

A vertical photograph on the left side of the slide showing a hand holding a string attached to a blue and white striped kite flying against a clear blue sky.

Nonclinical Drug Development – A Successful Path Forward

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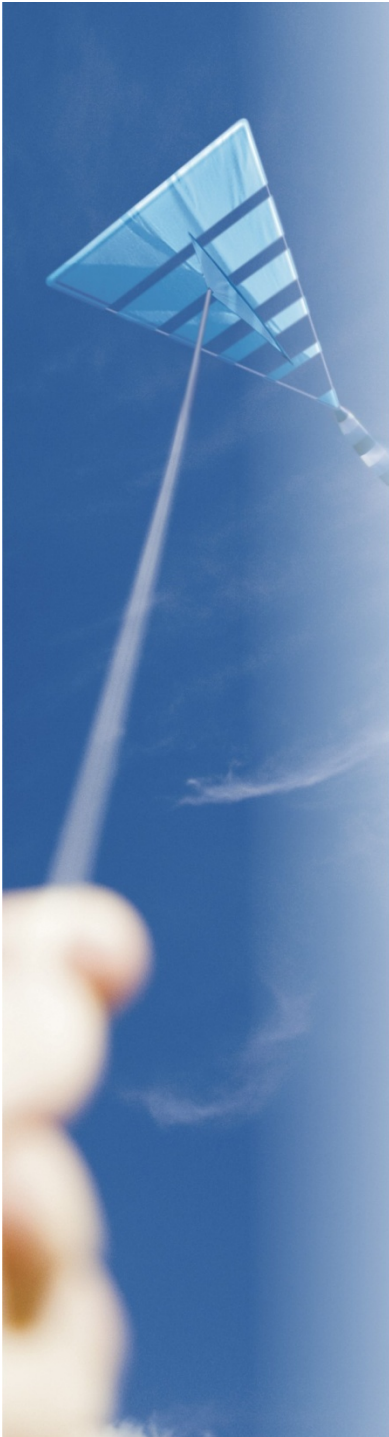
Objectives

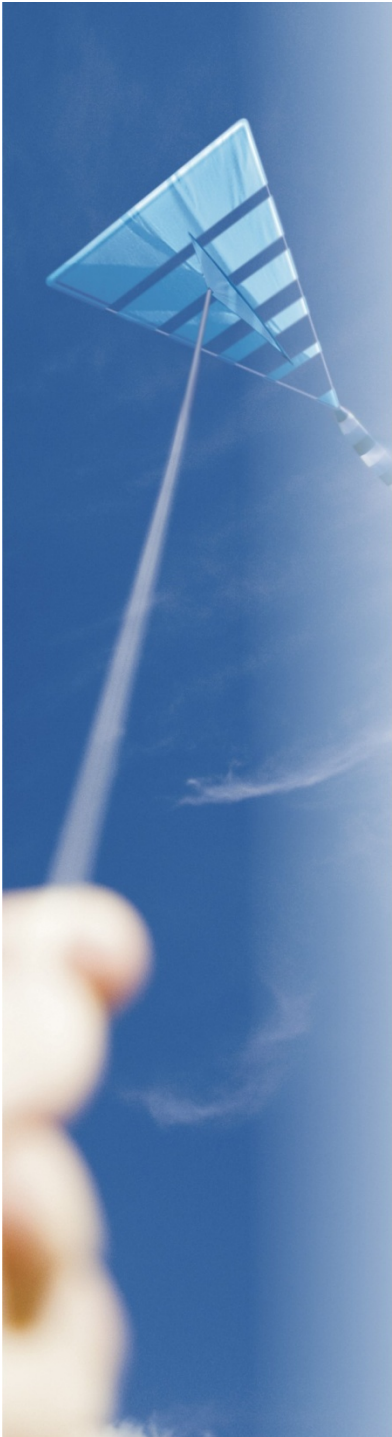


We will cover:

- Nonclinical Study Types
 - Pharmacodynamic (PD), Safety Pharmacology, Pharmacokinetic (PK), Toxicology
- Nonclinical Regulatory Milestones
 - FDA
- Nonclinical FDA Interactions
 - Successful planning & execution

