principles of 3Rs—replacement, reduction, and refinement—which may limit the number of animals that can be used. Another case may be one in which a drug has biphasic or dual activity depending on the dose (e.g., target potentiation at high doses and suppression at low doses). At the very least, the dosing paradigm should be based on the candidate's absorption, distribution, metabolism and excretion (ADME) properties and the intended therapeutic application in the clinic.

The design of the preclinical GLP toxicology studies ideally would take advantage of the ETLA information and the early pharmacology profiling. If, for example, the literature or early evidence indicates particular organ toxicity, parameters that assess effects on this system certainly should be included in the study design, even if it means adding so-called nonstandard endpoints, such as humoral immunity parameters in the case of a suspected immunomodulator.

In general, the GLP preclinical testing phase also should be viewed as a risk management tool. Being able to write a convincing interpretation of the safety implications around a liability for an investigational new drug (IND) application requires having pertinent preclinical data addressing an anticipated liability. Reviewers and clinicians generally are more open to safety arguments supported by data than those with speculative declarations about a preclinical finding's relevance to clinical safety. Similarly, demonstrating the utility of a potential pharmacodynamic or toxicity biomarker in the GLP setting sometimes can be a deciding factor for taking the drug into human studies.

Several aspects of preclinical study design stand out above others because they are often the pivot points or deciding factors in a successful IND submission. These include proving relevant pharmacology (animal models and study design), using characterized test material at maximum dosing levels, and employing studies of sufficient duration (with adequate exposure).[13] For instance, clinical studies in the area of obesity treatments often need longer treatment timeframes (e.g., six weeks) to provide convincing evidence of efficacy. Incorrectly addressing these study elements can lead to project timeline delays and to the need to repeat studies.

Study Design and Species Selection

For biopharmaceuticals, the toxicology plan must be tailored to match the drug candidate's pharmacology and species specificity more than is the case with small molecule standard toxicology plans. A key point of emphasis in the original ICH S6 guidance, Preclinical safety evaluation of biotechnology-derived pharmaceuticals, is the design of appropriate toxicology studies and the use of a relevant animal model; a species that is pharmacologically responsive to the intended human drug. However, because biopharmaceuticals have unique attributes and mechanisms of action, choosing the most appropriate animal model for toxicology testing requires a case-by-case approach. The ICH S6 guidance section on species selection reinforces the notion that two species are needed, but in the case where there is only one relevant pharmacologically active model, there is no need to create a transgenic species or use a homologous molecule just to achieve that goal.[14] However, because the decision about whether one animal species is sufficient for the preclinical GLP studies is based mostly on experience and scientific judgment of the candidate biotherapeutic's mechanism of action, there is usually some degree of sponsor trepidation about whether regulatory authorities will concur with this judgment prior to submission of the IND. This is especially true when there are potentially viable alternatives for preclinical testing, such as the use of surrogate

animal models or when a drug homolog could be substituted. Fortunately, a good resource is available that reviews recommendations for species selection and the rationale for adopting different alternative approaches in situations where a conventional toxicology-screening model will not suffice for a candidate biotherapeutic's safety assessment.[15] If there are persistent uncertainties, a meeting with regulators to request guidance on the proposed submission package may be warranted. Designing studies for reproductive/developmental risk can be a challenging task, as the guidelines are flexible around species choice and design alternatives. The original ICH S6 guidance did not provide specific direction on which test species was acceptable, on study design or on the number of animals per dose group. The ICH S6 addendum incorporated recently into the main guidance[14] recommends developmental toxicity studies should not be conducted in non-human primates unless they are the only relevant species. Regulators prefer testing the clinical candidate (in nonhuman primates if that is the only relevant model), but alternatives to the drug molecule can be considered if scientifically justified.

The addendum further says if the mechanism of action, class effects, or information on genetic mutants indicates an adverse effect on fertility or pregnancy outcome, it may be sufficient to communicate the potential developmental or reproductive risk without further preclinical studies.

