【S-18】

Nonclinical Safety Assessment of New Drugs and Therapeutic Proteins

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Following selection of a drug candidate from an innovative drug discovery program, the early drug development process for new drugs and therapeutic proteins is dictated by the nonclinical data generated and regulatory requirements and guidelines. A comprehensive understanding of the appropriate guidelines and integration of key principles from these regulatory documents are vital for establishing the safety of new therapeutic products. The information provided in this presentation is focused on early development and is applicable to companies of any size undertaking the development process. Although the focus is restricted to the United States Food and Drug Administration (US FDA) (http://www.fda.gov/), most of the principles apply to other regulatory jurisdictions, *e.g.*, the EU (http://www.emea.eu.int/), Japanese Ministry of Health, Labour, and Welfare (http://www.mhlw.go.jp/english/), Health Canada (http://www.hc-sc.gc.ca/indexe.html), *etc.* However, despite the availability of all of these guidelines, the drug development process is still associated with a high risk of failure for individual compounds as marketable therapies and real costs are often much greater than projected costs. Although many drugs fail because of a lack of efficacy in the clinic or display a poor pharmacokinetic profile, it is possible that regulatory-based decisions that were either limited in scope or did not foresee potential issues with respect to future development milestones could also contribute to drug failure. For example, it has been estimated that the total research and development costs for a successful new drug are ~$800 M (in year 2000 USD$) (DiMasi *et al.*,2003), with only approximately 1 in 10,000 compounds reaching the market (DiMasi *et al.*, 1991). With respect to approval times, in a survey of 554 therapeutics (504 small molecules, 40 recombinant proteins, and 10 monoclonal antibodies) approved in the US between 1980 and 2001, it appears that the increased number of approvals and decreased approval times observed during the mid to late 1990s are not continuing at the same rate in the 2000s (Reichert, 2003). It is proposed that FDA's ongoing initiative to publish new and/or update guidelines, together with an increased level of communication with companies, and collaborative efforts to improve clinical trial designs should facilitate a more effective drug

development process (FDA, 2002).

Despite the drug initiatives being undertaken as part of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (www.ich.org), there can be subtle differences in the required studies or regulatory pathways in various regions and Sponsors should be aware of the potential implications of specific jurisdictional issues that may not be captured in guidelines established during the ICH process. In addition, it is important to consider that guidelines (including those in the areas of safety pharmacology, pharmacokinetics and ADME, and toxicology), no matter how current or up to date, inherently have limitations associated with their interpretation and implementation. Articles have been published for select therapeutics products such as oncology (DeGeorge *et al.,* 1998) or inhalation drugs (DeGeorge *et al.,* 1997), and, although not official FDA documents, are used by the appropriate reviewing divisions. However, most guidelines are designed to provide general direction for typical situations and cannot be applied universally for any drug in all situations. Links to FDA and ICH guidance documents (draft and final), including internal policies and procedures and contact information of key Pharm/Tox staff can be accessed from the FDA Regulatory Pharmacology & Toxicology homepage (www.fda.gov/cder/pharmtox.htm).

Goals of Nonclinical Safety Assessments

The primary goals of nonclinical safety evaluation in early drug development for a new drug or therapeutic protein are: i) to assist in identifying an initial safe dose and subsequent dose escalation schemes in humans [*e.g.,* identification of the Maximum Recommended Starting Dose in healthy volunteers (FDA, 2005a) or the determination of the starting dose in Phase I trials in cancer patients based on a dose that is severely toxic in 10% of rodents (www.fda.gov/cder/cancer/docs/doseflow.pdf)]; ii) to identify potential target organs for toxicity in humans, and whether such toxicity is dose-dependent and/or reversible; and iii) to identify safety parameters for clinical monitoring. In addition to these goals, the objectives of nonclinical studies are important in terms of optimally defining both pharmacological and toxicological effects and mechanisms, not only prior to the initiation of human studies, but throughout the clinical development as well as post-marketing review.