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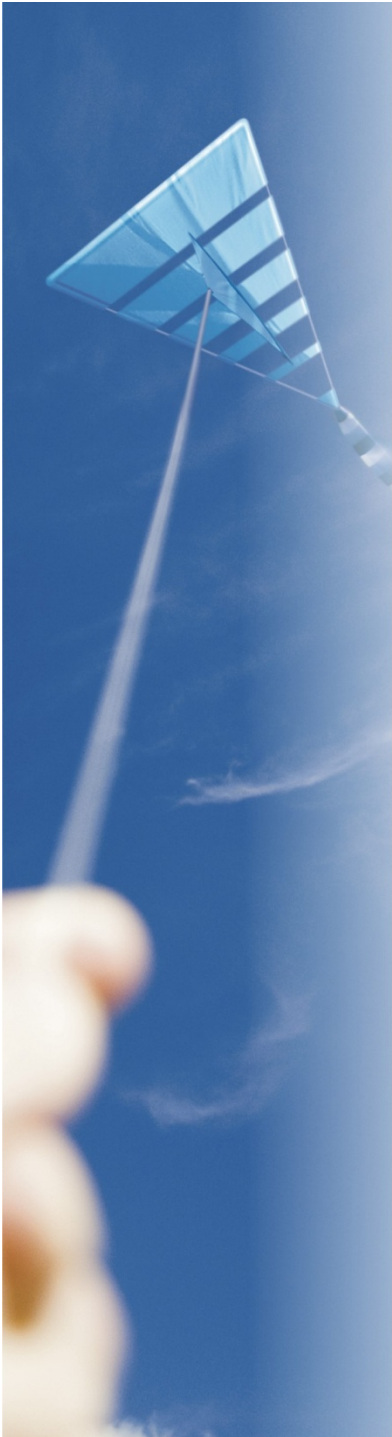
Nonclinical Studies



Pharmacology

- Primary Pharmacodynamics (Efficacy, “Proof-of-Concept”)
 - Goal: determine mode of action or effects in relation to the desired therapeutic target
 - PD studies are usually conducted non-GLP
 - Efficacy “low hurdle” with FDA; safety is the “high hurdle”

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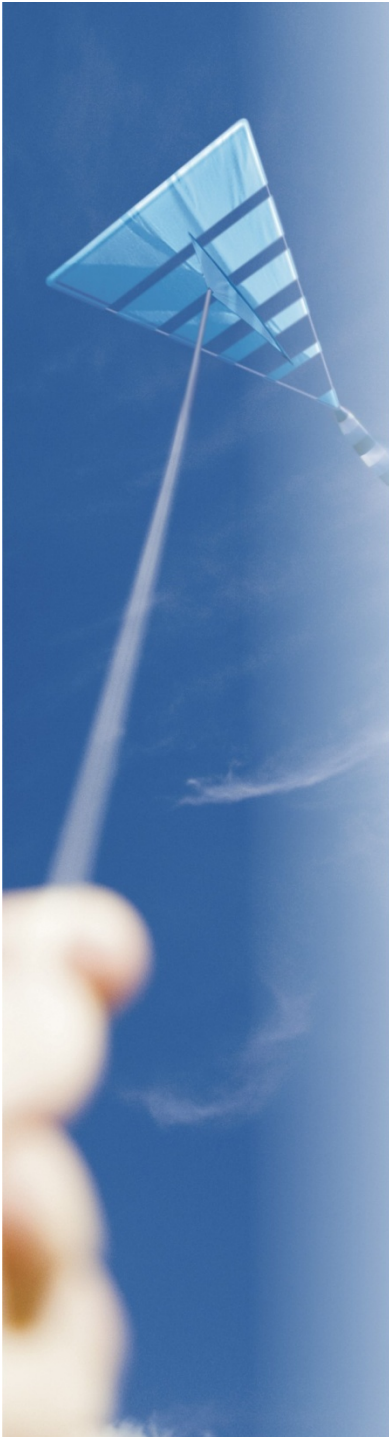
Nonclinical Studies



Pharmacology (cont'd)

- Secondary Pharmacodynamics
 - Goal: determine mode of action or effects not related to the desired therapeutic target
 - Secondary PD studies may not be needed; literature may provide necessary information

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Nonclinical Studies



Pharmacology (cont'd)