For monoclonal antibody drug candidates active only in nonhuman primates, it is recommended that combined embryo-fetal postpartum developmental (EFPPD) studies be considered rather than separate embryo-fetal and perinatal/postnatal toxicity studies. It is further recommended the dosing interval cover gestation days (GD) 20–100 (rather than GD 20–50) because of the prolonged circulating half-lives of most intact human monoclonal antibodies in primates. For fertility testing, a standalone nonhuman primate study is not necessary, but there should be an assessment of reproductive organs in standard toxicity studies with the candidate biological. If there are special concerns, parameters should be added to provide more detail such as gonad weights, sperm viability/motility, and reproductive hormones. Sponsors should realize regulators recognize these studies are for hazard identification rather than true risk assessment due to the relatively low number of study animals assigned to each treatment or dose group.

Dose Levels and Duration

One of the most important aspects of preclinical study design is the choice of dose levels. Much consideration is given to selecting treatment doses that will yield the maximum pharmacological effect or provide a tenfold exposure multiple over the maximum estimated exposure in the clinic, as well as a pharmacologically active dose. Again, the more extensive the early pharmacological profiling studies have been in terms of pharmacokinetic or ADME characterization, the greater the confidence level for projecting initial GLP toxicity study dose levels. Factors that strongly influence the dose range selected for a preclinical study include the study duration, gender differences and inherent ADME properties, including those that are species-specific. For example, the drug's *in vivo* Cmax and its halflife are properties determining the dose frequency and the potential toxicity profile in the study. For many biologicals, the clearance of the drug is dependent on receptor-binding mechanisms rather than kidney filtration mechanisms. If a justification is provided, the maximum dose can be predicated on data calculations showing that if all the receptors are occupied at a given dose, increasing the dose beyond this maximum level is not informative, according to the ICH S6 guideline addendum.[14] For chronic preclinical toxicology studies, six months is considered a sufficient length of time to evaluate the hazards associated with chronic, repeat dosing. The addendum to the ICH S6 guidance recommends an evaluation of recovery (from toxicity) be included with a statement that recovery is not intended to detect delayed toxicity. This topic presumably refers to the characteristically long circulating halflives of many monoclonal antibodies, which may take six to nine months to clear completely from an animal given the very high doses administered. Operationally, this referral to delayed toxicity in the guidance

provides for the design of shorter recoveries (less than 5.5 halflives) where evidence of physiologic recovery is sufficient rather than demonstration of complete recovery. However, even with a shorter recovery period, there still may be cases where there is evidence of "delayed" toxicity since pharmacological levels of the monoclonal antibody have not receded sufficiently to allow for a rest period from drug activity. Parenthetically, some confusion may be avoided by referring to a "washout period" rather than a "recovery period" when dealing with monoclonal antibodies in preclinical studies.

For preclinical evaluations, the value of immunogenicity data is primarily as an interpretive aid for judging the toxicology study's validity. That is, did neutralizing anti-drug antibodies develop in any of the treatment groups that resulted in altering the pharmacokinetics or pharmacodynamics of the test article? If the answer is "No," and there is no immune system-related toxicity, then it is not necessary to conduct a preclinical immunogenicity assay. Strategically, because the decision occurs after all the data are available poststudy, it is highly advisable to have a validated immunogenicity assay in place prior to beginning toxicity studies. In addition, it is also a best practice to also bank frozen serum from individual animals before and after treatment in the event immunogenicity testing is necessary.[13]

Integrating the Preclinical Data Analysis with Risk Management Tools (Guidelines)

One of the main goals of drug candidate preclinical testing is to provide a basis for determining a safe starting dose for FIH studies. Two guidelines most relevant to this are the European Medicines Agency's (EMA) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products[16] and the US Food and Drug Administration's (FDA) Guidance for Industry—Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.[17] Both documents provide advice on how to take preclinical safety information that may have identified potential safety concerns and apply it to the design and conduct of human clinical trials, beginning with the estimation of the initial dose. Some of the factors to be considered for biotherapeutics are reviewed below.

EMA Guideline on Requirements for First-in-Man Clinical Trials with Investigational Drugs

This regulatory document is intended to assist sponsors in the transition from preclinical safety development to early clinical development, in part by determining certain risk factors for categorizing the candidate drug's relative risk, such as being potentially high or low risk prior to administration to humans. There are three main risk factor categories:

1. Mode of action
2. Nature of the target
3. Relevance of animal species and models

The mode of action category addresses the concern about investigational drugs that may have a novel mechanism of action with the potential to produce severe adverse reactions. Such was the case with the Tegenero clinical trial,[18] where a cytokine storm was triggered after subjects received an initial dose of a CD28 agonist. An example of a drug with potentially low risk might be a monoclonal antibody that is highly specific for a single cellular target (such as a tumor antigen). On the other hand, if the *in vivo* activity of that same monoclonal antibody induces massive cytokine release due to tumor cell lysis, this may increase the risk category.

