

The Nuts, Bolts, and Best Practices in IND Filing

- Report of CABS Preclinical Development and IND Filing Workshop

On Saturday, November 21, 2009, the Chinese American Bio-Pharmaceutical Society (CABS) presented a workshop on “Preclinical Development and IND Filing: the Nuts, Bolts, and Best Practices”, with 150 CABS members and guests in attendance. The venue was the Genentech Hall Auditorium on the UCSF Mission Bay Campus in San Francisco. Aspects of pre-clinical development---the what, why and how of non-clinical safety testing and clinical development planning to support IND filings were the focus of the half-day event. In addition, data not required for the IND but important for internal decision making during the development of a given drug substance into a drug product were covered. The workshop was co-sponsored by MPI Research and Optivia Biotechnology, Inc. and moderated by the current CABS Executive Council President, Shichang Miao, Ph.D. of ChemoCentryx Inc. and Cuiping Chen, Ph.D., CABS Executive Council member from Depomed, Inc.

After introductory remarks by Dr. Miao, E. Jon Popke, Ph.D., Director of Biopharmaceutical Research and Development, MPI Research, gave a brief presentation. He focused on the pre-clinical services and value provided by this CRO to its pharmaceutical and medical device clients. MPI has a recently established a joint venture operation in China, Medicilon-MPI Preclinical Research (Shanghai) LLC, that currently supports GLP (Good Laboratory Practices) studies in small animals. The Shanghai facility expects to continue to expand its capabilities. Check www.mpiresearch.com for more information on services available at both the Shanghai and Michigan locations.

David Lustig, VP Business Development at Optivia Biotechnology, Inc., in Menlo Park, CA, the second industry sponsor of the event, also gave a short presentation. He focused on Optivia’s use of polarized mammalian and other cell models for in vitro transporter gene assays. This type of in vitro approach can play a significant role in ADME (Absorption, Distribution, Metabolism and Excretion) and in identifying if a drug is a perpetrator resulting in an unsafe condition. For more information on Optivia Biotechnology, check their website www.OptiviaBio.com.

The remainder of the workshop was filled with valuable insights and practical approaches to the support data necessary for a high-quality IND package. CMC (Chemistry, Manufacturing and Control), DMPK (Drug Metabolism Pharmacokinetics), non-clinical studies, clinical development planning and how to interface with regulatory agencies were among the topics covered by the speakers. All highly experienced in the pre-clinical requirements for small molecule IND filings, the speakers came from local Bay Area pharmaceutical companies to share their knowledge and experience with the attendees. Here are summaries of their presentations.

Workshop Overview

Cuiping “Tracy” Chen, Ph.D., Director of Pharmacokinetics at Depomed, Inc. gave an overview of what the workshop would cover, laying the foundation for the afternoon’s presentations by defining an IND for the audience. She defined the IND as “a request for authorization from the FDA in the US or its equivalent in other countries to administer





determine if the product is reasonably safe for initial use in humans and if the pharmacology justifies commercial development. Thereafter, data and information is collected to support that the product will not expose humans to unreasonable risks when used in early stage clinical testing. The data in the IND needs to show that the drug is safe for humans, that it can be consistently produced, what the risks to subjects exposed to the drug will be and whether the clinical investigators are qualified to fulfill their clinical trial responsibilities.

an investigational (not yet approved) drug to humans”. Dr. Chen described the IND as analogous to “A bridge one had to cross”. Content and structure of the IND application were presented and the suggestion to use the ICH guideline “Common Technical Document” (CTD) format for the IND. The CTD has 5 modules that can be used from IND to NDA filing, for FDA and European Union (EU) submissions, thus making filing more efficient.

Dr. Chen noted that the primary goal during preclinical development is to

CMC for Your IND

The next presentation entitled “CMC for Your IND” was presented by Dr. Bert Ho, Ph.D. from ChemoCentryx, Inc. Dr. Ho touched on what goes into the IND for CMC including information and data on the Drug Substance or API (Active Pharmaceutical Ingredient) and the Drug Product—the formulation to be given to humans. For each category, manufacturing processes and location, physicochemical characteristics, analytical methods, specifications and stability data are required for the IND. Dr. Ho cautioned the audience not to provide more data than is required, to prevent someone else having sufficient information to replicate your drug. He also recommended keeping specifications as wide as possible at this stage to provide flexibility for future scale up. Validating stability methods and beginning stability studies early, demonstrating batch to batch consistency and using reference standards and compendium methods as much as possible were suggested to avoid delays in approval time.

Dr. Ho also provided a number of “Points to Consider” and “Common Problems” with CMC and IND filings. Some of these are provided below.

