CREATE Bio Program:
A Roadmap from Concept through Preclinical Development and First-in-Human Trials
Developing Promising Protein and Peptide Therapies for CNS Disorders

National Institute of Neurological Disorders and Stroke

Rho Federal Systems Division, Inc.

created for the

National Institute of Neurological Disorders and Stroke (NINDS)
Division of Translational Research (DTR)

Cooperative Research to Enable and Advance Translational Enterprises for Biologics (CREATE Bio) Program

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Table 1: LIST OF ABBREVIATIONS

API	active pharmaceutical ingredient
BIO	Biotechnology Industry Organization
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CREATE Bio	Cooperative Research to Enable and Advance Translational Enterprises for Biologics
CRO	clinical research organization
CTM	clinical trial material
ECG	Electrocardiogram
eCTD	electronic Common Technical Document
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HED	human equivalent dose
HPLC	high-performance liquid chromatography
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IP	intellectual property
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PI	principal investigator
PK	Pharmacokinetics

SBIR	Small Business Innovation Research
TPP	target product profile

Table 2: Comparison of CREATE Bio Optimization and Development Track Activities

Activity	Optimization	Development	Section
Basic Research	No	No	5
Target Validation	No	No	5.1
Screening	Yes	No	5.1
Biological Agent or Lead Optimization	Yes	No	5.2
Preclinical Safety	Yes	Yes	5.3
Pre-IND Meeting	Yes	Yes	7
IND Submission	No	Yes	8
Phase 1 Clinical Trial	No	Yes	4.3.3
Phase 2 Clinical Trial	No	No	4.3.2
Phase 3 Clinical Trial	No	No	4.3.1

EXECUTIVE SUMMARY

The role of the National Institute of Neurological Disorders and Stroke (NINDS), Division of Translational Research (DTR), Cooperative Research to Enable and Advance Translational Enterprises for Biologics (CREATE Bio) program is to facilitate the acceleration of preclinical optimization and development of biological therapies for neurological disorders. Recent advances in technology point to the ability to deliver peptides, antibodies, and protein therapeutics across the blood-brain barrier in animal models. Despite these advances, most central nervous system (CNS) therapeutic targets are accessed by small molecule therapeutics. However, small molecules are limited in their ability to be selective, often affecting more than the desired target. Additionally, some diseases cannot be treated with small molecules. Thus, there is a need to develop biotechnology- and biologics-based therapeutics that target CNS disorders. As with any product or indication, a well-thought-out development program for a biologic targeting a CNS disorder needs to begin with the end in mind. The target product profile (TPP) is a living document that provides information on the indication, patient population, and desired safety, efficacy, and manufacturing properties of the therapeutic that will ultimately go into the Package Insert (Label) for the marketed therapeutic. The TPP provides the basis for planning an integrated development program, beginning with a clinical development program, then the nonclinical and manufacturing programs, to support the clinical program and ultimately marketing authorization. A team of expert scientists, regulatory affairs professionals, and consultants are needed to bring a therapeutic from concept through an Investigational New Drug application (IND). Communication between the disciplines (clinical, manufacturing, nonclinical, and also commercial input) is essential to designing a robust program that will lead to a successful IND and development program. As progress is made towards an IND, the product sponsor or investigator often requests a formal pre-IND meeting with the Food and Drug Administration (FDA). This formal meeting is beneficial when properly timed to address specific regulatory and scientific questions. When preparing the IND for submission, it is important to make reference specifically to any regulatory advice from the pre-IND meeting. A successful IND is only the beginning of the drug development process. Starting the drug discovery and development process on the right foot with a well-considered TPP, integrated development plan, and team ensures the best possibility for a successful translation from the bench to the clinic and ultimately to the market.

1. INTRODUCTION

The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS supports its mission by advancing biotechnology product- and biologics-based therapies including peptides, proteins, and monoclonal antibodies through the DTR CREATE Bio program. The program includes stage-appropriate funding opportunity tracks for both academic and Small Business Innovation Research (SBIR)-sponsored cooperative agreement projects. The Optimization Track supports optimization in order to obtain a candidate appropriate for entering the Development Track, and the Development Track supports preclinical IND-enabling studies for the candidate,

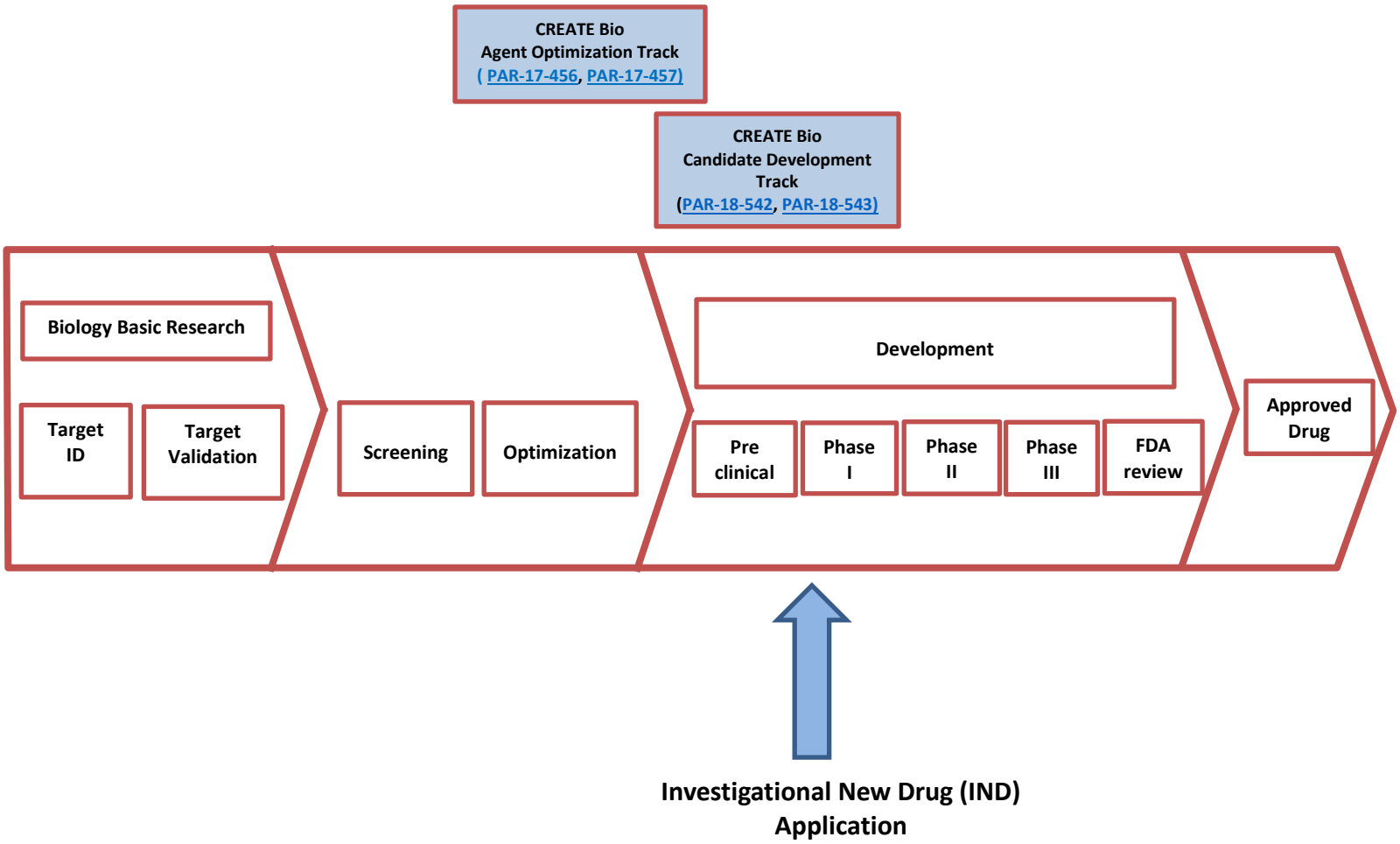
as well as early-phase clinical trials. NINDS also has contracts with consultants such as Rho Federal Systems Division, Inc. that work directly with NINDS program staff to better educate and inform investigators on how to advance their preclinical project towards regulatory approval and early clinical trials. In addition to the obvious benefits of NINDS government non-dilutive funding, the NINDS CREATE Bio program support also benefits investigators by allowing them to retain their IP rights, as well as giving projects a credible "stamp of approval" from the National Institutes of Health's (NIH's) peer review system.

More information about NINDS CREATE Bio and other programs can be found on the NINDS DTR website https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research.

It takes many years, a lot of money (current estimates are in the range of $2 billion), and extensive expertise to develop a drug or therapeutic entity. Additionally, this endeavor is fraught with a high failure rate, so it is difficult to raise money and easy to get discouraged. Yet, therapeutics remain a vital component of our health and well-being and could address many unmet medical needs. This white paper is designed to provide an overview of the drug discovery process for proteins, monoclonal antibodies, and peptide therapeutics targeting CNS disorders starting with early preclinical development and leading to a successful IND application that will support the initial clinical trials.

The intent of the white paper is to provide investigators and small businesses with a framework to enable development of novel therapeutics that target CNS disorders and stroke, regardless of whether their exit strategy is after proof of concept or they intend to carry the product to market. An overview of the development process is shown in (Figure 1). The focus of this white paper is to provide some guidance for investigators who are at the lead optimization through IND phase of developing their therapeutics.

Figure 1: Overview of the Development Process (Spack, E.)



2. THE TARGET PRODUCT PROFILE: BEGINNING WITH THE END IN MIND

2.1. What is a target product profile?

A TPP is a living strategic planning document that maps out a product development program, from beginning to end (FDA Guidance for Industry: "Target Product Profile – A Strategic Development Process Tool," March 2007) (Figure 1). The TPP serves as a reference for initial planning and provides guidance throughout the development program, from initial basic research on a compound through the regulatory review that follows the clinical trial phase (Phases 1, 2, and 3 clinical trials). Additionally, the TPP is a communication tool that can be used to discuss the product development program with all stakeholders, including internal parties but also external partners and regulatory authorities. The TPP is a valuable guide that can be prepared at any point during the development program – although the earlier, the better – given it will be useful irrespective of program status or product type (drug or biologic; novel or derivative).

2.1.1. The TPP ensures clear alignment of development program objectives

The key value of a TPP is to define the product relative to the ideal (sine qua non) marketed features and any competing products – the core success criteria. Once the target product is defined, it becomes possible to identify and refine possible indications and then begin to build the development program needed to support a marketing application for the product. This involves laying out essential studies, including the high-level design and analysis strategy of as many of these studies as possible. The studies should be designed such that the outcome will determine whether the product meets these essential success criteria. Be sure to include clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) studies and considerations in the development plan. It is crucial to develop the TPP with key stakeholder input early on to ensure each study is well designed and aligned to major development goals; this will reduce the risk of conducting failed, wasted studies.

When developing a TPP, also consider the following:

- Regulatory precedence and regulatory pathways for development. Some products will make use of data from approved "reference" products; these will be developed and reviewed under the 505(b)(2) or 351(k) development pathways. The TPP for such products should be developed with consideration of the precedent studies/endpoints and/or labeling claims from the reference listed product (or similar class of products). By contrast, a truly novel biologic (developed and reviewed under the 351(a) pathway) may have substantial sections of de novo text to support target marketing claims.
- Information about the competitive landscape as a whole, including anticipated marketability, valuation, reimbursement, etc. Note that some sponsors choose to have 2 versions of the TPP: one version that is more robust and includes "sensitive" financial information and outlines specific risks, and another version focused on targeted labeling claims and planned studies that may be shared with external parties including regulatory authorities.

Once the initial TPP is developed, it can be used to track or identify current, planned, and not-yet planned major activities for the development program. The TPP should include prespecified go/no-go ("fail fast") decision points at major milestones to ensure that any necessary modifications to the development program at these important junctures occur in a timely and process-driven manner. Some activities that may represent or inform decision points include manufacturing feasibility, Phase 1 clinical trial safety results, Phase 2 clinical trial efficacy results, pivotal reproductive toxicology study findings, funding, etc. Criteria for these key items must be quantitative and unambiguous. For example, regarding Phase 1 clinical trial safety data, an actionable

criterion such as “incidence rate of insomnia < 5% in the treatment group and < 1.5-fold higher than the placebo group” is preferable to “acceptable rates of insomnia.” In this example, the specificity of the criterion might be based on an analysis of current competing products or a general understanding of the indication and important comorbidities faced by affected individuals.

For this hypothetical safety criterion, the project team should plan a data review meeting with all key parties to examine the data when they are sufficiently complete and validated to allow productive analysis. The ideal outcome of such a meeting is that the criterion, data, and responsibilities of the decision makers are all clear, and that a final go/no-go decision is rendered via the meeting. Of course, even with excellent and clearly defined quantitative criteria, often the data can be ambiguous or the emotional investment in the product may override dispassionate decision making. A high-functioning management team characterized by commitment, mutual trust, and accountability can help minimize the risk of ill-informed and unwise decisions. In the end, deciding a product should “fail fast” is not a failure for such a management team.

Finally, in addition to helping inform key go/no-go decisions, the outcomes of these essential studies can influence draft target labeling claims for the product. In this sense, a well-heeled TPP can “grow up” to become the annotated draft package insert for the product at the time of Biologics License Application (BLA) submission.

2.2. What does a TPP look like?

Like any planning document, there are many ways to lay out a TPP. A tabular layout, exemplified in (Table 3), can clearly summarize targeted minimum and ideal results for each criterion. TPPs can include the known data or studies planned to collect those data, alongside known data from competitor products.