The above example also applies to the second risk factor category, the nature of the target, or the downstream physiological effects occurring as a result of drug/target interactions. This is where the quality of the preclinical study information proves its value. Do the data provide information on the target specificity, drug distribution, biomarkers, and pharmacology? How do disease and individual human variability affect these factors? Is there any human experience with similar drugs or disease targets? It stands to reason the more comprehensive the preclinical safety studies,

the better the discussion of this information's relevance in relation to overall human risk-assessment predictions.

The strength of the rationale regarding mechanism of action and target interactions rests primarily on the principle that relevant animal species and models were used to obtain this information. Simply put, a relevant model is one that is pharmacologically responsive to the investigational drug.

However, no single animal model fully simulates or reproduces the human condition. It also should be obvious the quality or sagacity of preclinical data interpretation is an important component of judging the adequacy or relevance of the animal studies performed with the drug. As seen in the retrospective analysis of Tegenero, it was not that the cynomolgus monkey was an inappropriate test species so much as there was a lack of prior knowledge about the differences in CD28 immunobiology between humans and nonhuman primates combined with misinterpretation of the significance of the safety signals from those studies.[18] It is very important sponsors document and justify in detail the steps taken or the rationale used to justify the species selection prior to conducting the preclinical studies and provide a discussion of how the preclinical data (e.g., pharmacology, target toxicity) did or did not support the decision.

Important for supporting that rationale are data obtained from pharmacology studies in the relevant animal model together with pharmacokinetic and toxicokinetic evaluations. Without a dose-response curve or knowledge of the relationship of plasma levels with pharmacological and toxicological endpoints, it is essentially impossible to have a defensible dose justification for FIH.

FDA Guidance for Industry—Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

This separate guidance also aids in transitioning from the preclinical phase to the clinical, but with an emphasis on applying preclinical study data to the selection of a safe starting dose for FIH dosing. There are many reviews covering multiple aspects of dose selection for FIH trials.[19–23] Fundamental to all dose selection strategies is the reliance on preclinical toxicity data in the context of adequate ADME characterization. Again, the obvious theme in each review is the more comprehensive the preclinical data, the more confidence there can be in dose projections.

"The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose of a new therapeutic in healthy (or asymptomatic) human volunteers."

"As a general rule, an adverse effect observed in nonclinical toxicology studies used to define a NOAEL for the purpose of dose-setting should be based on an effect that would be unacceptable if produced by the initial dose of a therapeutic in a Phase 1 clinical trial conducted in adult healthy volunteers."[24]

Traditionally, the starting dose for an FIH study is derived from calculations, or dose extrapolations, based on the NOAEL determined in the most sensitive animal species in toxicology studies. In general, this has worked well for small molecule, chemical drug entities, provided the appropriate allowances for species differences in ADME characteristics (e.g., metabolism, drug distribution) are factored into the equations prior to administering the agent to humans. However, for biologicals, the biotherapeutic often has no pharmacologic activity or toxicity in the normal animal models used in preclinical testing, even when relatively large amounts of drug are repeatedly administered in these studies. Other preclinical data available then must be considered, such as the mechanism of action, binding affinity, and projected similarities in pharmacokinetics between the models and humans. In other words, it is necessary to rely on preclinical pharmacokinetic data, which may be available only from discovery studies that used a disease animal model. A large portion of the 2005 FDA guidance for estimating the maximum safe starting dose[17] addresses this situation, which obviously aims to avoid another Tegenero-type

incident with an FIH biotherapeutic. Generally, the default safety factor for a starting dose is determined by dividing the human equivalent dose derived from the animal NOAEL by a factor of 10.[17] But the guidance warns this may not be acceptable, and a larger factor is warranted where higher risk is perceived, such as with those variables listed in **Table 6-2.** The starting dose for a biotherapeutic candidate, in many cases, is based on the pharmacologically active dose rather than on toxicity (NOAEL). This dose may be significantly lower than the calculated maximum recommended safe dose (MRSD), especially when a safety factor is then applied to the pharmacologically active dose. A pertinent example is the administration of drugs that target T lymphocytes, which could potentially trigger a cytokine storm in a host at pharmacological doses. Applying a safety factor to the pharmacologically active dose calculation is similar to the minimum-anticipated-biological-effect-level (MABEL) approach detailed in the EMA guideline.[17] Hence, it is important to perform a comprehensive preclinical pharmacology characterization to optimally position the dose justification for the sponsor's IND application and subsequent FIH trial.