Regulatory Authorities Expectation

Prior to running a clinical trial in the US, it is codified in the Federal Regulations that an Investigational New Drug Application must be filed (21 CFR Part 312). Further, 21 CFR Part 312 states that preclinical toxicity studies (conducted in compliance with Good Laboratory Practices (GLP) regulations) should be conducted to determine the safety of the therapeutic compound for the proposed clinical trial. The duration of a planned clinical trial and the period

of exposure in humans are key factors in developing the nonclinical testing program. These parameters will impact the type and duration of the nonclinical studies needed to support the proposed clinical trial and, ultimately, the clinical development program. As provided in the ICH M3 guidance entitled "Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals", the minimum duration of repeated dose toxicity studies to support clinical trials is summarized in Table 1. In general, repeated dose studies should be at least equal to, if not greater than, the duration of the clinical trials, up to the maximum recommended duration of the toxicology studies.

Table 1 Duration of Repeated Dose Toxicity Studies to Support Phase I and II Trials in the European Union, and Phase I, II, and III Trials in the United States and Japan (ICH, 2000)

Duration of Clinical Trials	**Minimum Duration of Repeated Dose Toxicity Studies**	
	Rodents	**Nonrodents**
Single dose	2 weeks[1]	2 weeks[1]
Up to 2 weeks	2 weeks	2 weeks
Up to 1 month	1 month	1 month
Up to 3 months	3 months	3 months
Up to 6 months	6 months	6 months[2]
> 6 months	6 months	Chronic[2]

[1] In the United States, as an alternative to 2-week studies, single dose toxicity studies with extended examinations can support single dose human trials.

[2] Data from 6 months duration in nonrodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9-month nonrodent study should be available before the treatment duration exceeds that supported by the available toxicity studies.

However, for single dose clinical trials conducted in the US, FDA considers data generated in single dose toxicity studies adequate support (provided that histopathology was conducted) (61 Federal Register 43934 August 26, 1996). Exploratory INDs are another approach that Sponsors are taking to initiate clinical trials based on a minimal nonclinical safety dataset yet still ensuring the safety of trial participants. The goal of the exploratory INDs is to allow Sponsors to dose humans at sub-therapeutic doses for the purposes of identifying a lead candidate for further development based on the PK profile, including biodistribution *via* imaging applications, as well as a further understanding of the relationship between the mechanism of action and disease treatment.

As the development program moves forward into later stage clinical trials, the duration of a given clinical trial will be dictated by the disease state and new efficacy data that will have been generated in previous clinical trials. To support a proof-of-concept trial in patients, the necessary duration of nonclinical studies should be proactively identified and conducted to expedite development and to avoid regulatory delays (later in the drug development program).

Nonclinical Studies

Prior to embarking on the conduct of the nonclinical studies to support early clinical development, efficacy, safety, and quality data are required. As the focus of this presentation is on nonclinical safety studies, comments are restricted to safety. GLP toxicology studies must be tailored for each new drug or therapeutic protein (*e.g.,* identification of the appropriate animal models, an understanding of the anticipated toxicities). Although there may be a large variability in the amount of nonclinical data generated by different companies in support of early clinical trials, it is ultimately dependent on the type of therapeutic agent and the indication. However, now with the transfer of therapeutic proteins from CBER to CDER at FDA and the fact that the integration of former CBER reviewers into various reviewing Divisions within CDER is essentially complete, Sponsors should expect a consistent interpretation of the guidelines. In addition to the design of these safety studies, the relative timing is of importance to support the early phases of drug development. A summary of the relevant pharmacology/toxicology guidelines for evaluating the safety of new drugs and therapeutic proteins is provided in Table 2.

Although it is ideal to use the same GMP material in the nonclinical and clinical studies, this typically is not an option during early development for emerging companies due to limited resources and aggressive investor-driven timelines. For the purposes of the nonclinical safety studies, the test material does not need to be manufactured to GMP standards, as GMP material is not required until the first clinical trial (as per GCP guidelines). However, it must be demonstrated that the material used in the nonclinical studies was comparable to the material intended for clinical trials (or if there are significant differences that these do not impact on the safety of the material) and that the material has the same identity, purity, and potency as the material intended for clinical trials.

As the final formulation of a drug product is difficult to predict in the early stages of development for a therapeutic compound, if an unapproved excipient is added to the drug product at a later stage of development, but was not tested in the animal toxicity studies, nonclinical safety data will need to be generated to support its use (FDA, 2005b). The impurity profile of an active pharmaceutical ingredient should be established early in development (*i.e.,*

knowledge of general product specific and process specific impurities). This information can prevent delays at later stages if a novel impurity is found in a drug substance or drug product or if impurities are present at a level greater than that previously characterized, which could both necessitate further safety studies and temporarily halt development [ICH Q3A(R), ICH Q3B(R), ICH Q3C(R)].