Table 3: Sample Target Product Profile for Ischemic Stroke-Revascularization

Product Targets	Minimum Acceptable Results	Ideal Results
Primary Product Indication	Emergency medicine for acute stroke patients immediately on hospital arrival	Emergency medicine for acute stroke patients in the community even before arrival to a hospital
Patient Population	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA or replacement of tPA
Treatment Duration	Acute	Acute
Delivery Mode	IV	IV
Dosage Form	Solution in pre-filled syringes	Solution in autoinjectors
Regimen	Bolus	Bolus
Efficacy	20% or more favorable in comparison to placebo on minimal or no disability 30 days after treatment in patients using Modified Rankin Scale (score≤1) and NIHSS (score≤1). Exploratory endpoint: imaging evidence of revascularization	30% or more favorable in comparison to placebo on minimal or no disability 30 days after treatment using Modified Rankin Scale (score≤1) and NIHSS (score≤1). Exploratory endpoint: imaging evidence of revascularization
Risk/Side Effects	Devoid of symptomatic intracranial hemorrhage and significant mechanism related adverse effects	Devoid of any symptomatic intracranial hemorrhage and any mechanism related adverse effects
Therapeutic Modality	Protein	

2.3. How is a TPP developed?

2.3.1. Stakeholder involvement in TPP development

The TPP is the quintessential multidisciplinary document. All relevant stakeholders within the organization must contribute to formulation and maintenance of the TPP, weighing in on the "living" document "early and often," both during initial development and in periodic updates. Stakeholders may include (but are not limited to):

- Clinical or scientific disease/indication experts
- Experts in manufacturing, nonclinical, medical/clinical, and regulatory disciplines
- Marketing, intellectual property management, and finance experts
- External groups such as partners, investors, vendors, and possibly patient advocacy groups, especially for rare/orphan diseases where such groups' participation in development planning can greatly affect the logistical (e.g., enrollment) and clinical (e.g., patient relevance) success of a clinical program.

The process of deliberating key success criteria among all stakeholders should help to prioritize which indication(s) and development pathways to pursue for the program. Prioritization should include consideration of unmet medical need; strength and number of competitors; regulatory precedence, pathways, and guidelines to facilitate development planning; identifiable complications or difficulties in proposed indication or medical space (e.g., number of competing trials); and options for labeling extension in the target indication or related indications. Take advantage of the available FDA review processes and designations that may be applicable for your product (e.g., breakthrough designation, accelerated approval, orphan drug designation, priority review [FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014]).

2.3.2. Impact of competition on the TPP

In addition to obtaining stakeholder buy-in on the strategic development plan, it is crucial to consider competing products and identify the aspects of the development program that make it unique, different, marketable, and hopefully profitable. Competition relates to product attributes such as dosage/strength and route of administration, the specific indication and treatment population targeted, benefit:risk ratio, and intellectual property considerations. Use various resources, such as competitive intelligence websites (e.g., Pharma Intelligence) or development websites (e.g. clinicaltrials.gov) to help understand the competition. For example, considering alternate routes of administration or reduced frequency of dosing could be an important product discriminator (e.g., intravenous instead of intrathecal; monthly instead of weekly). Another important consideration is the competitor's funding (if known) and the ability of the competitor to move a product forward in development compared to the organization's ability to do so. A small consortium of investigators or a biotech company may have a great product but lack the means (financial, resourcing, or otherwise) to get to market at the same rate that a large, well-funded, and well-resourced pharmaceutical company can. Thus, consider logistical and practical issues such as time to market in light of competition.

Competitive information can be obtained from a wide range of websites, including the following:

- FDA's Center for Biologics Evaluation and Research (CBER)'s lists of biologics approvals: https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/
- FDA's Center for Drug Evaluation and Research (CDER)'s lists of biologics approvals: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsAreDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm

- Drugs@FDA (database of FDA's approved drug products): https://www.accessdata.fda.gov/scripts/cder/daf/
- Clinicaltrials.gov (database of current and completed clinical trials): https://www.clinicaltrials.gov/
- Pharmaintelligence (publisher of the industry news magazine Pink Sheet and many other industry information sources): https://pharmaintelligence.informa.com/

Concurrent trials for the same or competing products also pose a challenge for development in the form of enrollment restrictions/lack of available clinical trial participants, resourcing constraints at investigative sites who participate in multiple overlapping studies (especially specialized sites for rare indications), time to market and patent considerations, etc.

2.3.3. Constructing the TPP

In constructing the TPP, the planning team must "begin with the end in mind" and determine what parameters are most relevant to include in the document. At a minimum, the following categories from the standard package insert should be included: 1) Indications and usage; 2) Dosage and administration; 3) Contraindications; 4) Adverse reactions; 5) Clinical pharmacology; 6) Nonclinical toxicology; 7) Clinical trials (safety, efficacy); and 8) How supplied/storage and handling (CMC topics such as packaging, stability, solubility).

For each of the TPP categories, consider the scientific rationale for the proposed studies (clinical, nonclinical, and CMC) and the information supporting the scientific premise (including published literature and product labeling from any reference products) that will be used to support target marketing claims. For nonclinical content, consider the nonclinical data needed to support the safety of the product, including required toxicology, pharmacokinetics (PK), carcinogenicity, and impurity studies that may need to be conducted at specific points during the program. The clinical development plan should include the target indication for the investigational studies, the intended population, and competing products. In addition, the clinical plan should account for established or required clinical endpoints needed to demonstrate safety and efficacy (as applicable) in the respective clinical trials and outline the anticipated safety profile of the product (including known or expected adverse reactions such as immune reactions or anti-idiotypic antibodies [for monoclonal antibody therapeutics]). The CMC content of the TPP should consider technical aspects such as route of administration, dosage, and storage conditions, but also perceived manufacturing or stability issues that may impact shelf life, cost, time to market, and other logistics.

Also bear in mind that the team does not need to develop this plan on its own, and external counsel is often advisable at this stage. Although existing guidelines and regulatory precedence can be a helpful starting point for developing the plan, it may be necessary for the team to enlist the expertise from experienced regulatory consultants to provide input on the overall regulatory strategy for the program, including potential risks and mitigation pathways. One area of particular ambiguity is the 351(k) BLA pathway for biosimilars. Currently, only a handful of biosimilars have been approved by the FDA for marketing, and the advantages of following this development pathway are not entirely clear. This area of regulatory evaluation is rapidly evolving, and it is hoped that the 351(k) pathway will prove to be an expedited approval pathway in the near future as science advances.

2.4. How is a TPP used and maintained?

Throughout the development program, the TPP should undergo cross-functional review by team members of relevant disciplines and key stakeholders. These reviews should be regularly scheduled (e.g., annually or biannually, depending on the status of the program) and also occur each time newly acquired data have been obtained in the program. New data may include results from new studies, newly identified risks or other issues, and changes to the competitive or regulatory landscape that may impact the assumptions, study designs, and

defined success criteria. However, even in the absence of new data, the TPP should undergo periodic reviews; one may not know whether anything in the plan should be modified until specifically researching the changing market and/or regulatory landscape, considering the organization's goals and long-term development strategy, etc. The team should review the plan with careful consideration of any predetermined go/no-go pivot points to ensure an informed and timely decision for the program. Any updates to the TPP should also undergo multidisciplinary review.

2.5. Challenges or pitfalls in use/failure to use TPP

Several potential issues can arise during use (and misuse) of the TPP during product development. A common pitfall is a lack of team member alignment on TPP objectives and program strategy, which can occur when interdisciplinary input and stakeholder buy-in is not sought during initial drafting and subsequent maintenance of the TPP. Another common mistake is the failure to prospectively design studies that are clinically meaningful and scientifically addressable within the confines of the competitive landscape and current regulatory expectations. As noted above, it is also essential to predefine and obtain agreement on the decision points and go/no-go junctures in the TPP where diligent adherence to the decision criteria and process will help prevent spending unnecessary time and resources on what the data may reveal to be an ill-advised development strategy.

3. CORE PRODUCT DEVELOPMENT TEAM

3.1. Disciplinary Experts Required

After the principal investigator has identified or created the original therapeutic concept, several disciplinary experts are required throughout the development of a product for eventual therapeutic use. It is important to keep in mind the ultimate goal of providing a successful product to a well-defined patient population. Often the main investigator may have some (e.g., medical, clinical, nonclinical) but not all of the expertise required. These disciplines do not have to be uniquely represented by a single individual, but to expect one individual to be responsible for more than two or three disciplines is a recipe for development failure. Ideally, at least one member of the team has guided several products to market previously to assist them in development's many decisions. Obviously, some of these experts do not have to be employed full time, but ready access to their knowledge base is essential for success of the program. The individuals representing the required disciplines are listed below.

3.1.1. Program Manager

A critical member of the product development team is the program manager, who coordinates all of the development disciplinary efforts and monitors the progress and the budget of the development activities. Ideally, the program manager is an experienced regulatory scientist, understands the perspective of the regulatory authority, and is able to predict development requirements prior to having the regulatory authority request them. This role requires extensive experience.. Only the crafting of a comprehensive integrated product development plan and the meticulous execution and tracking of the prescribed tasks with monthly (weekly and daily at certain development time points) status reporting will result in success. Inasmuch as no plan is executed without significant issues arising, the program manager also must be a creative problem solver in order to keep a program alive. This is a position that should be employed full time to maximize efficiency of development cost and time. Conversely, the degree of flexibility in the product's overall planned timeline will determine what compromises can be made in the dedication of this individual to the program.

3.1.2. Therapeutic Medical Expert/Senior Clinical Scientist

A medical expert with many years of experience in patient care and clinical trials with an understanding of the ultimate therapeutic target is essential at every step of the development pathway. Understanding the anticipated therapeutic dose regimen is essential to designing toxicology studies and selecting the optimal dosage form. These physicians play a vital role in the design of the clinical investigational plan, leveraging their knowledge of previous development plans of marketed products. Ideally, they possess the needed scientific acumen and are experienced clinical trialists who collaborate with regulatory and statistical scientists in the design of protocols that will yield data that contribute to the overall marketing approval effort. These individuals also play a crucial role in collecting information from key opinion leaders and clinical sites to further advance the chances for success of the development effort. Most often they are called upon to determine the inclusion/exclusion criteria for clinical protocols and monitor the adverse events occurring during the conduct of the clinical trial. Also, FDA advocates the formation of a Safety Assessment Committee (Safety Assessment for IND Safety Reporting: Guidance for Industry, 2015) for the real-time assessment of the risks associated with data being generated by the clinical trials conducted under Good Clinical Practice (GCP) in the development program, and this individual is the logical chair of this committee. Senior clinical scientists may also serve in this capacity if they have sufficient experience. It is presumed that the NINDS principal investigator will serve in this role and, if he or she does not have sufficient experience, should identify a co-principal investigator who does, either from within their institution, a key opinion leader, a consultant, or a contract research organization (CRO).

3.1.3. Nonclinical Pharmacology/Toxicology Scientist

It is imperative that the team includes a nonclinical scientist who can bring the technology forward from discovery to market and is familiar with all the regulatory requirements and International Council for Harmonisation (ICH) guidelines governing these activities. The results from the primary pharmacology studies form the entire foundation for the development, so rigorous examination of these results from several perspectives is the only way to ensure the team is not proceeding into biopharmaceutical development without a valid hypothesis. Once the science is validated, the job of the nonclinical team is to ferret out any potential safety concerns that could terminate the program. Initially, this is done through safety pharmacology studies, typically at the maximum tolerated dose or several multiples above the intended therapeutic dose or highest clinical exposure (C_{max}). In these studies, basic organ systems are monitored to ensure that no significant alterations occur during administration of doses of the product sufficient to elicit the desired pharmacodynamic response. The toxicological evaluation of the product is then performed under the supervision of a nonclinical toxicologist who supervises the contract toxicology laboratory's performance of the required studies. The studies cover the gamut of safety studies conducted under the standards of Good Laboratory Practice (GLP) from the IND-enabling toxicity studies including the studies required in two species as well as potentially others (genotoxicity, reproductive toxicity, immunotoxicity, etc.) through to the eventual conduct of carcinogenicity studies if the product will be administered chronically for non-life-threatening indications. The nonclinical scientist also needs excellent project management skills to manage the sundry activities, organizations, and studies, as well as interpreting the data and preparing required documents for regulatory authorities. Typically, this expertise is needed prior to the IND during the preclinical phase of the program, and is reduced as the clinical program proceeds, unless carcinogenicity studies are required. The nonclinical scientist may still be required to conduct experiments to attempt to understand adverse events recorded in the clinical trials.

3.1.4. CMC Scientist

The CMC (chemistry, manufacturing, and controls) scientist must provide the program team with the required drug product to conduct the toxicology program as well as the clinical program. Again, the project management skills of this individual must be excellent in order to coordinate the sourcing of the active pharmaceutical ingredient (API), the formulating of the API into a drug product that can be dosed, the manufacture of the drug

product at a contract manufacturing organization (CMO), the analytical methods development for assaying the drug product in plasma, etc. More marketing applications submitted to regulatory authorities fail due to CMC issues than any other discipline, so it is imperative that a CMC scientist well versed in Good Manufacturing Practice (GMP) oversees the entirety of the drug product manufacturing. The CMC scientist is also responsible for providing the regulatory authorities with all relevant data and authoring the CMC documents. Inasmuch as deficiencies in the CMC arena are the leading cause of failed IND clearances (i.e., withdrawn INDs or clinical holds), and failure of marketing applications, the importance of experience in this position cannot be overstated.

3.1.5. Regulatory Scientist

In small companies developing biotechnology products, it is advisable to require each member of the team to be responsible for the regulatory requirements for their respective disciplines. However, individuals with exposure to multiple development regulatory disciplines can bring added value to any team to provide intelligent regulatory advice when discussing various strategies to approach the regulatory authorities. Also, many regulatory documents need to be prepared for regulatory authorities and these individuals can often serve as multidisciplinary authors. Such an individual can typically provide strong leadership to the entire team if he or she possesses the required program management and leadership skills. Again, the team will be much stronger if the required regulatory knowledge to get a product approved and on the market is held by each of the disciplinary experts.