End Result: Addressing Safety Issues in All Components of the Preclinical Safety Package

The goal of preclinical testing strategies is to minimize any potential risks to humans to whom a new pharmaceutical substance will be administered. Preclinical testing refers to the entire safety risk assessment process. As stated by Olejniczak and Gunzel:

"Thus, preclinical studies constitute a program whose results are to offer as much safety as possible during every phase of use in humans. ...Moreover, this program is not a sequence of certain tests which could be regarded or carried out in isolation but is rather intertwined into the development process of medicinal products."[26]

It is also important for biotherapeutics to include the different manufacturing components as part of the preclinical package, such as characterization of the production cell substrate, raw materials, impurities, and final active pharmaceutical ingredients.[27] The emphasis in an initial Phase 1 chemistry, manufacturing, and controls (CMC) submission generally should be placed on providing information that will allow evaluation of subject safety in the proposed study. A project can be placed on clinical hold if the formulation has unknown or impure components or suboptimal characterization of the impurity profile and potential health hazards that can be avoided by well-executed preclinical toxicology studies.

Briefly, the primary categories (also reviewed in Reference 21) that need to be addressed in preclinical studies for a successful regulatory submission are:

Scientific Review and Early Risk Assessment

- Comprehensive review of scientific literature and databases
- Initial determination of toxicology and safety liabilities
- Development of preclinical strategy and a risk mitigation plan

Table 6-2. Factors Affecting the Safety Margin Calculations for FIH

Steep dose-response curve	Unexplained mortality
Severe toxicities	Large variability
Non-monitorable toxicity	Nonlinear pharmacokinetics
Toxicities without premonitory signs	Inadequate dose-response data
Variable bioavailability	Novel therapeutic targets
Irreversible toxicity	Animal models with limited utility

Chemistry, Manufacturing, and Controls

- Description of manufacturing process
- List of reagents, solvents, and catalysts
- For biotech drugs, relevant information on animal/human sources of reagents
- Specification or proposed acceptance criteria and certificate of analysis
- Stability, including stability study summary and analytical procedures

Pharmacology

- Identification of relevant animal models, preferably two species
- Mechanism of action
- Receptor binding characterization and occupancy level
- *In vivo* target dose-response relationships in
- Normal and disease model
- Absorption, distribution, metabolism excretion, and duration of pharmacologic activity

Safety Pharmacology

- "Exaggerated pharmacology" effects on the drug target
- Unintended or off-target effects
- Identification of most sensitive animal species
- Characterization of drug effects on major organ system functions

Toxicology

- One, three-, or six-month repeat dose toxicology studies
- Genetic toxicology studies
- Reproductive toxicology studies
- Toxicokinetic evaluations
- Two species (unless justification for only one or alternatives)
- GLP tissue cross-reactivity characterization (antibody therapeutics)

Interpretation and Final Risk Assessment

- Analysis and integration of all relevant pharmacology, pharmacokinetics and toxicology data
- Risk determination
  - Seriousness of potential adverse effects
  - Calculation of safety factor
  - Calculation of first human dose
    - Based on no adverse effect level NOAEL (or highest NOEL)
    - Based on minimum anticipated biological effect level (MABEL)
    - Based on pharmacologically active dose (PAD)

Table 6-3. Hypothetical Risk Management Strategy for GLP-1 Agonist Biotherapeutics

Target Organs	Potential Risks Preclinical	Risk Management Plan
GI	Dose-dependent nausea and vomiting are common at the initiation of GLP-1 agonist therapy	Decrease the dose of the GLP-1 agonist and titrate slowly as tolerated
Hematopoietic	Decreases in erythrocyte counts, hemoglobin, platelets; increased reticulocytes	Monitor standard hematological parameters
Liver	Increases in AST, ALT	Monitor liver function
Heart	GLP-1 receptor agonists have the potential to influence traditional cardiovascular risk factors and cardiac physiology	monitor cardiac function
Kidney	Changes in urine osmolality and increased blood creatinine and urea nitrogen	Monitor standard blood chemistry and urinalysis
Pancreas	Pancreatitis	Monitor for symptoms of pancreatitis and evaluate if necessary; serum amylase or lipase levels should be evaluated and abdominal imaging if required
Thyroid	C-cell hyperplasia, adenoma	Monitor calcitonin serum levels
Immunogenicity	Anti-drug antibodies that cross-react with endogenous GLP-1	Monitor anti-drug antibodies and, if present, characterize for neutralizing of GLP activity