Safety pharmacology studies are designed and conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions (ICH 7A, ICH 7B). As cardiovascular, respiratory, and central nervous systems are vital organ systems, they are typically studied as a core battery of stand-alone studies, and these data are required prior to human exposure to the drug or therapeutic protein (*i.e.,* prior to Phase I). The core battery of safety pharmacology studies (cardiovascular, CNS, and respiratory) can sometimes be reduced for specific drugs, *e.g.*, biotechnology-derived products that achieve highly specific receptor targeting, where relevant safety pharmacology endpoints are examined in toxicology or pharmacodynamic studies (ICH S6). Repeated dose studies of specific durations typically need to be conducted in a rodent and a nonrodent species in order to support clinical trials of small molecules of specific durations. As mentioned earlier, the duration and dosing regimen used in the nonclinical studies should be at least equivalent to that intended in the clinical trials (ICH M3). Prior to receiving marketing approval for a therapeutic compound that is to be used intermittently throughout lifetime or for a chronic disease, chronic toxicity studies will need to be conducted, with the duration, design, *etc.* dependent on the drug or therapeutic protein and data generated to date for that compound (ICH S4A, 64 Federal Register 34259 June 25, 1999).

The standard battery of tests for genotoxicity as outlined in the ICH guidelines (ICH S2A, ICH S2B) includes (1) a bacterial reverse mutation test, (2) an *in vitro* test with cytogenetic evaluation of chromosomal damage in mammalian cells or an *in vitro* mouse lymphoma tk assay, and (3) an *in vivo* test for chromosomal damage using rodent haematopoietic cells (*i.e., in vivo* micronucleus assay). Although the complete battery of genotoxicity testing examining mutagenicity and clastogenicity is recommended by ICH guidelines and is generally required for all pharmaceutical products (note: *in vitro* assays are typically sufficient to support Phase I clinical trials, unless positive or equivocal findings are observed), the ranges and types of genotoxicity studies are not always deemed applicable or necessary for biotechnology products (ICH S6). Positive findings in genetic toxicology assays should be reviewed, integrated, and presented to regulators following a weight-of-evidence type of approach that takes into consideration the mechanism of action of the therapeutic compound (FDA, 2004).

Reproductive toxicology studies that investigate effects on fertility, mating, embryogenesis (*i.e.,*

in rodent and nonrodent species), parturition, and peri-natal development are generally required for all pharmaceuticals prior to the administration of the new drug to cohorts of women of childbearing potential [ICH S5A, ICH S5B(M)]. Reproductive toxicity studies are typically classified into 3 distinct sets of studies: Segment I (ICH Stages A & B), reproduction and fertility studies; Segment II (ICH Stage C), teratology/developmental toxicity studies; and Segment III (ICH Stages D, E, & F), peri-natal development studies. Reproductive toxicity studies are not often a requirement before Phase I. Depending on the patient population (*e.g.*, possible sex differences, severity of disease, *etc.*), type of therapy, and measures included in exclusion criteria in clinical trials, Segment II studies may be required at different points during the clinical development process for different products (*i.e.*, prior to Phase II, Phase III, or marketing registration for labeling purposes).

For new drugs, it is important to demonstrate that the therapeutic agent does not result in an increased susceptibility to infections or promote tumor development, either due to exaggerated pharmacological activity or by non-specific mechanisms (necrosis, apoptosis of immune cells, *etc.*). Nonclinical testing approaches have been developed to address immunotoxicity so that these endpoints/studies can now be integrated into a standard development program and, if necessary, equivocal findings addressed in subsequent follow-up or mechanistic-based studies (ICH S8, FDA, 2002). Although therapeutic proteins may be involved in immunosuppression based on their mechanism of action, and hence some may be potentially immunotoxic, the primary concern associated with this therapeutic class of compounds is the potential to generate anti-drug antibodies and it is important to characterize the antibody response and assess whether this is associated with the observed pharmacological or toxicological effects (ICH S6).