3.1.6. Clinical Pharmacologist

How the product is handled by the body is of utmost importance in determining the ultimate dose of the product to be marketed. It is essential to have a clinical pharmacologist or somebody well versed in pharmacokinetics (PK) on the team to provide input on the design and interpretation of PK studies in order to arrive at a safe and effective dose of the therapeutic product. As science advances and products are developed on the basis of well-understood mechanisms of action, genetic phenotypes, and well-defined populations, getting a product approved with a dose that "works" will become increasingly difficult.

3.1.7. Statistical Scientist

Aside from the medical expert, the individual most critical to product approval from both a nonclinical and clinical perspective will be the statistical scientist. For nonclinical studies, the statistican can ensure the scientific method is robust with unbiased experimental design, methodology, analysis, interpretation and reporting of results. The statistical scientist can also be called upon to support nonclinical toxicology results, CMC analytical and stability results, and PK analyses supporting the eventual marketing approval. By being responsible for the statistical analysis plans for the registration studies and the design of the analyses for the integrated summary of safety and the integrated summary of efficacy in the marketing application, the statistical scientist provides the regulatory authorities with the necessary confidence in the program's analytical rigor. The statistical scientist also typically ensures that any data submitted to regulatory authorities are in the accepted format (Clinical Data Interchange Standards Consortium [CDISC]) and are valid following a rigorous quality control process.

3.1.8. Health Economics Expert

In the current environment of concern regarding pharmaceutical product prices, it is highly advisable to design the clinical trials with an eye toward the eventual reimbursability of the product by third-party payers. Health economics experts are able to assist in the design of clinical protocols to include clinical endpoints that carry weight with reimbursement organizations from an economic perspective. These endpoints should be included in protocols beginning in Phase 2 of clinical development.

3.1.9. Commercialization Expert

The eventual goal of any pharmaceutical product development program is to provide a product to patients in need. Any commercialization expert knows it is impossible to begin a successful development program without assessing the ultimate customer needs and the commercial viability. For a pharmaceutical product, that customer is the patient in the current and future therapeutic environment. Consequently, the commercialization expert takes stock of the current standard of care for the indication being targeted, as well as any other competing products on the market or currently in development. One ignores this influence on the success of the product in development at one's own peril. In most therapeutic areas, competition is stiff enough that ignoring this perspective could lead to early termination of the development effort or, worse yet, approval of a product that is not needed by patients. An example of a nonindustry commercialization entity is the NINDS CREATE Bio program, which is dedicated to facilitating the preclinical optimization and development of biotechnology product- and biologics-based therapies.

3.1.10. Ancillary Disciplines

3.1.10.1. Data Management

This role is primarily responsible for the development of the case report form in collaboration with the medical expert, statistical scientist, and regulatory scientist to capture the data generated from the clinical protocol. A number of CROs provide a commercial electronic data capture (EDC) product (e.g., Medrio, Medidata) for this purpose that will generate data compatible with current regulatory standards (CDISC).

3.1.10.2. Pharmacovigilance

This role is primarily responsible for reporting expedited safety cases to the regulatory authorities in collaboration with a medical expert. These individuals may also author safety narratives for individual patients required by regulatory authorities that are then reviewed by a medical expert. A number of CROs provide this service using a commercial product (e.g., Argus, ARISg).

3.1.10.3. Regulatory Operations

In the current regulatory environment, it is standard practice to submit all documents to regulatory authorities in an electronic Common Technical Document (eCTD) format using commercial software (e.g., Lorenz docuBridge, Global Submit). It is common practice for organizations to establish a secure gateway account with regulatory authorities and submit all documents through this mechanism using the commercial software. This role requires specific technical expertise and a number of CROs provide this service.

3.1.10.4. Contract Research Organization

Outsourcing of development work has become standard practice in the pharmaceutical development world. CROs typically are employed to manufacture GMP product, perform the GLP toxicity studies, conduct the GCP clinical trials together with all associated other activities (e.g., the critically important task of investigational product management) as needed for all but the largest pharmaceutical companies. In fact, any of the individual disciplines listed above can be filled by an experienced consultant or a CRO who specializes in the desired discipline the team is lacking.

3.1.10.5. Additional Thoughts and Considerations

While a host of things needs to be considered in an effort such as this, a few noteworthy topics to ensure success are included here.

1. Technology Transfer Office /Patent Counsel /IP Firm. Protect your intellectual property (IP). A drug is typically worth much more to the inventor and the developers if it has a strong IP portfolio. Consult

with your university's technology transfer office /patent counsel and/or work with an outside IP firm. Intellectual property is the foundation by which you can get others interested in the development/commercialization process. The NINDS CREATE Bio program allows investigators funded through its progam to retain their IP rights. Reviewers of CREATE Bio applications for funding take into consideration any potential issues regarding the IP landscape and whether there is freedom to operate for the biologic therapy. Even more emphasis is put on the commercialization plan and strength of the IP portfolio for small business concerns that apply through the NINDS CREATE Bio SBIR program.

2. Chief Executive Officer (CEO) or President. If you are focused on the science or are inexperienced in raising capital, developing press releases, or navigating corporate issues such as insurance and contracts, then consider hiring or creating a relationship with someone with that experience. Individuals who run companies, large or small, can address not only these types of issues but good CEOs and Presidents can think strategically about how the drug will fit in the marketplace, how to work with payers, and how to position the agent as a viable fundraising tool. University technology transfer offices and state or national biotechnology organizations (e.g., Biotechnology Industry Organization [BIO]) can provide help in identifying such individuals.
3. Scientific/Development Advisory Board. Along with a CEO or President, having a small group of scientific and medical experts in the area of interest is helpful for a number of reasons. This group can critically challenge the team's assumptions, provide new avenues of experimentation, and provide introductions to new companies or collaborators. An advisory board of even two individuals would provide much-needed and objective input. It is imperative that these board members have successfully brought other products to market, ideally in a similar therapeutic field.
4. Partnerships. Corporate partners are absolutely critical for getting a product to market. These companies provide capital, expertise, and validation for the product and the development process. Potential partners can be found at international conferences such as the Biotechnology Innovation Organization (BIO) convention. In an academic setting, technology transfer officers often have contacts within these companies, and can help gain invitations to partnering meetings, one-on-one meetings, and other sponsored events.

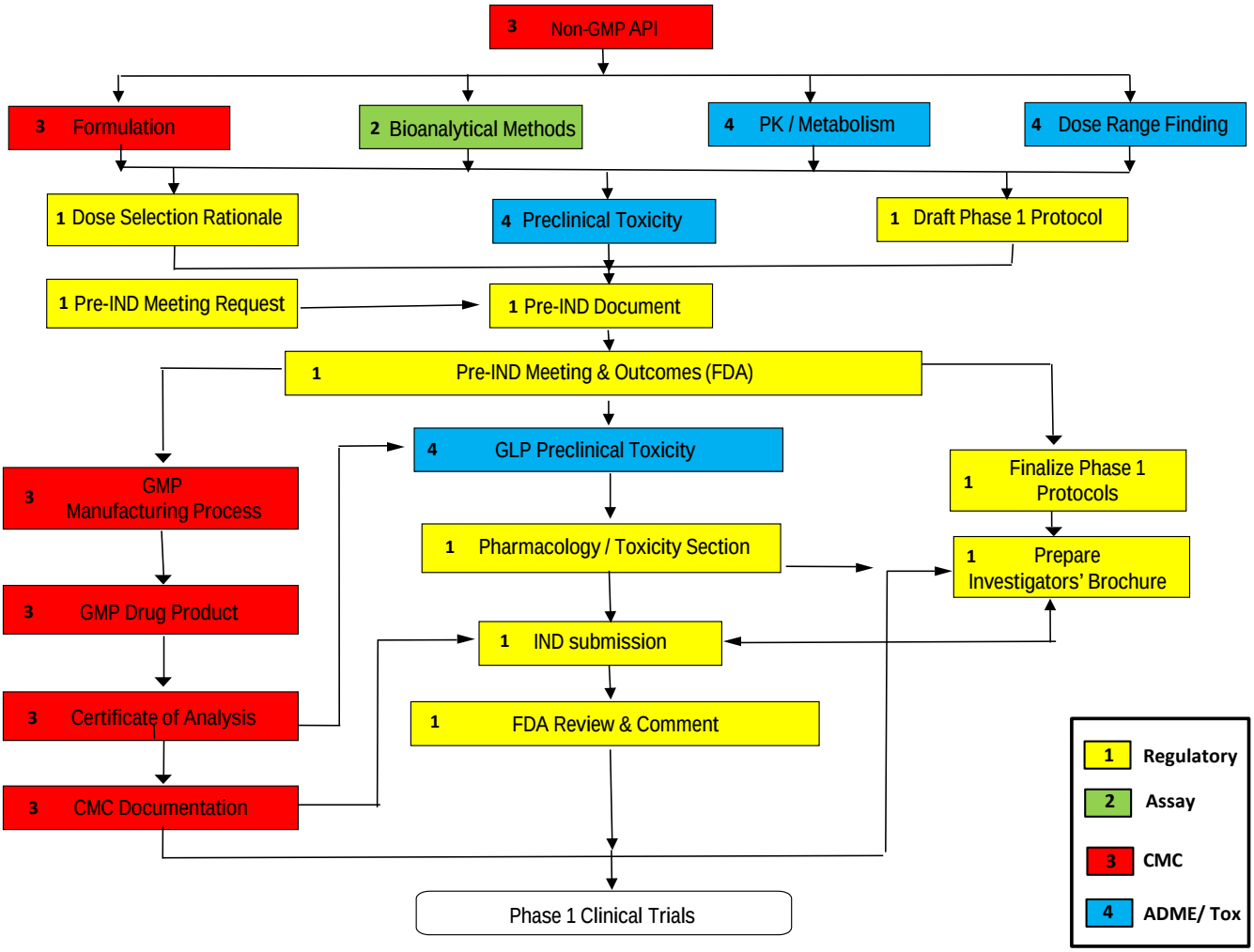
4. DEVELOPING AND IMPLEMENTING A STRATEGIC PLAN

4.1. Overview

While regulations require the original IND submission to outline only the initial year of clinical development, it is strongly recommended to map out the entire general investigational plan (Phase 1, 2, and 3 Clinical Trial) as well as all disciplines and activities supporting clinical development through marketing application submission to optimize efficiency of development. In planning for success, take advantage of past regulatory precedents in predicting the cost and timeline of the associated planned development and avoid missteps.

This section plan will be brief but will include a high level diagram of the overall integrated product development plan to include the 1) clinical; 2) nonclinical; 3) CMC; and 4) regulatory studies/activities, milestones, and timelines up through marketing application submission (Figure 2).

Figure 2: General Flow Chart for Preclinical Activities (Steinmetz, 2009)



4.2. Commercial Plan

While SBIR investigators will be aware of the value of a commercialization plan, academic investigators may view commercialization as premature at the initial development stage. A concerted effort to understand the current standard of care and competitive landscape must be made in order to determine whether the technology is in fact worth pursuing even at this early stage. Many products successfully navigate the regulatory approval process only to languish on the shelves of distributors due to a lack of clinical need and commercial market. The FDA has no interest in this element of the strategic plan, but developing this portion of the integrated product development plan is mandatory to ensure success of the entire plan. The ultimate goal of the NINDS CREATE Bio program is to bring new therapies to the market/patients; the program strongly encourages principal investigators and/or their collaborators to consider a commercial plan and obtain and retain any IP developed related to their therapy.

4.3. Clinical Development Plan

4.3.1. Phase 3 Clinical Trial

At the pre-IND stage of development it is only necessary to summarize the overall design (including a regulatorily approvable clinical endpoint), identify the target patient population, provide a rough estimate of the sample size, and approximate the timeline for recruitment of the identified subjects. This will give the regulatory authorities an idea of where the program is headed and allow them to comment at a high level if they see errors in the proposed development logic.

4.3.2. Phase 2 Clinical Trial

This is the most difficult stage of clinical trials to design as it requires much investigative work to arrive at the minimum effective dose and dose regimen to optimize chances for success in Phase 3 clinical trials. Consequently, these studies are data driven, relying on Phase 1 clinical trial results and successive Phase 2 clinical trial results unless the team is fortunate enough to demonstrate proof of concept and determine a minimum effective dosage in a single study. The initial dosage is determined from the safety profile and any pharmacodynamic results that were obtained as an indication of preliminary efficacy in Phase 1.

4.3.3. Phase 1 Clinical Trial

First, it is important to understand that Phase 1 commonly consists of the product's initial exposure in normal healthy volunteers (unless the product is known to be toxic to normal healthy volunteers but still may be efficacious for another target patient population), primarily to assess safety and pharmacokinetics to begin to understand the eventual dosage. The initial safe dose is extrapolated from the GLP toxicity studies in animals. Ideally, Phase 1 clinical trial data yield the maximum tolerated dose of the product, but this may be an unobtainable dose with biologics due to lack of any overt toxicity. Consequently, a maximum feasible dose may be identified that is limited by the product's solubility, administration volume, or some other CMC parameter. Additional Phase 1 clinical trials may be required to be conducted in parallel with Phase 2 clinical trials in order to assess the product's behavior in the presence of compromised organs, anticipated concurrent medications, behavior of an anticipated biomarker, etc.

4.3.3.1. Initial Phase 1 Clinical Trial Protocol

Focus on safety, tolerability, pharmacokinetics, and only on pharmacodynamics if it is possible without detracting from the primary safety focus of the trial. It is ideal to determine the behavior of the agent in normal healthy volunteers before adding interpretation of the vagaries of morbidities afflicting a patient population.

- The initial clinical trial should be a single ascending dose design to attempt to determine the maximum tolerated dose.