Points to Consider

- Outside the U.S. (EU & Canadian submissions) release and shelf-life specifications are required as well as an expiry date supported by stability data.
- Time to response to questions from Canadian regulatory agencies is often very short, 48 hour or less including weekends.
- Several months of long-term and accelerated stability data should be generated on development batches prior to IND submission; follow ICH (International Conference on Harmonization) storage conditions for testing efficiency to satisfy most regulatory submission stability requirements.
- Do real time and accelerated stability testing. Accelerated stability data may not accurately predict long-term storage conditions.
- Keep drug product dosage form as simple as possible for Phase 1 studies; expect to have formulation and dosage form evolve during development; must be stable for duration of studies.
- Tightening specs from a regulatory perspective is fairly easy; loosening specs can be very difficult.

Common Problems in early CMC of Drug Substance

- API lots for toxicology testing too clean to determine acceptable qualification limits; may not be able to achieve the same purity upon scale-up.
- Significant changes in manufacturing processes resulting in changes in impurities or impurity profile requiring repeat of toxicology studies.
- Inadequate or unstable analytical methods
- Poor dosage form or material selection

Non-Clinical PK

Cuiping “Tracy” Chen returned to cover “Non-Clinical PK” (pharmacokinetics) as an integral part of the safety and efficacy support data generation covering ADME. PK testing is typically done during lead optimization on two or more drug candidates showing efficacy in vitro, with multiple concentrations, non-GLP conditions and methods. PK characterization allows the candidate with better ADME to be distinguished and to determine the proper dose and dose range for definitive PK/TK and PK/PS studies. These early characterization PK studies can be used in the IND filing.

Two Approaches to Defining DMPK Studies

Dr. Chen then presented two approaches to defining the DMPK (Drug Metabolism-Pharmacokinetics) studies to be done during the non-clinical phase of drug development. One approach is based on including studies related to other disciplines. These cover fundamental characterization, support for non-clinical safety, prediction of the human PK, toxicology and clinical formulation selection and development. It can also be useful in developing exclusion/inclusion criteria for concomitant medicines in Phase 1 clinical trials and beyond. The second approach is based on each of the individual ADME categories.

The approach taken and the studies decided upon depend in part on the financial situation, leadership and philosophy of the company and the therapeutic area. Is it a drug to treat a life threatening condition or unmet medical need or to enhance quality of life? What is the target population? The list of studies may vary, but those studies that provide a better mechanistic insight into the efficacy and safety profile of the molecule are most useful.

Animal Model Selection, Metabolites, Doses and Sampling Time Points

Selection of the ideal animal model choice for non-clinical safety studies was discussed. The choice should be one in which the ADME is as close and predictive as possible to what will be seen in humans. At this stage, metabolites also need to be identified. These are typically elucidated using in vitro tissue preparations such as liver microsomes and hepatocytes and in vivo biological matrices such as plasma and urine. The information from the in vitro studies will assist the decision to quantitate or not to quantitate the metabolites in toxicology studies and even first in human studies. PK studies are also valuable for selecting doses and anticipating possible formulation needs for the toxicology studies and to select the right sampling time points for the toxicokinetic (TK) studies.

Clearance and Volume Distribution

While pharmacokinetic half life can be used to help predict dose frequency, clearance and volume distribution is typically used to predict half life. Predicting clearance in humans can be done by in vitro methods if the drug is cleared through metabolism, otherwise allometric methods can be used. Allometric scaling relates physiological functions for various species with their body weight. This approach works better when non-metabolic clearance is the main clearance mechanism for all of the animal species tested and predicted for humans. If drug clearance is by active transporters and/or metabolism, prediction of clearance is complicated and the confidence level of the prediction decreases. Prediction of volume distribution for humans is done through allometric methods as well.

PK studies are also useful in formulation selection as different types of dosage forms can affect solubility and thus PK. Enzyme inhibition/induction potential data is also important to generate as well to estimate drug-drug interaction potential and to determine exclusion/inclusion criteria for concomitant medicines in Phase 1 studies and beyond.

Dr. Chen reviewed minimal and front load scenarios for ADME studies to be included in an IND. These categories can also be used to define DMPK studies as an alternative to defining them from the function/discipline DMPK supports.

Additional studies may be done; they often depend on the company financial situation and philosophy, the therapeutic area, whether the drug will be used to treat a life threatening condition or to improve the quality of life, and whether an unmet medical need is being addressed.

Non-Clinical Safety Assessment from Idea to Clinical Candidate to Human Trials—Safely

The next presentation on “Non-Clinical Safety Assessment from Idea to Clinical Candidate to Human Trials--Safely” was expertly given by Dr. Linval R. DePass, Ph.D., DABT from Durect Corporation. Dr. DePass has done successful IND and NDA submissions and was previously at Syntex Pharmaceuticals and subsequently with Roche Pharmaceuticals after it acquired Syntex. He covered in detail three types of pre-clinical safety assessment approaches—in silico (computer-based), in vitro (cell based) and in vivo (whole animal based). He explored the advantages and disadvantages of each approach, the value of the approach, what you could predict from the data, and the tools available to implement the assessments. Finally he included summary charts of the major safety and toxicity studies required and the pre-clinical timelines from candidate selection to “First in Human” study commencement.