Carcinogenicity studies for drugs are not required until registration, and in certain instances as a post-approval commitment or not at all (ICH S1A, ICH S1B, ICH S1C, ICH S1C(R), FDA, 2001). Although standard carcinogenic bioassays are not required for therapeutic proteins, additional mechanistic studies may be needed to fully evaluate the risk of carcinogenic potential of the compound based on the intended patient population, duration of treatment, and biological activity (ICH, S6).

Conclusion

Regulations and guidelines should be consulted early in the development process to ensure that the design of the planned nonclinical safety studies will support the clinical development program and be considered acceptable by international authorities. However, most guidelines are designed to provide general comments and the nonclinical safety studies should be tailored for each new drug or therapeutic protein. For companies that are not certain of the nonclinical

regulatory requirements for their new drug or therapeutic protein, presenting a well-thought out plan and rationale to regulators for the purposes of obtaining feedback (*e.g.*, as part of a pre-IND meeting) is highly recommended to ensure regulatory success.

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TABLE 1. Summary of Selected FDA GUIDANCE DOCUMENTS RELATED TO THE Nonclinical Safety Assessment of New Drugs and Therapeutic Proteins

Topic	Guideline	Link
Pharmacology		
Safety Pharmacology	ICH S7A Safety pharmacology studies for human pharmaceuticals (2001).	http://www.ich.org/MediaServer.jser?@_ID=504&@_MODE=GLB
	ICH S7B Safety pharmacology studies for assessing the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals (DRAFT, 2004).	http://www.ich.org/MediaServer.jser?@_ID=2192&@_MODE=GLB
Toxicology		
Single-dose toxicity	Single dose acute toxicity testing for pharmaceuticals (FDA, 1996).	http://www.fda.gov/cder/guidance/pt1.pdf
Repeat-dose toxicity	ICH S4A Duration of chronic toxicity testing in animals (rodent and non-rodent) (1999).	http://www.ich.org/MediaServer.jser?@_ID=497&@_MODE=GL
	Duration of chronic toxicity testing in nonrodents (64 Federal Register 34259 June 25, 1999).	http://www.fda.gov/cder/guidance/62599.pd
Genotoxicity	ICH S2A Genotoxicity: specific aspects of regulatory genotoxicity tests for pharmaceuticals (1996).	http://www.ich.org/MediaServer.jser?@_ID=493&@_MODE=GL
	ICH S2B Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (1998).	http://www.ich.org/MediaServer.jser?@_ID=494&@_MODE=GL
	Recommended approaches to integration of genetic toxicology study results (FDA, 2004	http://www.fda.gov/cder/guidance/6270dft.pd

Carcinogenicity	ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals (1996).	http://www.ich.org/MediaServer.jser?@_ID=489&@_MODE=GL
	ICH S1B Carcinogenicity: testing for carcinogenicity of pharmaceuticals (1998)	http://www.ich.org/MediaServer.jser?@_ID=490&@_MODE=GL
	ICH S1C Carcinogenicity: dose selection for carcinogenicity studies of pharmaceuticals (1995)	http://www.ich.org/MediaServer.jser?@_ID=491&@_MODE=GL
	ICH S1C(R) Addendum: addition of a limited dose and related notes (1997).	http://www.ich.org/MediaServer.jser?@_ID=492&@_MODE=GL
	Statistical aspects of the design, analysis and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals (FDA, 2001).	http://www.fda.gov/cder/guidance/815dft.pd
Reproductive and developmental studies	ICH S5A Reproductive toxicology: detection of toxicity to reproduction for medicinal products (1997).	http://www.ich.org/MediaServer.jser?@_ID=498&@_MODE=GL
	ICH S5B(M) Reproductive toxicology: toxicity to male fertility (1996).	http://www.ich.org/MediaServer.jser?@_ID=499&@_MODE=GL
Other studies		
ICH Q3A(R) Impurities testing: impurities in new active substances (2003)		http://www.ich.org/MediaServer.jser?@_ID=506&@_MODE=GL
ICH Q3B(R) Impurities in new medicinal products (2003)		http://www.ich.org/MediaServer.jser?@_ID=421&@_MODE=GL