- If the product will ultimately be administered more than once to a patient, then a multiple ascending dose design should be employed for the second trial. Sometimes this stage can be incorporated into the initial protocol along with the single ascending dose design.
- Pharmacodynamic markers (biomarkers) are useful to identify at this stage of development, if possible.

4.3.3.1.1.1. Maximum Tolerated Dose Determination

Handling of biological products by the body is far less predictable than small molecules; consequently, a single-dose maximum tolerated dose trial design is as likely as not to yield a toxicity one may use as an upper dose limit or frame of reference for future dosing decisions. Consequently, it is important to decide early on what the maximum feasible dose of the product will be, beyond which either solubilization or administration is impractical.

An alternative method of exploring the dose in Phase 1 clinical trials used for some biologics, such as immunotherapies that act as agonists on immune system targets, is to define the minimum anticipated biological effect level (MABEL). In these clinical trials, the dose is increased in an ascending fashion to define the MABEL, and then further escalated until the dose associated with maximum desired pharmacodynamic effect is exceeded by a small margin. This is done in the hope of minimizing any untoward immunologic reaction, but unfortunately does not provide any data on the therapeutic index (ratio of toxic to effective dose) of the product.

4.3.3.2. Immunogenicity/Immunotoxicity Considerations

- Proteinaceous and other biologics should always be assumed to have potential immunological side effects or attenuation of efficacy, so it is advisable to assay for antibodies in Phase 1 clinical trials and prepare for potential anaphylactic reactions.
- Methods to address/prevent immunogenicity include the following:
    - Manufacturing a humanized antibody of the species-specific antibody used in the nonclinical studies to reduce the chance of eliciting an untoward immune response
    - Site-directed changes of the antigenic region can also potentially reduce or eliminiate immunogenicity
    - Delivery (liposomes/exosomes) mechanisms that shield the antigenic portion of the biologic can also potentially reduce or eliminate immunogenicity
    - Pegylation has been shown in several instances to reduce or eliminate immunogenicity

5. NONCLINICAL DISCOVERY AND DEVELOPMENT

5.1. Target Identification and Validation

Drug targets for human disease emerge from basic research into mechanisms of disease biology. Validated molecular drug targets require that the project team address issues related to rationale, druggability, mechanism, and safety. The commercial viability of the approach may also be critical for recruiting industry partners at key junctures to support development. The molecular target is the protein that will bind directly to the proposed drug.

A validated target has:

- Rationale: A human genetic or pharmacological link to a selected disease population/modulation of the target has been shown to produce therapeutic benefit in an in vivo animal model of the disease population or of the relevant circuit dysfunction using a directly translatable and quantifiable endpoint.

The scientific premise of how target modulation leads to a therapeutic impact is a critical aspect of target validation.

- Druggability: Druggability is used in drug discovery to describe a biological target (such as a protein) that is known to or is predicted to bind with high affinity to an agent. A tool agent exists to modulate the target or a family member. Biochemical and cellular assays exist to support development of structure-activity relationship for on-target and off-target activities. Post-translational modifications or alternative splice form activities can be measured with these or other assays.
- Mechanism: A clear set of laboratory objectives that specify required mode and degree of target engagement are needed for efficacy. Pharmacodynamic measures of target engagement are available to monitor activity in animals and people. Disease-induced changes in target expression or distribution have been examined. Common human single nucleotide polymorphisms in target documented and functional consequences have been considered.
- Safety: Known pharmacological risks associated with target mechanism are documented. The tissue distribution of the target is understood in preclinical species, humans, and patients. The most likely off-target activities associated with closest sequence homology are identified and considered for safety risks.

5.2. Lead Optimization through Candidate Selection

Identification of the correct agent requires a clearly defined set of objectives based on the TPP and a well-designed screening system to select the molecule that will meet those objectives. Laboratory objectives for an agent include specific criteria for the mode of binding to target (e.g., agonist, partial agonist, inverse agonist, noncompetitive inhibitor), the potency (e.g., K_i exhibits 30-fold selectivity over family member targets X, Y, and Z), brain penetration (yes/no), dosing paradigm (e.g., oral, once daily; intravenous, once monthly), and duration of expected treatment (e.g., subchronic daily treatment for 2 weeks, chronic treatment for years). Each of these laboratory objectives will have bearing on the design of the candidate selection process. In the case of proteins or monoclonal antibodies, actual modification of the protein's activity is unlikely to be required. However, alteration of the protein to enhance bioavailability, exposure (particularly for compounds targeting the CNS), and stability may be desired.

For peptides, chemical modification or replacement of amino acids, lengthening or shortening of the peptide, or other types of chemistry may allow enhancement of the desired drug properties. A robust assay to allow rapid assessment of these types of modifications is required to fully explore the range of changes possible. This assay can either be cell-based (e.g., neurite outgrowth assay) or a biochemical (e.g., amyloid-beta aggregation blockers) assay but should have the ability to test large numbers (1000 to 10,000) of agents in a reasonable amount of time. Regardless of the starting point of the candidate, these assays are critical for backup agent identification, intellectual property protection, and possibly follow-on agents.

Any agents exhibiting the appropriate properties in these assays will need to be tested in the appropriate animal disease model. Such a model ideally is developed in a mouse or rat so reasonable numbers of agents can be tested in a cost- and time-effective manner. In cases where the efficacy model is cumbersome or expensive, more effort needs to be focused on the biochemical/cell-based assays to provide a short list of desired candidates. Also, use of these models will begin to introduce the concept of the pharmacokinetics and pharmacodynamics of the agents.

Additionally, these models may provide insights into the bioavailability of the agents as well as the optimal route of administration and dosage. These parameters may indicate to the developer that modifications such as pegylation or formulations that stabilize the agents may be necessary to incorporate for optimal biological activity. Agents that become candidates for drug development typically have good efficacy with the least amount of agent administered.

Critical features defined by the TPP objectives may require additional in vitro absorption and metabolism data from compounds slated to progress in vivo to ensure that structure activity relationships being developed will

support expected dosing profiles and target organ disposition. A collection of critical off-target assays to ensure required selectivity of the candidate drug must be available to test molecules progressing from functional assays. Agents expected to be tested in vivo will require PK studies to ensure target organ exposure in concentration ranges needed to support hypothesis testing.

To effectively deliver a therapeutic to a preclinical species for the duration of a study, researchers must choose a dose, a formulation, and a route of administration that will support target organ exposure long enough to test a therapeutic hypothesis. Because most therapeutics developed for humans are optimized for human metabolism parameters, many agents developed for humans are rapidly metabolized and cleared in rodents, requiring alternative formulations and routes of preclinical administration. It will be critical to choose carefully the optimal species in which to perform preclinical PK and metabolism studies. Particularly complicating is the fact that most of the targets will be central as opposed to peripheral. CNS localization may make delivery more difficult with more common delivery methods (oral, intravenous), so alternative delivery methods (intrathecal, intracranial, intraocular) may need to be explored. As the targets will typically be in the CNS, species more comparable to humans in this respect (such as swine or nonhuman primates) may be preferred. Proper formulation of drugs and vehicles to ensure appropriate exposure is a critical factor in preclinical study design. Essential to achieving this objective is the development of analytical methods that can measure the pharmacokinetics of the agent in various species. These pharmacokinetics include plasma but may encompass CNS exposure or other target systems (e.g., lymphatic).

Selecting the correct dose to achieve exposure of the therapeutic that is adequate to test a hypothesis in preclinical species requires knowing the potency of the agent at the desired drug target and the dose of agent required to achieve target organ exposure that will result in the concentration of therapeutic required to engage the molecular target within the target organ compartment. If the therapeutic target is in the brain, then the kinetics of agent disposition and clearance, including blood-brain barrier penetration, in the test species must be understood to select a dose of agent adequate to test the hypothesis.

5.3. Nonclinical Safety Testing, IND-Enabling Studies

It is recommended to hold a pre-IND Meeting with the FDA before starting IND-enabling nonclinical studies which arerequired to support the initial clinical trial and are conducted following candidate selection. These studies typically use active ingredients that have been manufactured and tested according to GLP standards. However, active ingredients manufactured using GMP are also acceptable. In accordance with Title 21 of the Code of Federal Regulations (CFR), Part 58, for GLP studies, the identity, purity, and impurity profile of the therapeutic must be characterized. Additionally, stability data are required to support the duration of the in-life portion of the GLP toxicology studies. It is important for the nonclinical project team member or consultant to work with the CMC team member to ensure sufficient quantities of the active ingredient are made to support the needed studies. Dose range-finding studies are typically conducted in advance of general toxicity studies and safety pharmacology studies to support dose selection.

5.3.1. Species Selection for Nonclinical Safety Testing

There are several considerations for selection of nonclinical species for safety testing. This is particularly challenging for biologics that may not work as well across species. Typically, FDA expects evaluation of the toxicological profile of the agent in two species, a rodent and a nonrodent. For rodents, mice and rats are most frequently used. For nonrodents, dogs, minipigs, and monkeys are frequently used. For biologics, only one species may be relevant (e.g., primate). The selection should take the following into consideration:

- *Pharmacology:* Is the pathway and/or target active and relevant in the particular species relative to humans?

- *Expression:* Is the expression of the target receptor, etc., similar across tissues in this species? If not, will this interfere with interpretation of the study and extrapolation to humans?
- *Potency:* Is the potency of the agent at the receptor similar across species? Potency assays should be conducted in pharmacology model(s), toxicology species, and humans. One can look at sequence alignments to get an idea of the similarity of the target across species as well.
- *Metabolism:* Human metabolites need to be covered in the toxicology species. This is not as difficult for biologics as it is for small molecules.
- *Toxicology:* Is the species selected sensitive to a particular drug class and the toxicological mechanism relevant for humans?

5.3.2. Safety/Secondary Pharmacology Studies

These studies evaluate the effects of the therapeutic on vital organ systems. For peptides and small molecules, safety pharmacology studies are commonly conducted as stand-alone, single-dose studies. However, for proteins and biologics, safety pharmacology studies are most frequently incorporated into the toxicology studies. The ICH Guidance S7A "Safety Pharmacology Studies for Human Pharmaceuticals," November 8, 2000, describes recommendations and regulatory expectations for a core battery of safety pharmacology studies for an initial IND. The core battery includes the following:

- Central nervous system – Effects of the therapeutic on motor activity, behavioral changes, coordination, sensory/motor reflex responses, and body temperature are evaluated in either a functional observational battery, modified Irwin's test, or other appropriate test.
- Respiratory system – Respiration rate and function such as tidal volume or hemoglobin oxygen saturation are measured using appropriate methodologies. These studies can be conducted in telemetered monkeys or in plethysmography chambers for rodents.
- Cardiovascular system:
    - To evaluate the potential for long QT syndrome, an in vitro study is conducted to assess the therapeutic potential for inhibition of the IKr human potassium channel in cells transformed to express the human ether-à-go-go gene. This is typically conducted for peptides only. Significant inhibition with less than a 30-fold half-maximal inhibition concentration (IC_{50}) safety margin relative to free maximal plasma concentration may warrant additional investigation (Redfern, 2003).
    - In vivo evaluations to assess effects on blood pressure, heart rate, and cardiac rhythm and morphology are typically in conscious telemetered nonrodents such as dogs, monkeys, or pigs, etc. when conducted as a stand-alone study. Evaluation of the effects on the cardiovascular system can also be incorporated into general toxicology studies.

Additional safety pharmacology studies may be warranted based on adverse effects observed in toxicology studies, known class effects, or potential unintended off-target effects based on in vitro secondary pharmacology studies.

5.3.3. Toxicokinetic Studies

Toxicokinetic (TK) studies are to be conducted according to GLP standards using a validated method with appropriate sensitivity in the selected toxicology species by the same route of administration, formulation, dosing frequency, and duration as intended in humans. Recommendations for bioanalytical method validation are described in the FDA Draft Guidance for Industry "Bioanalytical Method Validation," September 2013.

The following assessments should be obtained in the toxicokinetic study:

- C_{max} – maximum concentration in plasma
- T_{max} – time to maximum concentration in plasma
- AUC_t – area under the plasma concentration-versus-time curve from time zero to last measurable concentration
- Effect of sex on toxicokinetics
- Accumulation after repeat dosing (if the therapeutic is to be administered in a repeated dose) – measure TK on Day 1 and near end of study or at steady state
- Dose proportionality
- Accumulation upon repeat dosing

Additionally, it is important to understand and assess the PK/TK of the therapeutic agent in the brain early in the development timeline, although this is not a requirement for an initial IND unless clinical signs suggest accumulation. These studies (or additional PK studies in appropriate animal models) should evaluate the terminal elimination phase of the therapeutic to estimate the apparent clearance, volume of distribution, and half -life. Where possible, a description of the allometric scaling from animals to humans and anticipated pharmacokinetic properties humans should be provided in the IND.

5.3.4. General Toxicology Studies

5.3.4.1. Acute Toxicity Studies

Single-dose toxicity studies are not a requirement for drugs expected to be administered in a repeated-dose manner. The exception is for a GLP expanded acute general toxicity study to support an initial clinical trial with administration of a single dose. Typical study design for an expanded acute study includes typical GLP toxicology study dosing and endpoints. However, the animals are often sacrificed 2 or 3 days after dosing and then another group is sacrificed 14 days after dosing. For therapeutics anticipated to be administered repeatedly, single-dose toxicity studies can be informative for determining a maximum tolerated dose for dose selection for safety pharmacology, and repeat-dose, non-GLP dose range-finding studies.

5.3.4.2. Dose Range-Finding Studies

Dose range-finding studies are critical for dose selection for the pivotal GLP toxicity studies. For peptides, this includes determination of a maximum tolerated dose for the pivotal GLP study. For proteins and monoclonal antibodies where the only toxicity may be pharmacology related, the dose range-finding study will evaluate a range of doses with the high dose typically a 10- to 20-fold multiple of the anticipated maximum human exposure or a maximum feasible dose based on solubility and volume needed for administration. In cases where lower multiples are justified, a lower starting dose for the initial clinical trial may be considered.