Conclusion

The safety-monitoring process for a novel drug begins in the preclinical phase before the first human dose is administered. The data produced in this process are used to support the safety-related conclusions put forward in the investigator's brochure, informed consent document, clinical trial protocols, and other regulatory submission documents, such as the IND application and the new drug application. The overall goal is to have strategies in place for managing any identified toxicology risks and to estimate a safe starting dose and dose escalation plan for the FIH clinical trial. Taking an example from the previously discussed hypothetical GLP-1 analog drug candidate where the ETLA identified several potential toxicology liabilities (**Appendix 6-1**), the ensuing preclinical studies validated these concerns and identified new issues, including the potential for thyroid C-cell carcinoma, for which a risk management or minimization strategy was formulated to enable the IND application and the FIH study (**Table 6-3**). Therefore, a thoughtful and purposeful preclinical safety assessment provides a foundation for an integrative interpretation of all relevant information to establish a safe starting dose and minimize the potential for adverse clinical events during subsequent clinical trials.

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Appendix 6-1

Example and Case Study: Early Toxicology Assessment for a Hypothetical Novel Glucagon-like Peptide-1 Analog

Target Description/Indication/Mechanism
Molecule—Glucagon-like peptide-1 (GLP-1) is a single molecule, 30-amino acid peptide that binds with activity to either GIP or GLP-1 receptors. It is secreted from gut endocrine L-cells in a glucose-dependent manner.

Pharmacology—GLP-1 is an incretin in normal physiology and a potent stimulant of insulin synthesis and release and beta cell mass. It inhibits glucagon secretion, slows gastric emptying and has an anorectic effect. These actions lower blood glucose in both normal subjects and in patients with type 2 diabetes.

Known Issue—The side effects of GLP-1 receptor agonists mimic the pharmacology of native GLP-1. Intravenous or subcutaneous administration of GLP-1 causes nausea and vomiting in a dose-dependent manner; the doses above which GLP-1 causes GI side effects are higher than those needed to regulate blood glucose. May delay gastric emptying. May alter PK of drugs that require rapid GI absorption. Hypoglycemia caused by GLP-1 agonists is rare

Target Population—Type 2 diabetics not reaching goal with current GLP-1 agonist therapies.

Target Distribution: Ubiquitously Expressed

Receptor location	• Islets, stomach, small intestine, adipose tissue, adrenal cortex, lung, pituitary, heart, testis, bone, and brain
Islets	• Stimulates glucose-induced insulin secretion • Increase insulin gene transcription and biosynthesis • Induces beta cell neogenesis, proliferation, differentiation
Adipose tissue	• Stimulates lipoprotein lipase • Stimulates lipogenesis • Increases fatty acid and glucose uptake • Enhances insulin-dependent FAA incorporation • Inhibits glucagon- and adrenergic receptor-stimulated lipolysis
CNS	• Induces proliferation of hippocampal progenitor cells • Stimulates sensorimotor coordination • Increases memory recognition

Toxicity Associated With Target
Effects in genetically modified mice. Knockout Mice—Single incretin (glucagon-like peptide-1, GLP-1) receptor knockout mice as well as double incretin (both GIP and GLP-1) receptor knockout mice exhibited reduced body weight gain and adipose tissue accretion after a 20-week high-fat diet. Over-expressing GLP-1 Transgenic Mice
Mice transgenically expressing a GLP-1 analog, exendin-4, exhibit comparatively similar glycemic responses (to wild-type mice) following treatment with GLP-1 analogs. Body weight and basal food intake were not significantly different from wild-type mice.

Dipeptidyl Peptidase-4 (DPP4) Inhibition Causes Elevated Level of GLP-1—Inhibition of DPP4 has been shown to raise circulating active incretin levels (GIP and GLP-1). Apart from its glucose-dependent manner of stimulating insulin secretion, GLP-1 (analogues and GIP) has been demonstrated to stimulate pancreatic beta-cell growth, differentiation, proliferation and survival. Similarly, studies in both humans and in animal models have established DPP4 inhibition results in an enhancement of glucose tolerance, insulin sensitivity and beta-cell glucose responsiveness.