Q3C Impurities: residual solvents (1997)	http://www.ich.org/MediaServer.jser?@_ID=423&@_MODE=GL
ICH M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals (2000)	http://www.ich.org/MediaServer.jser?@_ID=506&@_MODE=GL
ICH S6 Preclinical safety evaluation of biotechnology-derived pharmaceuticals (1997)	http://www.ich.org/MediaServer.jser?@_ID=503&@_MODE=GL
ICH S8 Immunotoxicity studies for human pharmaceuticals (DRAFT, 2005)	http://www.ich.org/MediaServer.jser?@_ID=1706&@_MODE=GL
Immunotoxicology evaluation of investigational new drugs (FDA, 2002)	http://www.fda.gov/cder/guidance/4945fnl.PDF
Nonclinical studies for the safety evaluation of pharmaceutical excipients (FDA, 2005)	http://www.fda.gov/cder/guidance/3812dft.pdf

Nonclinical Safety Assessment of New Drugs and Therapeutic Proteins

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OBJECTIVE OF PRESENTATION

- To provide some points to consider when planning and conducting a preclinical development program to enable First-in-Human (FIH) studies

  Assumptions:
  - Candidate selected (*i.e.*, screening completed)
  - U.S. FDA focus
  - Early development

  However, most comments made would apply to any stage of the development process

REGULATORY EXPECTATIONS 21 CFR Part 312 States That:

- Nonclinical safety studies should be conducted to determine the safety of proposed clinical trials
  - Pharmacology (efficacy *in vitro* and/or *in vivo*)
  - ADME (Disposition including PK/TK – characterize exposure at efficacious and toxic doses)
  - Toxicology (Identify safety/hazard in relevant test systems)
- Conducted in conformance with GLPs
- Note: 10-day safety reporting rule includes nonclinical findings

GENERAL TOXICOLOGY CONSIDERATIONS

- The types of studies and amount of toxicology data (including the timing of such studies relative to the clinical development program) will depend on a number of factors, including:
  - Product type and the similarity to existing agents with known safety profiles;
  - Proposed indication in humans (*i.e.*, cancer *vs* rheumatoid arthritis);
  - Proposed duration of administration (*i.e.*, short term *vs* chronic)
  - Target population (*i.e.*, adults, infants, pregnant women, elderly, *etc.*);
  - Proposed route(s) of administration; and
  - Use pattern considerations (*i.e.*, concomitant medications, adjuvant therapy)

DESIGN OF THE TOXICOLOGY PROGRAM TO SUPPORT EARLY CLINICAL DEVELOPMENT

- Studies should be designed specifically for the therapeutic under development
  - Relevant animal species (*i.e.*, pharmacologically active)
    - Particularly for biologics / therapeutic proteins
  - Knowledge of expected toxicities
    - Dose range finding data and pilot studies
    - Drug class effects (published literature, *Freedom of Information*, E.U. EPARs, scientific meetings, *etc.*)
    - First principles
    - Interaction with regulatory authorities

DESIGN OF THE TOXICOLOGY PROGRAM TO SUPPORT EARLY CLINICAL DEVELOPMENT

- Conducted in accordance with Good Laboratory Practice (GLP) regulations/principles
  - FDA (21 CFR 58), OECD, and JMHLW
  - Covers personnel, facilities, equipment, operations, test article, data entry, reports, *etc.*
  - Does not cover interpretation or evaluation of data
  - Result of IBT scandal of the 1970s
  - Contributes to the timing and expense of studies
  - Sponsor has obligations
    - Ensuring the integrity of the data - monitoring the study
  - For biotechnologicals, GLP data are not always obtainable (*i.e.*, specialized studies or individual assays)

OBJECTIVES OF EARLY TOXICOLOGY STUDIES

- Identify the target organs / systems of the drug
  - monitoring in clinical trials
  - gender differences
  - expected (based on pharmacology)?
- Characterize the dose-response relationship of toxicity
  - no observed adverse effect level
    - Important for Maximum Recommended Starting Dose (MRSD)
  - lowest observed effect level
  - shape of the dose-response curve

OBJECTIVES OF EARLY TOXICOLOGY STUDIES (continued)