Often, a smaller number of animals (both male and female, if possible) are used for dose range-finding studies. These studies are not regulated and thus, the study design can be varied depending on the need. Endpoints for evaluation of toxicity may include clinical signs, body weight, food intake, clinical chemistries, and sometimes macroscopic evaluation after necropsy, particularly for any target organs or organs where macroscopic findings are identified. Dose range-finding studies are often of shorter duration than the proposed GLP toxicity studies. For example, a single dose of a monoclonal antibody with a one-week observation period may be sufficient for selection of doses for a 28-day, once weekly repeat-dose toxicity study in nonhuman primates.

5.3.4.3. Pivotal GLP Toxicity Studies

General toxicology studies conducted in accordance with GLP standards are typically required for therapeutics. The objective is to characterize the toxicity profile of the therapeutic when administered by same route,

duration, and frequency as intended for the initial clinical trial(s), to identify the highest safe dose evaluated in the study (no observed adverse effect level [NOAEL]), target organs of toxicity, and exposures associated with safe and toxic dose levels. For pediatric indications, toxicology studies should be conducted in age appropriate juvenile animals to cover the intended age range. In addition to general toxicity, specific assessments are often included in juvenile toxicity studies to evaluate the potential effects of the therapeutic on development of specific organ systems (including the CNS).

General toxicology studies are normally conducted in two species, rodent and nonrodent. However, for many biologics, only a single species may be relevant (often nonhuman primates). If the data are not clear as to whether toxicology studies should be conducted in only one species, this can be discussed at a pre-IND meeting. For peptides, toxicology studies are often conducted in a manner similar to small molecules as per recommendations described in the ICH Guideline M3 (R2) "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," January 2010. Recommendations for nonclinical safety evaluation of therapeutic proteins and antibodies, as well as other biotechnology-derived pharmaceuticals, are described in the ICH Guidance for Industry "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)," parent guideline 16 June 1997, addendum 12 June 2011.

Toxicology studies should be conducted using the same or very similar formulation by the same route and duration of administration as anticipated for the initial clinical trials. They should be conducted using the active ingredient made by the same/similar method as that intended in the clinic.

The number of animals per dose group should be justified. Typically, at least 10 rodents/sex/group or 4 nonrodents/sex/group are used for toxicology studies of up to 3 months duration. Recovery groups (5/sex/group for rodents, and 2 or 3/sex/group for nonrodents) are usually included to evaluate the recovery of any adverse effects seen during the dosing phase of the study or any delayed effects. The recovery time for evaluation will depend on several factors such as the half-life of the molecule and any known toxicities that may take a long time to resolve. Satellite groups of male and female rodents can be used for plasma toxicokinetics assessment. Typically, toxicokinetics can be assessed using plasma taken from nonrodent main study animals.

In-life toxicology endpoints for GLP studies typically include clinical observations, body weight, food consumption, clinical pathology, urinalysis, ophthalmology, and electrocardiograms (ECGs). Safety pharmacology endpoints such as cardiovascular, pulmonary, and CNS are often evaluated in nonhuman primates. Postmortem endpoints include evaluation of any macroscopic lesions, organ weights, and histopathology of a standard list of tissues. Additional endpoints may be added based on known effects of the therapeutic or class effects.

Assesssment of the potential for immunotoxicity is often part of the general toxicity studies. If the weight of evidence from general toxicological studies suggests an effect of the therapeutic on immune function, additional testing may be needed to fully characterize the immunotoxicity profile.

5.3.4.4. Dose Selection

Dose selection is one of the most important aspects in the design of a nonclinical toxicology study. For all biologics, the lowest dose should be similar to or a small margin above the anticipated human efficacious dose. For the high dose, it depends on the type of biologic. For a peptide, the regulatory expectations are similar to that of a small molecule and should follow the ICH M3(R2) guidance. The high dose should meet one of the following criteria:

- Limit dose of 1000 mg/kg if this dose results in a mean exposure margin of 10-fold to the clinical exposure and the clinical dose exceeds 1 gram per day. If this is not the case, then 2000 mg/kg is the limit dose.
- Maximum tolerated dose – a dose that produces limited toxicity when administered for the duration of the test period. It should not induce overt toxicity such as appreciable necrosis, organ dysfunction, or

reduce the lifespan of the animals for chronic studies, and should not result in equal to or greater than 10% reduction in body weight gain as compared to control animals.

- Dose that provides a 50-fold margin of exposure to the clinical systemic exposure may be acceptable. However, the maximum dose for the clinic may be limited to 10-fold below the human equivalent of the NOAEL. This depends on the class and toxicity profile of the drug.
- Maximum feasible dose – justification is required to demonstrate that the highest dose was the maximum feasible dose. This dose should still be above the anticipated maximum human exposure. If this is not the case, the sponsor should discuss with the FDA at the pre-IND Meeting.

For many proteins and monoclonal antibodies, there may be no toxicity observed in animal models at high multiples of the anticipated maximum human clinical exposure. Doses are selected to evaluate a dose-response relationship, identify a toxic dose (or a maximum dose), and identify a NOAEL. For therapeutics with little to no toxicity, the rationale for justification of dose levels should include any expected pharmacological effects, maximum feasible dose, and the potency of the therapeutic in the animal species compared to that in humans.

5.3.4.4.1. Immunogenicity Testing in Toxicology Studies

Because nearly all therapeutic proteins elicit an immune response, it is important to evaluate the immunogenicity potential of the therapeutic in the general toxicity studies. If the therapeutic protein is of nonhuman origin, the probability of an immune response is high. Modification of proteins may alleviate immunogenicity, but this is difficult to predict. Generally, more chronic treatment (greater than 6 months duration), route of administration (subcutaneous highest probability), biological activity of the protein, and patient characteristics are factors that contribute to immunogenicity.

The presence of antidrug antibodies can affect the pharmacokinetics of the drug as well as the toxicity profile. Immunogenicity responses can result in reduced efficacy due to high levels of neutralizing antibodies against the therapeutic, skin reactions, drug hypersensitivity, or anaphylaxis-like reactions, etc. Development of antidrug antibodies should be tested from serum obtained in repeat-dose toxicology studies with proteins and monoclonal antibodies (and often peptides). The typical screening assay is a binding assay such as an enzyme-linked immunosorbent assay (ELISA)-type immunoassay. Screening assays should be designed to detect all relevant immunoglobulin (Ig) isotypes. The expected isotypes are IgM and IgG. For mucosal routes of administration, IgA is also expected. Futher, if there is a known risk for anaphylaxis, IgE assays should be developed. An FDA Guidance for Industry "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products," April 2016 describes recommendations for development of antidrug antibody assays.

When interpreting toxicology results, take into consideration whether any antidrug antibodies are present in the serum. Positive results in animal studies are not usually predictive of human potential to develop antidrug antibodies. However, they are informative in terms of understanding the impact of antidrug antibodies on the pharmacokinetics, toxicity profile, and pharmacodynamics of the therapeutic in the animal models.

5.3.4.5. Tissue Cross-reactivity Studies for Monoclonal Antibodies

Tissue cross-reactivity studies are highly recommended by FDA for an initial IND and are conducted in accordance with GLP regulations. In some instances, the particular monoclonal antibody is not a good immunohistochemistry reagent and so the studies are not feasible. Tissue cross-reactivity studies are conducted in normal human tissues and are designed to determine the binding of the therapeutic to its intended target tissue(s), as well as binding to any unintended targets. Tissue cross-reactivity studies are also useful to evaluate target epitope distribution across species. These studies are typically the first performed when selecting a monoclonal antibody clone.

5.4. Nonclinical Regulatory Guidance

The pharmacology/toxicology reviewer at FDA will evaluate the nonclinical program with respect to ensuring adequate safety in the proposed clinical trial. Regulated nonclinical studies are conducted according to GLP standards set forth in 21 CFR, Part 58. Several FDA and ICH guidelines provide important recommendations for inclusion of specific studies in the initial IND. These are guidances to be used as scientifically justified. When science warrants changes to the study design, toxicology species, exclusion of specific studies, or inclusion of additional assessments or studies, the rationale should be provided in the IND. This may also be discussed at a formal FDA Type B pre-IND meeting. FDA comments and minutes from formal meetings are not binding and may change based on additional information or discussion. Some advice will require review of the data once the IND is submitted.

- ICH Guideline S6 (R1) "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals," parent guideline 16 June 1997, addendum 12 June 2011;
- ICH Guideline M3 (R2) "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," January 2010;
- ICH Guideline S7A "Safety Pharmacology Studies for Human Pharmaceuticals," 08 November 2000;
- FDA Draft Guidance for Industry "Bioanalytical Method Validation," September 2013;
- FDA Guidance for Industry "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products," April 2016.

5.5. Interpretation of Toxicity Studies and How They Inform the Clinical Plan

Once the toxicology studies have been conducted, the target tissues identified, and the toxicological profile characterized, safety margins can be estimated for the initial intended starting dose/exposure and the maximum dose/exposure intended in the first-in-human clinical trial. Factors such as severity, reproducibility, monitorability, and steepness of the dose-toxicity curve are taken into consideration when designing the initial clinical trial(s) and selection of doses. In particular, extra caution is warranted for novel first-in-class therapeutics and therapeutics that target the immune system.

Several guidances including ICH M3(R2) guideline, ICH S6 guideline, and the FDA Guidance for Industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers," July 2005, provide recommendations when considering a starting dose for initial clinical trials. These guidance documents provide general recommendations that need to be tailored to each particular therapeutic class with the intent to ensure the safety of human volunteers. For initial studies in patients, a risk-benefit analysis should be presented in the initial IND to justify the starting dose.

For peptides, the recommended starting dose is 1/10 of the NOAEL. The actual dose may be adjusted lower or higher depending on the safety profile observed in the toxicology studies. For proteins and monoclonal antibodies, either 1/10 the human equivalent dose (HED) of the NOAEL, the MABEL, or an additional safety factor depending on the toxicological profile and the class. An additional safety margin may be needed for those therapeutics. When calculating safety margins, it is important to consider the distribution of the therapeutic. Body surface area is taken into consideration when calculating a HED for peptides that are distributed systemically. However, for proteins and monoclonal antibodies, only body weight is considered, since these are large molecules and distribution is often limited to systemic cirulation. Allometric scaling between species based on exposure at the NOAEL in the toxicology species, predicted human clearance, and application of an appropriate safety margin can also be used to determine a human dose.

Clinical trials should incorporate monitoring for adverse findings observed in nonclinical studies. This may include assessments such as additional ECGs, additional neurological testing, additional clinical pathology increased visits, increased length of follow up after treatment phase, etc.

Initial dose escalation also takes into consideration the toxicological profile, including the dose-toxicity curve observed in toxicology species, and is designed to ensure safety for normal human voluteers. For initial studies in patients, a risk-benefit analysis is again used to justify dose escalation. In general, 2- to 3-fold increases in dose may be reasonable depending on therapeutic class, toxicity profile, etc. A slower or faster escalation will depend on any safety concerns, novel therapeutic class, and previous human experience.

The maximum dose may be the NOAEL or 1/10 the NOAEL depending on the safety profile of the drug and class as well as the patient population. Thus, it is important to consider the maximum intended human dose when designing toxicology studies. The maximum human dose may be capped at a lower dose level due to very severe, irreversible, or unmonitorable toxicities seen in nonclinical studies. Initial clinical trials for peptides, proteins, and monoclonal antibodies are not intended to identify the maximum tolerated dose, but rather a therapeutic dose range.

6. CHEMISTRY, MANUFACTURING, AND CONTROLS

6.1. Overview

In evaluating the safety of a product and the suitability of the IND, the FDA will review each IND on a case-by-case basis. Factors such as risk to the patients, number of patients, route of delivery, capability of the manufacturing and test sites to prepare and evaluate the material, as well as historical safety information about the class of product under evaluation will be considered. Because of these variables, it is difficult to have an absolute “minimal” list of items required for an IND. During the IND review period, FDA reviewers will take into account the complexity of the manufacturing process, number of batches manufactured using the proposed process, variability in those batches, the comprehensiveness of the analytical methods used to determine product quality, and stability of the product to determine whether the information contained in the IND is sufficient.

Biological products are typically manufactured using bacterial or mammalian-based expression systems. Because of this, the potential for unwanted viruses, or other sources of potential contamination need to be evaluated. The manufacturing processes for biologics must be designed to provide purification steps that have been demonstrated to inactivate or remove known or potential contaminants. Process validation studies to demonstrate inactivation or removal of viruses are required. In addition, process-related impurities such as host cell proteins, solvents, and column matrix material should be defined and limits established. Assays used to characterize the drug substance and control the process must be scientifically sound so that the composition of the drug substance used in toxicology studies can be compared to that proposed for clinical use. For the conduct of nonclinical safety studies, adequate stability data are required to demonstrate the test subject is administered material of known quality at the time of delivery.

6.2. CMC Development Plan

A CMC development plan coordinates the numerous sequential and parallel activities that support the development of a drug entity as part of the process for obtaining a cleared IND for a specific clinical indication in the United States. To minimize the time and cost for obtaining IND clearance for an experimental therapeutic, a thorough understanding and close coordination of the CMC, nonclinical, clinical, and regulatory processes and strategies is necessary. Thus, the CMC development plan and timelines must be evaluated and integrated as part of the overall product development plan. Key components of a typical CMC development plan are outlined below:

- Manufacture and characterization of the drug substance or API
- Analytical methods development
- Potency assay development
- Generation of stability data for the drug substance
- Preformulation and formulation development of the drug product
- Analytical development for the drug product
- Manufacturing of clinical trial material (CTM)
- Generation of stability data on the drug product

6.2.1. Drug Substance Manufacture

Manufacture of the bulk API progresses from laboratory to clinical scale as the technology is transferred to a larger facility that can manufacture the product more reproducibly. Selection of an API manufacturer is critical because API production supplies all subsequent pharmacology, toxicology, preformulation, and formulation activities. It is recommended that qualification of the API manufacturer, including an onsite evaluation of GMP capabilities, be performed before submission of the IND.