- Safety Pharmacology
 - Goal: determine undesirable PD effects on physiological functions at therapeutic range and higher
 - “Core battery” = Respiratory, CNS, Cardiovascular
 - Respiratory & CNS (e.g., FOB) are typically rat studies
 - CV typically in vitro (hERG) + in vivo (telemetered dog)
 - Follow-up studies may be needed if concerns arise
 - GLP

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Nonclinical Studies



PK

- A (absorption) = PK, F
- D (distribution) = tissue distribution, protein binding
- M (metabolism) = metabolites, pathways, enz. induct/inhib
- E (excretion) = urine, feces, expired air (“mass balance”)
- Usually conducted non-GLP

Note: TK presented in Tox section for CTD format, and not PK section

– GLP

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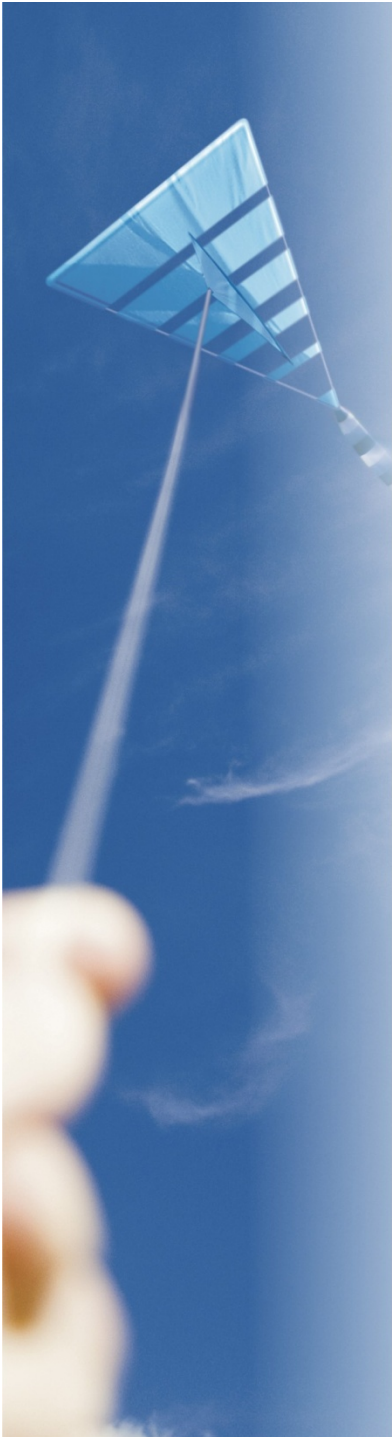
Nonclinical Studies



Toxicology

- Single dose and range-finding
 - Goals:
 - Establish toxicity profile (D-R): MTD, NOAEL
 - Identify target organ(s) of toxicity
 - Establish doses for future toxicology studies or first in human
 - Designs:
 - Standard test: 1 Control and 3 Rx Groups
 - Up and down: Successive dose in escalation fashion
 - Expanded acute: Standard test with full toxicity assessment

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Nonclinical Studies



Toxicology (cont'd)

- Repeated dose
 - Goals:
 - Establish toxicity profile (MTD, NOAEL) when administered repeatedly for a given period of time
 - Identify target organ(s) of toxicity
 - Reversibility of adverse effects
 - Establish dose(s) for future toxicology studies or clinical trials
 - Standard duration:
 - Subchronic: 7, 14, and 28 Days; 3, and 6 Months
 - Chronic: 6, 9, and 12 Months

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Nonclinical Studies



Toxicology (cont'd)

- Genotoxicity
 - Goal: Detect potential interactions with nucleic acids that ultimately leads to the induction of gene mutation and/or chromosomal damage.
 - “Standard battery”
 - in vitro bacterial mutation (Ames)
 - in vitro mammalian cell chromosomal aberration (e.g., HPBL)
 - in vitro mammalian cell chromosomal aberration (e.g., rodent micronucleus)