- Characterize the reversibility of toxicity
  - recovery group(s)
  - worsening of effect(s)
- Assess the systemic exposure at doses used in the toxicology studies
  - toxicokinetics
  - margins of safety relative to human exposures based on AUC and C_{max} (also determine T_{max}, Cl, Vd, t ½, %F)

OBJECTIVES OF EARLY TOXICOLOGY STUDIES (continued)

- Assist in selection of doses for longer term toxicology studies
  - important for rapid development
- Aid in selection of doses for first-in-human (FIH) studies
  - all other available data also considered

TYPICAL IND-ENABLING NONCLINICAL SAFETY PROGRAM

(small molecule, non oncology indication)

- Pharmacology (efficacy) studies, *in vitro / in vivo*
- DMPK (minimally single-dose rodent / nonrodent PK – clinical route)
- Acute toxicology (GLP)
  - Single dose rodent (~rat) and nonrodent (dog / primate)
  - By route of planned clinical administration (+ rodent iv ?)
- Repeated dose toxicology (GLP)
  - 14- to 28-day rodent / nonrodent with toxicokinetics
  - ± ECG / immunology / CYP450 induction, *etc.* (as needed)
- Genotoxicity (GLP) *"ICH Standard Battery"*
  - *In vitro* bacterial mutagenicity (Ames assay)
  - *In vitro* cytogenetics
    - chromosome aberrations in CHO cells, or
    - mouse lymphoma
  - *In vivo* chromosomal damage (*e.g.*, mouse micronucleus) (Not always needed prior to Phase 1)
- Safety pharmacology (GLP) *"ICH Core Battery"*
  - hERG inhibition (patch clamp)
  - CNS in rats / mice
  - Cardiovascular in conscious telemetered dogs (GLP)
  - Respiratory in rodents (or safety parameters incorporated into 14-day dog study)

TYPICAL IND-ENABLING NONCLINICAL SAFETY STUDIES

Generalized design of a repeated dose rodent toxicity study

Treatment Group	Dose (mg/kg/day)	Toxicology Groups: Main (Terminal) Male	Main (Terminal) Female	Recovery Male	Recovery Female	Toxicokinetics* Male	Toxicokinetics* Female
Vehicle	0	10	10	5	5	0	0
Low Dose	A	10	10	0	0	9	9
Mid Dose	B	10	10	0	0	9	9
High Dose	C	10	10	5	5	9	9

* Number of animals depends on blood volumes required, number of timepoints, *etc.*

TYPICAL IND-ENABLING NONCLINICAL SAFETY STUDIES

Generalized design of a repeated dose nonrodent toxicity study

Treatment Group	Dose (mg/kg/day)	Toxicology/Toxicokinetics Groups: Main (Terminal) Male	Main (Terminal) Female	Recovery Male	Recovery Female
Vehicle	0	3	3	2	2
Low Dose	D	3	3	0	0
Mid Dose	E	3	3	0	0
High Dose	F	3	3	2	2

TIMING OF PRECLINICAL STUDIES WITH RESPECT TO CLINICAL TRIALS

- ICH M3: *Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*
- Acute toxicology studies: before first dose in humans
  - A dose escalation study or data obtained from pilot work are acceptable alternatives
- FDA allows for single dose toxicology studies (with histopathology) to support single dose clinical trials
  - 61 Federal Register 43934 (Aug 26, 1996)
  - Screening INDs / Exploratory IND studies
- Duration of repeated dose studies should be at least equal to, if not greater than, duration of clinical trials, up to the maximum recommended duration of toxicology studies

TIMING OF PRECLINICAL STUDIES WITH RESPECT TO CLINICAL TRIALS

- Phase 3 trials: if >3 months clinical: 6 month rodent, chronic nonrodent
- Local tolerance, safety pharmacology: prior to human exposure
  - Some endpoints may be incorporated into toxicology studies
- Genotoxicity studies: *in vitro* mutagenicity studies prior to Phase 1, standard battery prior to Phase 2
- Reproductive toxicology studies:
  - Embryofetal development (ICH C-D): prior to Phase 3
    - Some indications (*i.e.*, rheumatoid arthritis) or some regions (Japan): prior to Phase 1 or 2 – depends on patient population
  - Fertility (ICH A-B) prior to Phase 3
    - for Japan: male repro. histopath < Ph1, then fertility < Phase 2)
  - Peri- / postnatal development (ICH C-F): prior to NDA
- Carcinogenicity studies: usually prior to NDA
  - Post-approval commitment for certain indications (*i.e.*, HIV)