6.2.2. Drug Substance Characterization

It is critical to have systems in place to track and demonstrate physical and chemical equivalence among all batches used for key activities such as toxicology and clinical trials. This is required as part of any CMC section submitted under ICH Quality guidelines (and will be a particular focus of any due diligence conducted as part of a partnering or outlicensing strategy). As part of an initial IND, the sponsor must provide some data supporting the chemical structure of the proposed agent. Please see (Table 4), Section 3.2.S.3.1 for a list of characterization tests commonly used for protein, peptide, and monoclonal antibodies.

6.2.3. Preformulation and Formulation

Preformulation and formulation activities use knowledge of the API's physical, chemical, and mechanical characteristics along with its compatibility with excipients to develop prototypes and finalize the drug product dosage form. The drug product is then scaled up in GMP facilities for production of CTM and, eventually, commercial lots. It is recommended to contract with a single organization to perform both formulation and analytical development and to manufacture CTM. Contracting with a single manufacturer will avoid the need for technology transfer at a time-critical point in development.

Preformulation activities are scientific investigations that are conducted to identify the physical and chemical characteristics of a drug substance, alone and in the environment in which it is likely to be formulated. The data obtained during preformulation studies are used to develop the dosage form that will be used in nonclinical studies and clinical trials.

Outside of the formulation constraints identified during the preformulation studies, several key factors must be considered before the dosage form can be finalized. These factors include: identifying the intended doses required for clinical trials; selecting suitable excipients; finalizing the qualitative and quantitative ingredients of the formulation; identifying process parameters to ensure a uniform and consistent product; and selecting an appropriate container closure system.

6.2.4. Analytical Method Development

The assays and test methods used to assess the critical physical and chemical properties of the API are identified during the analytical method development program. The development of these methods is crucial to the overall

development of the selected molecule as they are used to determine the impurity profile, degradation products, stability, and other key parameters of the drug. Analytical development and testing activities provide the information needed to establish release specifications for the API and provide insight as to the stability of the formulated drug product. In addition, monitoring the impurity profile of early API lots can ensure that as API development proceeds, new or heightened amounts of existing impurities are detected so that their impact on the toxicology and clinical database can be evaluated. Please see (Table 4), Section 3.2.S.3.1 for a list of product release tests commonly used for protein, peptide, and monoclonal antibodies.

Along with formulation development activities, the development of a stability-indicating, high-performance liquid chromatography (HPLC) assay that has been validated for the clinical dosage form is in the critical path. A stability-indicating assay is able to resolve the API from all excipients, impurities, and degradation products, thereby allowing a profile of the stability characteristics of the drug product to be created. Analytical and stability testing identifies the impurity profile, degradation products, and other key parameters of the drug in order to establish the release and stability specifications of the drug product.

6.2.5. Stability Testing

All supplies for the IND including drug product, matching placebo, and comparators (already marketed products) must meet predetermined quality specifications when packaged and labeled for use in unblinded and blinded clinical trials. While shelf life is being determined, all drug products used in human studies will be periodically tested to ensure product quality has not decreased over time.

Drug product stability must be addressed prior to an IND submission in order to generate data to support the use of the product in the clinical setting. Generally, stability studies for both API and drug product follow the recommendations in the ICH Q1A Stability Testing of New Drug Substances and Products guidance document. The amount of stability data required depends in part on the length of the proposed clinical trial. For clinical trials of very short duration, the initial IND can contain limited stability data. However, long-term stability should be generated in parallel with the clinical trial.

6.3. CMC Regulatory Guidance

When reviewing the CMC section of an IND submitted for a Phase 1 clinical trial, the FDA examines the documentation from the perspective of safety. The regulations pertaining to the filing of INDs for both small-molecule and biologic-based products are described in 21CFR312. However, any biologic-based product must also adhere to the regulations provided in 21CFR600.

Additional guidance for various biologic modalities is also provided in both ICH and FDA guidance documents for industry. In addition to adhering to the applicable regulations and guidance documents, an understanding of the responsibilities of the different FDA reviewing divisions is also important. For example, cellular and gene therapy–based products are reviewed by CBER. However, products such as monoclonal antibodies, proteins, and nonvaccine immunomodulators are reviewed by CDER. As a result, a full understanding of the type of product being developed is crucial to ensuring advice is sought from the appropriate division. A list of some of the potential guidance documents that could be applicable to peptide, protein, and monoclonal antibody biologic modalities includes the following:

- 21CRF312, 21CRF210 and 21CRF211, and 21CRF600, 21CRF601, 21CRF610
- Guidance for Industry CGMP for Phase 1 Investigational Drugs (2008)
- ICH Guideline M4Q: The CTD - Quality
- ICH Guidelines: ICHQ2A and Q2B on Assay Validation
- ICH Guideline Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

- ICH Guideline Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used in the Production of rDNA Proteins
- ICH Guideline Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- ICH Guideline Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
- ICH Guideline Q6B Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- Container Closure Systems for Packaging Human Drugs and Biologics
- ICH Guideline Q1A(R2) Stability Testing of New Drug Substances and Products
- Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997).

A summary of the documentation that should be included in an initial IND for a biological product is provided in the Appendix (Table 4). Detailed descriptions of typical characterization and development studies were included so that creation of a development strategy and appropriate collection of information could be considered.

7. THE PRE-IND MEETING

7.1. Pre-IND meeting

7.1.1. Meeting Timing: factors to consider when choosing a date

Many factors must be considered when deciding on the timing of a pre-IND meeting. On occasions when the technology to be submitted in the IND is sufficiently novel that a discussion is required to educate the agency with regard to the mechanism of action, therapeutic effect, or manufacturing specifics and the resulting potential toxicities, a pre-pre-IND meeting may be requested prior to the formal pre-IND meeting. In most circumstances where the nonclinical and CMC activities are standard and no regulatory questions require FDA input in order to move to IND-enabling studies, the pre-IND meeting can wait until two to three months prior to the submission of the IND to allow a comprehensive review of the data to be contained in the IND with the agency. This minimizes the likelihood of additional questions arising between the conduct of the pre-IND meeting and submission of the IND.

7.1.2. Meeting Preparation

The preparation process can be broken down into four separate stages for a pre-IND meeting, and the FDA guidance "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Product" of March 2015 should be strictly adhered to during the preparation. The pre-IND Meeting is considered a Type B Meeting and as such requires the meeting request letter be submitted to FDA 60 days in advance of the desired meeting date and the meeting package be submitted to FDA 30 days in advance of the scheduled meeting date. It is advisable to propose several dates to the agency for the eventual meeting date to expedite the scheduling. Several potential responses exist for a request for a pre-IND meeting: 1) face-to-face meeting; 2) teleconference; 3) written responses only. A face-to-face meeting is desirable for a sponsor's first interaction with the agency with a new product, but this may not be offered by the agency depending upon its schedule and interest in the product.

7.1.3. Question Formulation

Question formulation is the paramount activity contributing to a successful pre-IND meeting. Question generation should not begin until all data intended to be included in the Pre-IND Meeting Package and the IND are generated, reviewed, and understood. Some sponsors prepare their briefing book prior to finalizing the questions to ensure no questions are missing. Only then can one be sure that the questions generated are sufficiently comprehensive and specific to result in a successful meeting. Questions should be organized by discipline, ideally in the following order: 1) clinical, 2) nonclinical, 3) CMC, and 4) regulatory, as each of the discipline questions potentially depends on information from the previous discipline. Questions should be preceded by a couple of paragraphs of context and potentially hyperlinks from these paragraphs to the relevant Pre-IND Meeting Package section to assist the FDA reviewer in completely understanding the question. The questions should be phrased to solicit a yes or no answer from the agency for absolute clarity. FDA will add additional details as necessary to explain its

answer. No open-ended questions should be asked to avoid being asked to investigate tangential questions posed by the agency that will not help advance development of the technology.

7.1.4. Meeting Request Letter Preparation

The 2015 FDA guidance on Formal Meetings contains an outline for the content of the letter required to request a pre-IND meeting. Efforts should be made to keep the information in the administrative sections to a minimum, with the questions composing the bulk of the letter. Attendees from FDA should be requested based on their expertise to respond to the included questions. At a minimum, include sufficient sponsor representatives to discuss each of the disiplines (clinical, nonclinical, CMC, regulatory) addressed in the questions. Adding statistical and clinical pharmacology experts to the sponsor's attendees is strongly recommended even though questions may not specifically include these disciplines, as the discussions in the meetings often address these topics. Everyone is responsible for recording notes of the meeting to the best of their ability. If attendees are not sufficiently talented or experienced in this regard, a professional scribe should be enlisted.

7.1.5. Meeting Information Package Preparation

A recommended outline for the format of the meeting package is contained in the 2015 FDA guidance. The Meeting Package should be prepared with the IND in mind, so that the text, tables, and figures used for the preparation of the Meeting Package can be repurposed for the ultimate IND submission. Questions generated for the Pre-IND Meeting Request Letter should be altered only if absolutely necessary, keeping in mind any additional FDA attendees who should be invited based on the changed question. The size of a meeting package should be no more than 50 to 75 pages if one expects the FDA reviewers to digest the material. Any extensive supporting data or text should be seriously evaluated before being included and then confined to an appendix (e.g., the Phase 1 clinical trial protocol or detailed synopsis).

7.1.6. Meeting Preparation

The questions generated for the meeting form the basis for the preparation procedures for the meeting, with each question analyzed for anticipated responses from the FDA. The meeting package should also be reviewed to identify any weaknesses in the data and anticipated FDA questions about these weaknesses. The anticipated FDA questions should be captured in a table, with a sponsor team member assigned to answer each question and compose a draft response. Any supporting slides required to adequately explain the answers to these potential questions should be prepared. At least two teleconferences should be conducted to review these anticipated FDA questions and rehearse the intended answers emphasizing clarity, brevity, and focused responses to allay agency concerns without raising additional questions. The day prior to the scheduled pre-IND meeting, the team should assemble in person if at all possible (or via teleconference, if needed) to iron out any last minute issues. With many FDA divisions, the team will have received preliminary FDA responses based on the agency pre-meeting prior to this face-to-face rehearsal (typically these responses are obtained the day prior to the meeting but they can be received as long as a week ahead of the meeting or not at all). Consequently, additional slides may be needed to respond to issues raised by FDA on the submitted questions or other additional questions derived from their review of the meeting package. This ensures all items are resolved by the end of the pre-IND meeting.

7.1.6.1. Meeting Conduct

For a face-to-face pre-IND meeting, arrival at the FDA White Oak Building, Silver Spring, MD is recommended at least 30 minutes prior to the scheduled meeting time to enable identification processing of attendees and issuing of badges for security (45 minutes for a large group of attendees). All attendees are required to present visual evidence of identification and FDA requests a prior alert to the meeting date of foreign attendees. Communication with the FDA regulatory project manager must be made in advance of the meeting if the intent is to present slides addressing any issues. FDA will expect to receive a copy of the intended slides for review by the FDA attendees prior to the meeting. No new material will be allowed to be presented at the meeting. A list of attendees from each institution should be exchanged at the meeting or immediately following the meeting through email with the regulatory project manager. The meeting is moderated by FDA with a sponsor attendee identified ahead of time who assigns each of the FDA questions when asked to a disciplinary expert on the sponsor team for a response. Answers to any FDA questions should be kept succinct and on point. Each of the sponsor attendees are required to take as accurate as notes as possible, ideally identifying the FDA attendee from whom a question originated. Following the meeting, the sponsor team may engage in informal discussions with the FDA attendees for a few minutes before adjourning to a hotel meeting room to corroborate perspectives on the meeting and assemble all copies of notes into as accurate transcript as possible. A copy of the sponsor's meeting minutes should be provided to the regulatory project manager at FDA within a week of the meeting to gain the sponsor's perspective prior to finalizing the FDA minutes. FDA's minutes will be issued within 30 days of the meeting date and are considered the official meeting minutes for future reference.

8. INVESTIGATIONAL NEW DRUG APPLICATION

8.1. Common Technical Document

In this section, we will describe Modules 1 through 5 in the common technical document. For each module, we will review the regulatory expectations. For Module 2, we will review how to describe the nonclinical program and summarize any existing safety, including publicly available literature, as it relates to the clinical development program. The requirements for an IND are outlined in 21 CFR, Part 312.23, IND Content and Format.

8.1.1. Adminstrative Information (Region specific) (Module 1)

Module 1 is a regional and largely administrative section. The following components are typically included in Module 1 for an initial IND:

1. Form 1571: This is a requirement and needs to be completed for each IND submission and amendment for the life of the IND.

   https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf

   Instructions:
   https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf

2. Form 1572: at least one is required from a principal investigator for the proposed trial and a curriculum vitae for this principal investigator is also provided.