Dr. DePass noted that in vitro as well as in vivo studies are conducted for the selection of clinical candidates as well as in preparation for “first in human (FIH)” clinical trials and IND submission. Many of the same tests are done for each with differences in objectives, dosing, duration, types and number of animals used. Typically, safety pharmacology, mammalian toxicology and genotoxicity studies are included. The major difference is whether they are done non-GLP or GLP. Non-GLP studies are allowable for selection of clinical candidates while those for FIH studies, in anticipation of clinical trials, are required to be done GLP.

In Vitro and In Vivo Studies

For in vitro studies, Dr. DePass noted computer programs for “In Silico” assessments, the Ames assay for Genotoxicity, the hERG assay for cardotoxicity and a fibroblast assay for phototoxicity.

Multiple tools for “in silico” assessment were noted and that they are often used as an inexpensive screen for ranking compounds in early discovery and development. No compound is required, only the structure. This approach can also be useful to screen for the effects of impurities and metabolites.

Genotoxicity studies include testing for adverse effects on genes (point mutations) as well as chromosomes aberrations (mutagenicity). They are basically done to detect genotoxic carcinogens and are typically done non-GLP. A little bit of local history was added as the Ames assay was developed at UC Berkeley, by Professor Bruce Ames in the early 1970s. Still used extensively today, it assesses point mutations via a bacterial reverse mutation assay. The test also commonly tests for the genotoxic potential of metabolites by the addition of a rat liver microsomal metabolic activation system containing metabolic enzymes.

The micronucleus test is used to detect chromosomal aberrations using a micronucleus test. This type of test detects micronuclei formed either by an aneuploid event leading to chromosome loss or an acentric chromosome fragment detaching from a chromosome after breakage without reintegration into the daughter nuclei during mitosis (cell division). The test, validated in 2008, gives a good ($\geq 80\%$) concordance with definitive chromosome aberration test results and is typically done as part of the pre-clinical candidate screening process.

Cardiotoxicity Testing

In vitro cardiotoxicity testing is not done in support of clinical trials but rather to provide information to the company to help in clinical candidate selection. This testing usually occurs in the pre-clinical phase either using the in vitro hERG assay and/or the Purkinje fiber assay. The hERG assay is based on the discovery of a response to ether by *Drosophila* flies. Inhibition of the hERG potassium ion channel, resulting in QT prolongation syndrome can result in death due to ventricular arrhythmia. Several successful drugs have been withdrawn from the market due to QT prolongation, such as terfenadine and astemizole, thus making early detection of the drug's potential to inhibit the ion channel important. Costly investment in development of a drug that will likely never be commercializable or that will need to be recalled can thus be avoided. An IC₅₀ is determined, the concentration at which 50% of the potassium current is blocked. A value of < 5 or $10 \mu\text{M}$ is considered a red flag. More importantly, a ratio of the IC₅₀ divided by the predicted efficacious concentration (EC₅₀) of ≤ 10 -30 is of concern. A difference of 50 or greater between the IC₅₀ and the EC₅₀ is preferred.

Another type of cardiotoxicity testing that was discussed is done using a Purkinje fiber (APD) assay. Fibers, taken from the inner ventricular walls of the heart beneath the endocardium, conduct electrical signals enabling the heart to contract in a coordinated fashion. This test more closely mimics the structure and function of the heart than the hERG assay and tests multiple ion channels and not just the potassium ion channel response to the drug. The data can also be used to verify the hERG assay results. The data from both tests taken together (hERG and Purkinje fiber assays) increases the probability of uncovering a QT interval prolongation effect by the drug. If hERG IC₅₀ is low and APD increases in the Purkinje fiber assay, the probability of QT interval prolongation is high. Increased APD in rabbit Purkinje fibers correlates well with QT prolongation for many drugs.

Dr. DePass reviewed in great detail the requirements of the various other in vivo tests for clinical candidate selection and FIH and discussed FDA expectations and preferences for safety pharmacology, mammalian toxicity and genotoxicity. He also noted that for IND filings post FIH (Phase 2, 3 and pre-NDA) testing requirements expand to include reproductive and carcinogenicity studies. Typically all studies are of longer duration.

After briefly covering ICH requirements for FIH filings, Dr. DePass ended his presentation by addressing FDA's view of safety versus toxicity. FDA requires safety but not absence of toxicity. They evaluate the margin of safety based on the indication, the target population and the risk/benefit ratio of the drug compared to alternative, established therapy safety and toxicity profiles.

Dr. DePass left the audience with a final thought—"Safety and toxicity are relative; dose responses are real".