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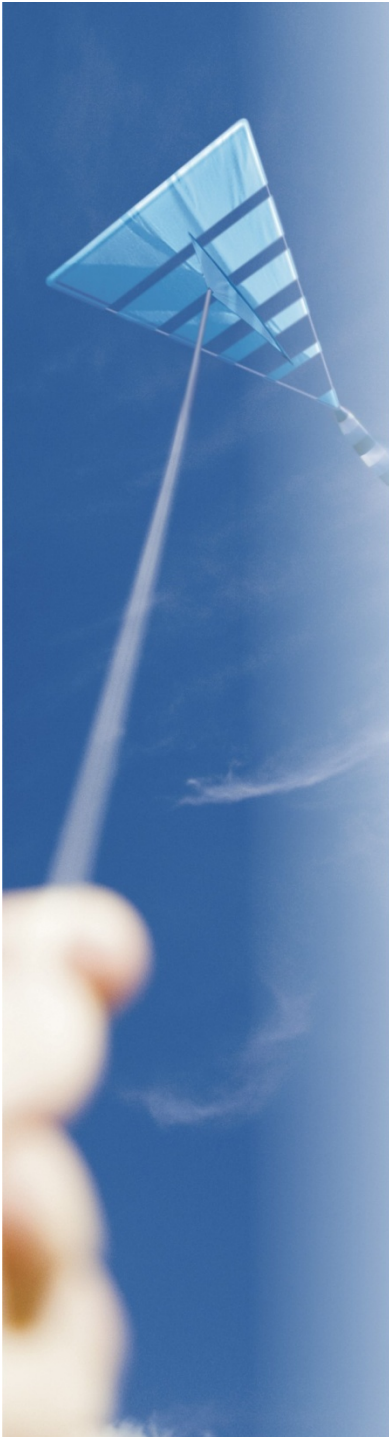
Nonclinical Studies



Toxicology (cont'd)

- Carcinogenicity
 - 2-year mouse or 26-week transgenic mouse and
 - 2-year rat bioassay
- Developmental and Reproductive Toxicology
 - Fertility (typically rat), Teratology (typically rat & rabbit), Peri- and Post-Natal (typically rat)
- All pivotal toxicology studies should be GLP

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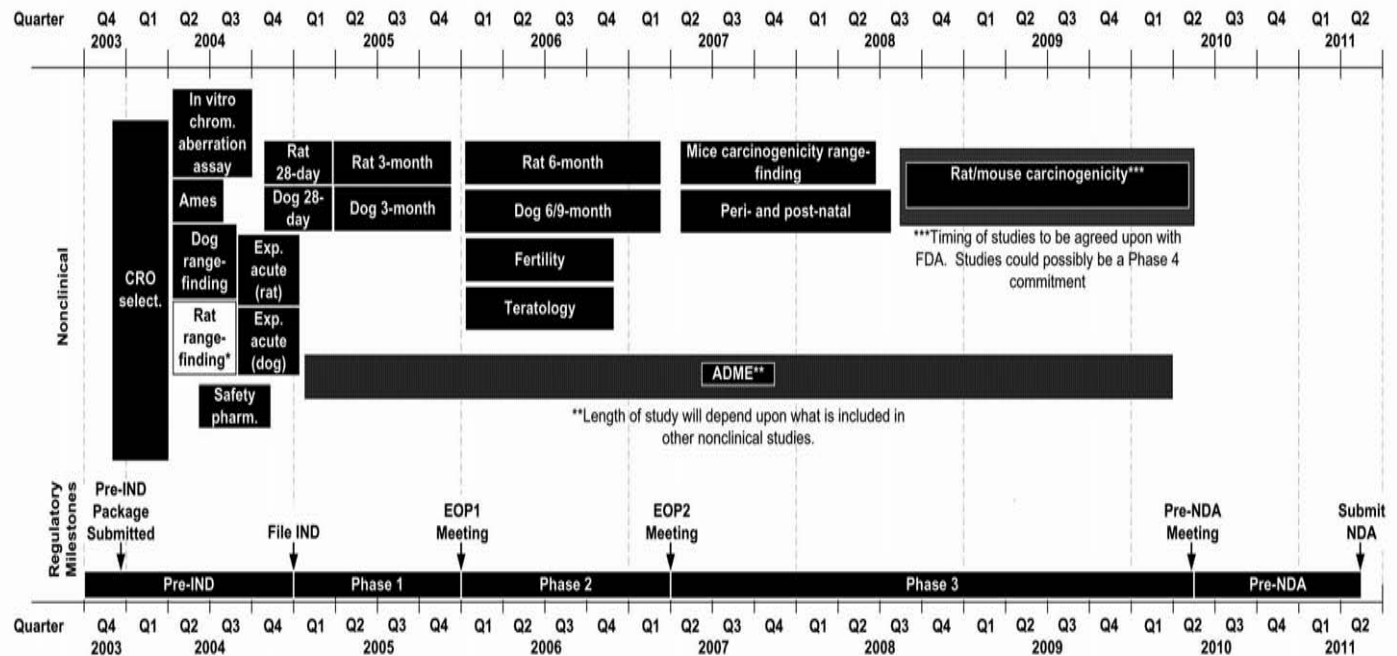
Phases of Nonclinical Drug Development