Other Effects
Cardiovascular—Physiological changes in the levels of glucose, insulin, GLP-1 and ghrelin may influence the activity of the heart and the blood pressure.

Adipocytes—Potential changes in fatty acid metabolism and increase in body fat.

Bone—Enhanced bone mass.

Gastrointestinal—Delayed gastric emptying.

Cancer—Pancreatic beta cell proliferation, hyperplasia and adenomas of thyroid C-cells.

Reproductive—Glucose regulation important for organogenesis and development.

Literature References (Abridged)

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Previous Experience

Extensive literature reports on the clinical use of GLPs including with Exenatide, Exendin-4 and liraglutide

Early Toxicity Liabilities Assessment Summary

There is extensive preclinical and clinical information on safety signals for GLP-1, with nausea and weight loss being the most significant effects. The literature suggests that any side effects associated with this activity should be manageable and associated with glucose dynamics and fat metabolism.

Recommendations

Although information to date indicates that the side effects for GLP-1 are relatively mild, it must be kept in mind that the candidate GLP-1 co-agonist molecule is a novel protein that has the potential for unexpected pharmacology and/or toxicology profile. Therefore, although this molecule qualifies as a protein candidate, it would be appropriate for this program to plan for pilot toxicology studies to provide guidance for species and dose selection for IND enabling toxicology studies.

Timeline for Addressing Risks—Pre-Lead, Pilot Toxicity Studies, GLP Toxicity Studies, and in Clinic

Reproductive—Based on the target mechanism, it is likely that reproductive and developmental toxicity will be observed. This risk should be characterized appropriately during the development of a clinical candidate (i.e., during Phase 2 or beyond).

Autoimmunity/Immunogenicity—This should be characterized appropriately during preclinical development stages and all clinical trial phases. There will be a need to determine the potential for anti-drug antibodies that cross-react with their endogenous counterparts such as glucagon (i.e., autoimmunity). Immunogenicity assays should be in place prior to the start of preclinical safety studies.

Risks to Candidate Development—Low, Medium, High

Developmental /Reproductive Risk: Medium—see above Other Effects
Cancer Risk: Medium—see above Other Effects

7 Risk Management in Medical Devices and Artificial Intelligence

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Introduction

This Chapter 7 describes the International Organization for Standardization (ISO) standards for risk management for medical devices, ISO 14971:2019.[1] A historical overview is given on how the standard developed over time, to show its close relation with the European directives for medical devices and the latest revision of ISO 14971 with the European Medical Device Regulations. Because of this close relation the European context is described in this chapter. In other jurisdictions this integration of ISO 14971 is less precise and thus less critical. The relation to other standards like ISO 13485[2] is also explained, as well as its relationship with clinical evaluation and benefit-risk analysis, which is described in more detail in Chapters 11 and 15.

ISO 14971 provides a generic process for risk management of all kinds of medical devices, applicable to the entire lifecycle, from design and development through decommissioning and disposal. The standard is primarily aimed at medical device manufacturers, but it can also be used by other parties involved in the lifecycle of the device such as suppliers. It can also be applied to other products that are not necessarily considered to be medical devices in all jurisdictions, but can be subject to device regulations or similar regulations, such as the products without an intended medical purpose listed in Annex XVI of the EU Medical Device Regulation (MDR).[3]

Risk Management History in the Medical Device Industry

With the introduction of the European Active Implantable Medical Devices Directive 90/385/EEC (AIMDD),[4] medical devices directive (MDD)[5] risk analysis became an essential requirement. Risks needed to be reduced as far as possible while accounting for the general acknowledged state of the art and a high level of protection of health and safety. European standard EN 1441:1997[6] Medical devices—risk analysis was developed together with the European directives. EN 1441 provided a risk analysis method to investigate the safety of medical devices by identifying hazards and estimating risks based on available information. The standard was to be used in combination with the essential requirements of the directives.

EN 1441 was taken as a starting point for the development of ISO 14971-1[7] in 1998. ISO 14971-1 was intended to be the first in a series of standards about risk management. Plans changed and the first edition of ISO 14971 was developed