Clinical Development of Investigational New Drugs

The final topic of the workshop "Clinical Development of Investigational New Drugs" was co-presented by Dr. Hua Mu, M.D., Ph.D. and Dr. Ron Yu, Ph.D., both of Genentech. They covered the key steps in clinical development from IND to NDA (New Drug Application). These included the clinical development plan for the IND, key elements of the clinical study protocol, the IND for Phase

1 clinical trials, protocol amendments to the IND and the IND annual report. In addition, regulatory options such as fast track designation and orphan drug development and their potential value to companies were discussed.

Clinical Development Plan

A clinical development plan for an IND should include studies such as early exploratory, first in man, safety and tolerability, single and multiple dosing as well as repeat dose escalations, adverse event profiles, PK/PD and whether healthy volunteers or patients will be included.

Clinical Study Protocol

The key elements of the clinical study protocol are a protocol synopsis, background information, study objectives-- primary (safety), secondary (efficacy and/or PK/PD), and exploratory (e.g. biomarker analysis), study design and duration with stopping rules, the study population, a description of the treatment (including dose, administration, storage and compliance requirements) and a safety assessment (risks to the participants). In addition, any efficacy, PK and PD assessments if applicable, statistical analysis plan (including randomization and blinding as well as sample size justification), data collection, data management and QA, investigator requirements, references and appendices as appropriate should be included in the protocol.

The IRB

The requirement to have IRB (Institutional Review Board) review and approval prior to the initiation of any research/clinical study that includes human patients to protect their rights and welfare was noted by the speakers as well as the types of IND Phase 1 studies that can be conducted. Differences and key considerations for Phase 1 clinical studies of non-cancer and anti-cancer drugs were presented and examples given. The main differences noted were that healthy volunteers are typically used for the non-cancer drug studies whereas cancer patients are generally used in the cancer drug studies, even in Phase 1. Pharmacology/pharmacokinetic studies are typically included in clinical studies for anti-cancer drugs but not for non-cancer drugs.

Protocol Amendments

The presentation then shifted to circumstances requiring notification of the regulatory body after the IND has been submitted. A protocol amendment to an IND is considered necessary if there is a change in the protocol originally submitted in the IND that significantly affects the safety of the study subjects (Phase 1) or if the sponsor wants to conduct a clinical trial outside the scope of the protocol submitted. If a new investigator or co-investigator or additional trial sites are to be added, or



if the change can affect the scientific quality of the study (Phase 2 or 3), an amendment to the IND is necessary. Other examples that require an IND protocol amendment include an increase in dosage or duration of exposure of the subject/patient to the drug, an increase in the number of subjects in the trial, a significant change in design of the study or addition/deletion of testing done.

Annual Report Requirement

Once an IND has been approved, an annual report to the FDA is also required within 60 days of the anniversary date that the IND went into effect. The report should include information on each clinical study in progress and those completed during the period of the report and covered by the IND. The report typically includes the number of patients entered, the number of drop outs and a brief description of the results if the study is completed or if an interim analysis of the data has been done. A safety summary should also be included summarizing the major pre-clinical findings, any significant manufacturing or microbiological change, and updated investigational plan and investigator's brochure as well as any foreign marketing developments. A safety summary covers, in tabular form, the most frequent adverse events, all serious adverse events, all adverse events, patients who died during the period, dropout rates and safety reports.

Fast Track Designation and Orphan Drug Development

The presentation concluded with a brief mention of Fast Track Designation (FTD) and Orphan Drug Development regulatory strategies. FTD is a designation granted by FDA whereby the likelihood of a priority NDA review can occur for drugs being developed to treat serious or life-threatening illnesses. A typical NDA review can take 10 months or more, whereas a priority review could be only 6 months in duration. This designation can be of strategic importance to smaller companies who need to get their product to market in the shortest possible time with limited funding. However, it does not guarantee approval. A request for FTD can be made anytime between the date of the original IND submission to the time prior to NDA approval. The request should include documentation to support that the drug meets the criteria for FTD and any data or published reports not submitted with the IND filing. The need for early and frequent communication of the sponsor with FDA such as in pre-IND and end of Phase 1 meetings was emphasized to maximize the value and increase the probability of success of the FTD approach.

Orphan Drug Development (ODD) if approved by the FDA grants market exclusivity for an indication for 7 years. The population requiring the drug treatment must be <200,000 subjects in the U.S. Unlike the FTD, application can be made at any time prior to submission of the NDA. ODD approval does not imply FTD, accelerated or guaranteed approval but has benefits to companies developing drugs for small size markets.

Workshop Concluding Remarks

Dr. Cuiping "Tracy" Chen concluded the program by thanking all the speakers for their excellent presentations, the sponsors for their support, and the CABS members and guests for their attendance and excellent questions throughout the presentations.