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

3. Form 3674: Certification of Compliance with Requirements of Clinical Trials.gov Data Bank.

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM354618.pdf

FDA Guidance for Industry "Form FDA 3674 – Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions," revised June 2017, https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm562439.pdf

4. Investigators Brochure (21 CFR, Part 312.23(a)(5))
5. General Investigational Plan (21 CFR, Part 312.23(a)(3).
6. Investigational Drug Labeling (21 CFR, Part 312.6)
7. Environmental Assessment (21 CFR, Part 25.40, claim of categorical exclusion due to therapeutic in development under IND)
8. Pre-IND meeting minutes and briefing package
9. Any letters of authorization for Drug Master Files and/or letters of authorization to cross-reference other INDs, as appropriate

8.1.2. Clinical (Modules 2.7, 2.5, and 5)

ICH M4E Guidline "Format and Structure of Benefit-Risk Information, Efficacy," 15 June 2016, provides general guidance on the presentation of studies within these sections. The Clinical Summary, Module 2.7, is typically not needed for novel therapeutics since they often will not have been investigated in clinical trials. However, if the therapeutic has been investigated in clinical trials conducted outside the United States, or is under investigation for other indications, the results of those studies, particularly safety, as relevant to the proposed indication for the IND should be described in Modules 2.7.3 (efficacy), 2.7.4 (safety), and 2.5 (clinical overview). If literature exists regarding the safety of the therapeutic in humans, this information should also be summarized in Module 2.5. In vitro clinical pharmacology studies, bioanalytical and immunogenicity method development, validation studies, and results from human studies should be described in Module 2.7.1 and 2.7.2.

Module 2.5 should summarize the clinical plan, any clinical trials conducted with the therapeutic, and the available safety data that can inform the intended clinical trial and development program.

Module 5 will contain the protocol for the proposed initial clinical trial, any study reports from studies conducted outside the United States, clinical pharmacology studies, bioanalytical methods, and immunogenicity method development and validation studies conducted to support the development program. The location of the study reports within Module 5 is described in ICH M4E.

8.1.3. Nonclinical (Modules 2.6, 2.4, and 4)

ICH M4S(R2) Guidance "Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4," 20 December 2001, provides general guidance on the presentation of of studies within these sections. Requirements for the pharmacology and toxicology information for an IND are also set forth in 21CFR312.23(a)(8). Module 2.6 contains nonclinical written and

tabulated summaries and is often the largest module for most initial INDs, particularly for new molecular entities. This module has 7 sections that will be discussed briefly here. The nonclinical study reports are provided in Module 4; however, sufficient information should be provided in each section to enable the FDA reviewer to understand the basic study design and findings. A common best practice is to present similar studies in a similar format even if they are described in a different manner in the study reports. Each study summary should include the objective of the study, rationale for study, a brief description of the study design, results, and conclusions for the study as well as what the data mean for the development program. Providing this information facilitates FDA review of the nonclinical sections.

8.1.3.1. Module 2.6.1: Introduction

This section should introduce the FDA pharmacology/toxicology reviewer to the therapeutic and the proposed clinical use. This section should include information on the structure of the therapeutic (including a diagram where possible) and its pharmacological properties. This section should also provide information on clinical indication, dose, and duration of use.

8.1.3.2. Module 2.6.2, 2.6.4, and 2.6.6: Written Summaries of Pharmacology, Pharmacokinetics, and Toxicology

The written summaries will contain a brief description of each study conducted. In vitro studies should precede in vivo studies. Studies of the same type should be ordered by species, by route of administration, and then by duration (shortest duration first). Each study described in this section should have a report.

Written summaries should not only describe each study that was conducted, but also why the study was conducted (objective), the overall study design including dose levels, dose frequency route and duration, formulation, number/sex/age of animals per group, high-level description of methods, results, and conclusions for the study, and most importantly what it means to the development program. It is often easier to author the main body of each written summary, then author discussion and conclusions, and finally the brief summary. Tables and figures can be added in text or provided at the end of the document. It is helpful to have tables of similar information presented in a similar manner. There is no page limit for Module 2.6; however, it should not exceed 100 to 150 pages for a full development program as per the ICH M4S guideline, and possibly less for an initial IND depending on the nonclinical program. In practice, most INDs and NDAs exceed this recommendation, often with 50 pages for each written summary (2.6.2, 2.6.4, and 2.6.6) and 30 pages for the nonclinical overview (2.4).

The discussion and conclusions sections should provide a concise overview of the key findings of studies described in the written summary. It should also provide interpretation where possible and potential relevance to the proposed clinical program. It is important to integrate any findings with dose and exposure and relate this to the proposed clinical program.

8.1.3.3. Modules 2.6.3, 2.6.5, and 2.6.7: Tabulated Summaries of Pharmacology, Pharmacokinetics, and Toxicology

Study data are presented in a tabulated format in these sections, enabling the study director to review data presented in a familiar and organized manner. Several examples of recommended formats are provided in Appendices B and C of ICH M4S(R2). Although study reports are

submitted with an initial IND, the tabulated summaries represent the primary review of the study data, so providing detailed information is important.

8.1.3.4. Module 2.4: Nonclinical Overview

Nonclinical Overview, Module 2.4, should integrate the pharmacology, pharmacokinetics, and toxicology results, conclusions, and interpretation as described in Module 2.6 with the clinical program, and also what may be known about the class of molecules from the literature. This section should discuss safety margins for any adverse findings relative to the starting dose and maximum anticipated human exposure. For systemically available peptides, body surface area should be taken into consideration when calculating a HED. For proteins and monoclonal antibodies, HED is often described in an mg/kg basis for therapeutics that are distributed systemically. For therapeutics that are localized to a specific compartment, compartmental volume for the nonclinical species and humans is often used to determine safety margins. It is important to not only consider dose in terms of concentration in a compartment or systemic levels, but also the concentration of the dosing solution if appropriate as this may relate to toxicities including findings at the injection site.

8.1.3.5. Module 4: Nonclinical Study Reports

Nonclinical information, including study reports and literature references, is located in Module 4. Individual study reports should reside in Module 4.2. The order of presentation is described in ICH guideline M4S(R2). Literature references are provided in Module 4.3.

8.1.4. Chemistry, Manufacturing, and Controls

Chemistry, Manufacturing, and Controls Overview, Module 2.3, is not required for an initial IND and many companies choose not to include it since it is a redundant overview of Module 3.

Module 3 should contain the elements outlined in (Table 4) of the Appendix.

8.2. 30-Day Review Period

Once an IND is filed, it is reviewed by the FDA during a 30-day review period. If the FDA has not notified the sponsor of any clinical hold issues, the IND goes into effect 30 days after receipt of the IND. During the review period, FDA may request additional information or they may want to discuss the proposed clinical protocol in a teleconference. It is important to be available during this period of time. Typically, requests for information have very short timelines to enable full review of the IND in a 30-day period.

9. SUMMARY

Government funding sources such as the NINDS CREATE Bio cooperative agreement program support biologic preclinical and clinical therapy development for neurological disorders and stroke. Successful navigation through the drug optimization and development process to IND requires careful planning, beginning with a TPP and expert team members including regulatory, clinical, nonclinical, CMC, and commercial. Small business will often supplement the company staff with consultants to round out the expertise needed to bring a therapeutic to IND and beyond to marketing authorization. Key aspects of the TPP, such as dose level, dosing regimen, safety,

and efficacy are considered as early as lead optimization and selection of a candidate to bring through IND-enabling studies to an IND if the risk-benefit warrants continued progression. An integrated development plan is designed to address key aspects of the TPP and ultimately the Package Insert (Label). The clinical plan is developed first, beginning with the pivotal Phase 3 clinical trial designed to address key aspects of the TPP and Label, then Phase 2 clinical trial, and ultimately Phase 1 clinical trial. The nonclinical and CMC plans are designed to support the clinical program and ultimately marketing authorization. There are many key dependencies between the disciplines that require careful management and timing. Thus, successful translation of any therapeutic development program requires an integrated team, an integrated plan, and communication between team members. A properly timed and well-considered formal FDA pre-IND meeting provides an opportunity to gain input and agreement on specific aspects of the development program to ensure a successful IND application. The initial IND in CTD format begins the documentation and scientific rationale that will ultimately form the basis for a marketing authorization application.

Table 4: CMC Information Needed for an Initial IND for a Biological Product.

Requirement	Information Required	Comments
3.2.S Drug Substance		
3.2.S.1 General Information		
3.2.S.1.1 Nomenclature	Information on the nomenclature of the drug substance should be provided. For example: • Recommended International Nonproprietary Name (INN) • Compendial name if relevant • Chemical name(s) • Company or laboratory code	
3.2.S.1.2 Structure	The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. Specifically for biological products: The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications and relative molecular mass should be provided, as appropriate.	
3.2.S.1.3 General Properties	A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for the therapeutic.	
3.2.S.2 Manufacture		
3.2.S.2.1 Manufacturers	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.	

3.2.S.2.2 Description of Manufacturing Process and Process Controls	Information should be provided to adequately describe the manufacturing process and process controls. An overview of the process should include a flow chart and a process narrative.	Process flow chart: Describe the entire process from first step in the process (i.e., isolation of gene of interest) to the final bulk drug substance. Process narrative: Information should be provided on the manufacturing process, which typically starts with vials of the cell bank and includes cell culture, harvests, purification and modification reactions, filling, storage, and shipping conditions. Specific items to be included: • Cell culture and harvest o The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature should be included. • Purification o A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers, other reagents, major equipment, and materials. • Filling, storing, and shipping o A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided.
3.2.S.2.3 Control of Materials	Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials, including biologically sourced materials (e.g., media components, monoclonal antibodies, enzymes), meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically sourced materials, this can include information on the source, manufacture, and characterization.	• Control of source and starting materials of biological origin o Describe the cell line/tissue chosen for isolation of the gene. o Summaries of viral safety information for biologically sourced materials should be provided. o If possible, identify source of the cell line (ATCC), age, gender, and species of donor. o For human cell lines, include donor medical history (if available), provide cell culture history before and after receipt, describe any identity testing, and tests for adventitious agents. • Source, history, and generation of the cell substrate o Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the master cell bank should be provided as described in ICH guidances Q5B and Q5D. • Cell banking system, characterization, and testing o Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the master and working cell banks) should be provided as described in Q5B and Q5D.

3.2.S.2.4 Control of Critical Steps and Intermediates	Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps of the manufacturing process to ensure that the process is controlled should be provided. Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.	For biological products, stability data supporting and storage conditions should be provided.
3.2.S.2.5 Process Validation and/or Evaluation	Full process validation is typically not required for Phase 1 INDs.	
3.2.S.2.6 Manufacturing Process Development	A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical and clinical batches.	For biological products: The developmental history of the manufacturing process should be provided. The description of changes made to the manufacture of drug substance batches used in support of the nonclinical and clinical studies should include, for example, changes to the process or to critical equipment. The reason for the change should be explained.
Note: The purification schemes for proteins and monoclonal antibodies (mAbs) should include the following information: • Production techniques that will prevent the introduction of and eliminate contaminants, including animal proteins and materials, DNA, endotoxins and other pyrogens, culture media constituents, components that may leach from columns, and viruses. • Incorporation of one or more steps known to remove or inactive retroviruses. Industry practice is usually to include two orthogonal (i.e., based on different mechanisms), robust viral removal steps. Note that inclusion of those steps does not eliminate the need for viral clearance studies. o Robust viral removal/inactivation steps are defined as those that have been shown to work well under a variety of conditions with a variety of mAbs. o Examples of removal/inactivation steps include low pH, heat, solvent/detergent treatments, and filtration. • Demonstration of the ability of the purification scheme to remove adventitious agents and other contaminants by means of a clearance study. • Limits should be set on the number of times a purification component (e.g., a chromatography column) can be reused. Such limits should be based on actual data obtained by monitoring the component's performance over time.		
3.2.S.3 Characterization		
3.2.S.3.1 Elucidation of Structure and Other Characteristics	For desired product and product-related substances, details should be provided on primary, secondary, and higher-order structure; posttranslational forms (e.g., glycoforms); biological activity, purity, and immunochemical properties, when relevant.	• Physicochemical characteristics: o Provide evidence that the molecule or agent is the one expected. Summarize the analyses performed and the results for structural determination (primary, secondary, and tertiary) of the molecule. Compare results with reference product or published data (if possible). Potential studies include: ▪ Molecular formula determination (vs theoretical) • Amino acid analysis

		• Amino acid sequencing (minimum N and C terminal) • Peptide mapping ▪ Molecular weight determination (vs theoretical) ▪ Spectrophotometric analysis ▪ Physicochemical characteristics ▪ Determination of posttranslational modifications ▪ Glycosylation profiles • Carbohydrate characterization and variation • Biological and immunological characteristics o Bioidentity, bioactivity, and specific activity compared with reference product.

Notes on characterization of purified monoclonal antibodies (mAb)

Before a mAb can be studied in humans, a precise and thorough characterization of antibody structural integrity, specificity, and potency should be conducted and described in the IND. The mAb should be as free as possible of non-Ig contaminants. A properly qualified in-house reference standard with known characteristics, specificity, and potency should be used for lot-to-lot comparisons. The reference material should be stored under appropriate conditions and periodically tested to ensure its integrity.