AVOID RED FLAGS – ADDRESS REVIEWERS' EXPECTATIONS

✓ Content
✓ Format

AVOID RED FLAGS – ADDRESS REVIEWERS' EXPECTATIONS

- Have sufficient nonclinical data been submitted?
  - Are proposed clinical doses safe?
    - Are adverse effects expected at effective doses?
  - Is proposed clinical exposure duration safe?
- Will special clinical monitoring be needed?
  - Are there irreversible or unmonitorable effects?
- What is known about related compounds?
- Has maximum recommended starting dose (MRSD) been set appropriately?

Cited by Dr. Ken Hastings, CDER

AVOID RED FLAGS – ADDRESS REVIEWERS' EXPECTATIONS (continued)

The NOAEL *(No Observed Adverse Effect Level)*

- An important IND-enabling endpoint
  - For FIH MRSD, need NOAEL from each repeated-dose toxicology study
  - NOAEL → HED → MRSD
- Based on integrated study results
  - In-life (*e.g.*, clinical signs, body weight (gain))
  - Clinical pathology (*e.g.*, hematology, chemistry)
  - Histopathology
- Exceptions (*i.e.*, oncology)

AVOID RED FLAGS – ADDRESS REVIEWERS' EXPECTATIONS

Is the clinical protocol reasonably safe to initiate as proposed?

IND-ENABLING NONCLINICAL SAFETY STUDIES FOR BIOLOGICS

Differences between drugs and biologics -- *a generalization*

Drug	Biologic
Single entity	Possibly >1 component
Low molecular weight	High molecular weight
Familiar antecedents	Potentially unique
Known impurities	Unfamiliar impurities
Often orally dosed	Often parenterally dosed
Maximal tolerated dose	Optimal biologic dose
Meaningful chronic tox	Uncertain chronic tox
Species-independent	Species-specific
Biotransformed	Degraded

IND-ENABLING NONCLINICAL SAFETY STUDIES FOR BIOLOGICS

- "Standard" toxicology studies may be inappropriate or inadequate
  - Toxicity may be extension of pharmacology
  - Safety margins may be lower than for drugs
- Ensure well-characterized test material (representative of clinical supplies)
- Ensure test material comparable across nonclinical program

IND-ENABLING NONCLINICAL SAFETY STUDIES FOR BIOLOGICS

- Use relevant animal species
  - One relevant species with justification
  - Limited toxicity testing - "nonrelevant" species
- Evaluate immunogenicity
- Toxicokinetics (plasma, target organ)
- Alternatives to "standard" tox models
  - transgenic animals
  - homologous proteins
  - animal disease models

CONCLUSIONS

- A successful preclinical development program must start with a strategy and end with a high quality regulatory filing that anticipates the questions of the Regulator

CONCLUSIONS (continued)

- Guidelines are designed only to provide general direction for typical situations; they cannot be applied universally to all products and all situations

CONCLUSIONS (continued)

- Discussions with Regulators (particularly for new technologies) support a Sponsor's own experience and the more general suggestions offered by published guidance documents

CONCLUSIONS (continued)

- Toxicology studies should not be considered a box-checking exercise to simply satisfy Regulators
  - contribute much to the understanding of the product
  - if not designed, conducted, and/or interpreted correctly, they can add considerable time and expense to the program

Additional Resources

FDA GUIDANCE RELATED TO PRECLINICAL SAFETY EVALUATION

- FDA Regulatory Pharmacology and Toxicology homepage:

  www.fda.gov/cder/pharmtox/default.htm
  - Links to all FDA guidance documents (draft and final)
    - ICH
    - FDA
  - Internal policies and procedures
  - Contact names of Pharm/Tox staff within CDER
- Other sources *(examples)*
  - Oncology Drugs - DeGeorge, *et al.*, 1998. Regulatory consideration for preclinical development of anticancer drugs. Cancer Chemother Pharmacol 41:173-185.
  - Inhalation Drugs - DeGeorge, *et al.*, 1997. Considerations for toxicology studies of respiratory drug products. Regul Toxicol Pharmacol 25:189-193.