1. Structural Integrity
    a. A combination of sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), HPLC, mass spectrometry, or other appropriate physicochemical methods should be used to show that the purified antibody is not fragmented, aggregated, or otherwise modified. Side-by-side comparisons of production lots to the in-house reference standard should be performed.
2. Specificity
    a. Assays should provide evidence that the binding of the mAb to the target antigen is specific. Once the specificity of the mAb is characterized, it should be screened for cross-reactivity with human tissues. The following are some suggestions on the design of specificity studies:
        i. Direct binding assays should include both positive and negative antibody and antigen controls. At least one isotype-matched, irrelevant (negative) control antibody should be tested. Negative antigen controls should include a chemically similar, antigenically unrelated agent, if available (e.g., similar chemical nature, size, charge, and charge density).
        ii. Whenever possible, the protein bearing the reactive epitope should be biochemically defined, and the antigenic epitope itself determined. If the antigenic determinant is a carbohydrate, the sugar composition, linkage, and anomeric configuration should be established.
        iii. If possible, specificity studies using antigenic preparations of defined structure (oligosaccharides or peptides) should be conducted to characterize antibody specificity, means of inhibition, or other techniques. For complex biological mixtures, the lots of antigen and/or inhibitors used for direct binding tests should be standardized. Inhibition of antibody binding by soluble antigen or other antibodies should be measured quantitatively.
        iv. Once the specificity of an antibody has been determined, it is important to quantitate antibody binding activity by affinity, avidity, immunoreactivity, or combinations of these assays, as appropriate.
3. Potency Assays and Potency Specification
    a. Potency assays are used to characterize the product, to monitor lot-to-lot consistency, and to assure the stability of the product. Potency may be measured by a binding assay, a serologic assay, activity in an animal model, and/or a functional assay performed in vitro or in vivo. It is desirable that the assay(s) bear the closest possible relationship to the physiologic/pharmacology activity of the product. The assays should be sufficiently sensitive to detect differences of potential clinical importance in the function of the product. In particular, when the performance of the antibody depends not only upon antigen binding but also on other functions, it is desirable that the potency assay(s) measure all such functions. Documentation of the potency assay's performance, including sensitivity, intra- and inter-assay variation, and robustness, should be provided.
        i. Antibody binding activity may be quantitated by ELISA, radioimmunoassay, radioimmune precipitation, cytotoxicity, flow cytometry, or any other standard method. Activity should be expressed as specific antigen-binding units per mg or microgram of antibody. Product should be compared to an in-house reference standard. Appropriate measurements of antibody affinity, if established, may be a useful adjunct to other assays. Parallel-line bioassay or a similar, valid statistical procedure should be used in calculating potency.
        ii. The potency of a mAb may also be tested by measurements of in vivo function in animal models, although such assays are often cumbersome and difficult to standardize and should not be the sole measure of potency.

<table>
<tr><td colspan="3">iii. The permissible range of values in potency assays that reflects adequate biological activity of a product should be based on experience with a particular antibody. Ideally, potency assays should be correlated with in vivo activity in order to develop control tests which will ensure an effective product. This implies that multiple production lots should be used during the clinical development program and potency assay results should be correlated with clinical performance.</td></tr>
<tr><td>3.2.S.3.2 Impurities</td><td>Information on impurities should be provided. Data on observed impurities for relevant batches (e.g., nonclinical, clinical, and stability) should be provided in tabulated format.</td><td>Process-related impurities: Host cell proteins, host cell nucleic acids, cell culture-derived components (e.g., serum, antibiotics), downstream process additives, (e.g., enzymes, reducing agents, ligands). Process impurities are often treated as product residuals.

Product-related substances: Molecular variants of the desired product formed during manufacture and/or storage that are active and have no deleterious effects on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

Product-related impurities: Aggregates, truncated forms, other modified forms (deamidated, isomerized, oxidized, etc.). Degradation products are considered product-related impurities.</td></tr>
<tr><td colspan="3">3.2.S.4 Control of Drug Substance</td></tr>
<tr><td>3.2.S.4.1 Specifications</td><td>Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities as conditions of approval.

Specifications are legally binding criteria that a medicinal product must meet.

The specification for the drug substance should be provided in a tabular format and should include the tests, methods used, and acceptance criteria.</td><td>A specification is defined as a list of tests, with references to analytical procedures, with appropriate acceptance criteria that are numerical limits or ranges, or other criteria for the tests described.

Specifications should take into account:
Characterization studies
performed in development phase
following significant process changes
relevant and up-to-date methods
Analytical considerations
reference standards and materials
validated
Manufacturing process and process controls
Pharmacopeial specifications
Shelf life
Statistical concepts
Examples of quality tests for peptides, proteins, and mAbs are provided below.<table><tr><td>Peptides:
Identity
Sequence
Molecular weight
Peptide purity</td><td>Proteins:
Appearance
Identity
Structure
Molecular weight</td><td>mAbs:
Appearance
Identity
Protein content
Specific activity</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td></td><td>Optical purity
Amino acid composition
Counter ion
Peptide content
Moisture
pH
Residual solvent</td><td>Quantity
Purity and impurities
Potency
Solubility
pH
osmolality
Microbiological quality
Endotoxin</td><td>Purity
Process impurities
pH
Microbiological quality
Endotoxin</td></tr>
<tr><td>3.2.S.4.2 Analytical Procedures</td><td>The analytical procedures used for testing the drug substance should be provided.

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.</td><td colspan="3">Typical methods used to characterize biologicals and their degradation products:
<table><tr><th>Methods</th><th>Examples</th><th>Applications</th></tr><tr><td>Column chromatography</td><td>HPLC, FPLC, low pressure LC; size exclusion, reversed-phase, ion-exchange, hydrophobic, affinity columns; coupled with UV, fluorescence, RI, and other analytical instruments as detectors</td><td>Most physical and chemical degradations, excipient impurities, leachates</td></tr><tr><td>Electrophoresis</td><td>SDS-PAGE, native PAGE, isoelectric focusing, capillary electrophoresis, etc.</td><td>Degradations with changes in size and/or charge</td></tr><tr><td>Spectroscopy</td><td>CD, fluorescence, FTIR, UV, Raman, NMR, etc.</td><td>Structural changes, chemical modifications of side groups</td></tr><tr><td>Thermal analysis</td><td>Differential scanning calorimetry, thermogravimetric analysis, thermomechanical analysis, etc.</td><td>Protein structure, lyophilized cake structure, powder characterizations</td></tr><tr><td>Light scattering/ turbidity</td><td>Dynamic light scattering, other light scattering devices, turbidity, particle size determination, particle counter, etc</td><td>Aggregation, precipitation, molecular weight determination</td></tr><tr><td>Other microcharacterization methods</td><td>Peptide mapping, peptide sequencing, amino acid analysis, mass spectrometry, other specific analyses for individual reactive groups</td><td>Identification of impurities and chemical degradation, analysis of complex proteins, e.g., antibody and glycoprotein</td></tr></table></td></tr>
<tr><td colspan="5">Note on analytical methods regarding forced degradation studies:

To confirm the appropriateness of the selected analytical methods for monitoring the stability of the active pharmaceutical ingredient, forced degradation studies should be conducted to confirm the methods are stability indicating. Forced degradation studies involve the intentional degradation of a molecule to an</td></tr>
</table>

appropriate extent by means of various stressing agents (temperature, light, chemical agents, mechanical stress). The purpose is to mimic what could happen under the proposed storage conditions and confirm the methods can detect any changes in product quality, should they occur. Biological products usually degrade via different pathways following different kinetics (first order to higher order). The extent of degradation considered appropriate for forced degradation studies cannot be unequivocally established and may vary from product to product. The extent of degradation should be targeted depending also on the knowledge of the molecule (e.g., considering pCQAs, biological activity, etc.) and of the variability of the technique/method used to measure the degraded product. Various stressing conditions or agents can be investigated. Examples include the following: - Elevated temperature (at least 10°C increment above the accelerated testing temperature as recommended by ICH Q1A and below the lowest melting temperature Tm) - Freeze/thawing - Low and high pH (e.g., below pH 4 and above pH 8 also combined with elevated temperature if needed, for deamidation) - Oxidizing conditions (chemical agent such as hydrogen peroxide, t-butyl hydroperoxide or 2.2'-azobis(2-amidinopropane) dihydrochloride (AAPH)) - Light (e.g., using conditions prescribed in ICH Q1B or milder conditions depending on the molecule) - Agitation - Addition of metals (may lead to oxidation) - UV exposure (may lead to aggregation or to a detectable change in higher order structure) The actual conditions used should be defined and/or optimized on a case-by-case basis and proper controls should be used.		
3.2.S.4.3 Analytical Method Validation	Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided. The summaries of method validations should be provided in tabular format.	
3.2.S.4.4 Batch Results	Test results for batches used in nonclinical studies and for the proposed clinical studies should be provided in tabular format.	A summary of the drug substance history should be provided in tabular format. For each drug substance batch, provide: • Date of manufacture • Site of manufacture • Batch size • Container closure system • Use of drug substance batch (e.g., stability, nonclinical studies, and clinical studies) Drug substance test results should be provided in tabular format. Recommend providing data in side-by-side columns to facilitate review across batches. It is recommended to include pictures of PAGE gels for both protein and mAb products.

3.2.S.5 Reference Standards	Information on the reference standards or reference materials used for testing of the drug substance should be provided.	
3.2.S.6 Container Closure System	A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and their specifications.	
3.2.S.7 Stability		
3.2.S.7.1 Stability Summary	The types of studies conducted, protocols used, and the results of the studies should be summarized.	
3.2.S.7.2 Stability Commitment	The protocol used to evaluate the stability of drug substance to be used for clinical investigation should be provided	
3.2.S.7.3 Stability Data	Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphic, or narrative.	
3.2.P Drug Product		
3.2.P.1. Description and Composition of the Drug Product	A description of the drug product and its composition should be provided.	The information provided should include, for example: • Description of the dosage form • Composition (i.e., list of all components of the dosage form and their amount on a per unit basis [including overages, if any]) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications) • Description of accompanying reconstitution diluents • Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable
3.2.P.2.Pharmaceutical Development	A summary should be provided on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application.	Specific topics for this item include: • 3.2.P.2.1 Components of the Drug Product o Drug substance o Excipients • 3.2.P.2.2 Drug Product o Formulation development o Overages o Physiochemical and biological properties • 3.2.P.2.3 Manufacturing Process Development

		• 3.2.P.2.4 Container Closure System • 3.2.P.2.5 Microbiological Attributes • 3.2.P.2.6 Compatibility
3.2.P.3 Manufacture		
3.2.P.3.1 Manufacturers	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.	
3.2.P.3.2 Batch Formula	A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.	
3.2.P.3.3 Description of Manufacturing Process and Process Controls	A flowchart of the manufacturing process and a brief description of the manufacturing process should be provided.	A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type and working capacity, where relevant. Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified.
3.2.P.3.4 Controls of Critical Steps and Intermediates	Critical Steps: Tests and acceptance criteria (with justification, including experimental data) performed at the critical steps identified in the manufacturing process should be provided to ensure that the process is controlled.	Most biologic-based products are administered parentally via injection. As a result, the drug product will need to be manufactured under aseptic conditions or include a sterilization step such as filtration or terminal sterilization. • Sterile and aspetic processes can be challenging to control and execute in early investigational phases • For drug products manufactured in pharmacies, operations should adhere to the guidelines provided in USP <797> Pharmaceutical Compounding – Sterile Preparations. • Pharmacies must take special precautions and conduct the appropriate training.

		• All aseptic manipulations should be conducted under appropriate conditions (e.g., Class 100 conditions in laminar flow hood). • All procedures intended to maintain the sterility of the components, in-process materials, and final drug product must be followed and documented. • Compatibility of drug product with sterilizing filter should be determined.
3.2.P.4 Control of Excipients	The specifications for excipients should be provided.	• The quality (e.g., USP, NF) of the excipients used in the drug product formulation should be provided. • If excipients are compendial grade (USP/NF), all that is needed is the certificates of analysis. • During formulation development, the FDA Inactive Ingredient Database should be consulted to determine acceptability. o For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product. For example, if a particular inactive ingredient has been approved in a certain dosage form at a certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product. • For non-compendial or novel excipients, additional nonclinical information is needed to ensure the safety of the excipient by the intended route of administration.
3.2.P.5 Control of Drug Product		
3.2.P.5.1 Specifications	The specifications for the drug product should be provided.	As with the drug substance, the specifications for the drug product should be provided in tabular format. The table should include the test, method, and acceptable ranges.
3.2.P.5.2 Analytical Procedures	The analytical procedures used for testing the drug product should be provided.	Depending on the type of product, a subset of the drug substance analytical methods could be used for assessing the quality of the finished drug product. At a minimum, methods should be used to confirm: • Product consistency • Identity • Purity • Potency • Sterility
3.2.P.5.3 Validation of Analytical Procedures	Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product should be provided.	The objective of analytical method validation studies is to demonstrate that the method is suitable for its intended purpose. Specific method parameters to be evaluated include: • Specificity • Accuracy

		• Precision • Linearity/range • Limit of detection/limit of quantitation • Robustness
3.2.P.5.4 Drug Product Batch Analysis	A description of batches and results of batch analyses should be provided.	A summary of the drug product history should be provided in tabular format. For each drug product batch provide: • Drug substance batch • Date of manufacture • Site of manufacture • Batch size • Container closure system • Use of drug product batch (e.g., stability, nonclinical studies, and clinical studies) Finished drug product test results should be provided in tabular format. Recommend providing data in side-by-side columns to facilitate review across drug product batches.
3.2.P.5.5 Characterization of Impurities	Information on the characterization of impurities should be provided.	• Forced degradation studies should be conducted to assess degradants that could be formed during manufacture and on stability. • Impurities and degradants should be identified, qualified, and quantified with validated stability-indicating analytical methods. • Common degradation and impurity pathways of proteins/peptides/mAbs include: o Covalant aggregation o Non-covalent aggregation o Deamidation o Disulfide exchange o Hydrolysis o Oxidation o Photolysis o Post-translational modifications o Conjugates o Isomerization o Fragmentation o Denaturation of tertiary structure o Adherence to container closure surfaces
3.2.P.6 Reference Standards	Information on the reference standards or reference materials used for testing of the drug product should be provided if	

	not previously provided for the drug substance.	
3.2.P.7 Container Closure System	A description of the container closure systems should be provided.	A general description of the container closure system should be provided, including: • Configuration (e.g., type I glass vial with rubber stopper and aluminum overseal) • Material of construction • Size (e.g., vial volume)
3.2.P.8 Stability		
3.2.P.8.1 Stability Summary	The types of studies conducted, protocols used, and the results of the studies should be summarized.	
3.2.P.8.2 Stability Protocol	A description of the stability protocol used to assess the clinical drug product should be provided.	Stability protocols should adhere to the applicable guidance in ICH Q1A.
3.2.P.8.3 Stability Data	Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphic, narrative).	

10. REFERENCES

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