- Develop a nonclinical plan
 - Work backwards from the clinical plan; nonclinical safety must support the clinic (e.g., route, frequency, duration)
 - Get FDA buy-in on the plan; a pre-IND meeting is **strongly** recommended
 - Map out the timing of the nonclinical program with respect to CMC, regulatory, and clinical milestones

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Phases of Nonclinical Drug Development



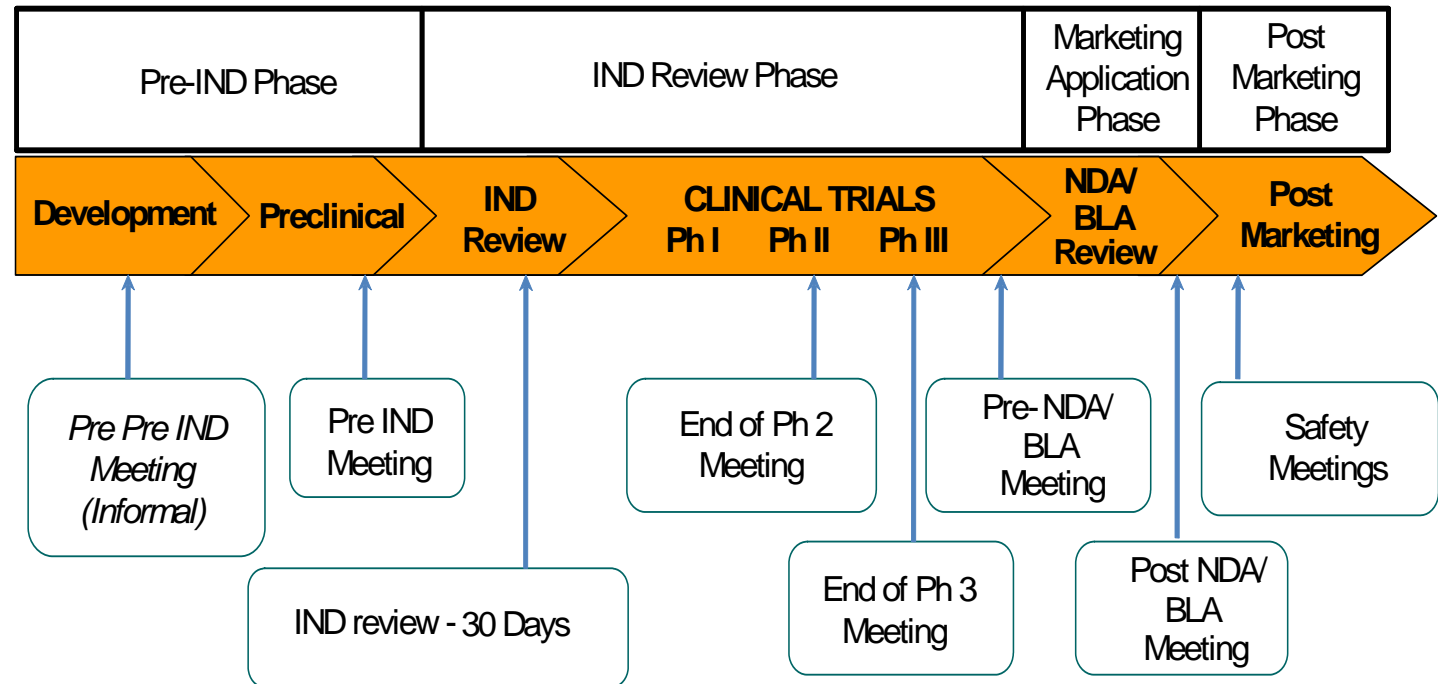
EOP1 = end of Phase 1; FSR = final study report; IND = Investigational New Drug Application.

Notes: Bar lengths are not representative of activity length. Timing of nonclinical activities assumes that adequate test article will be available.

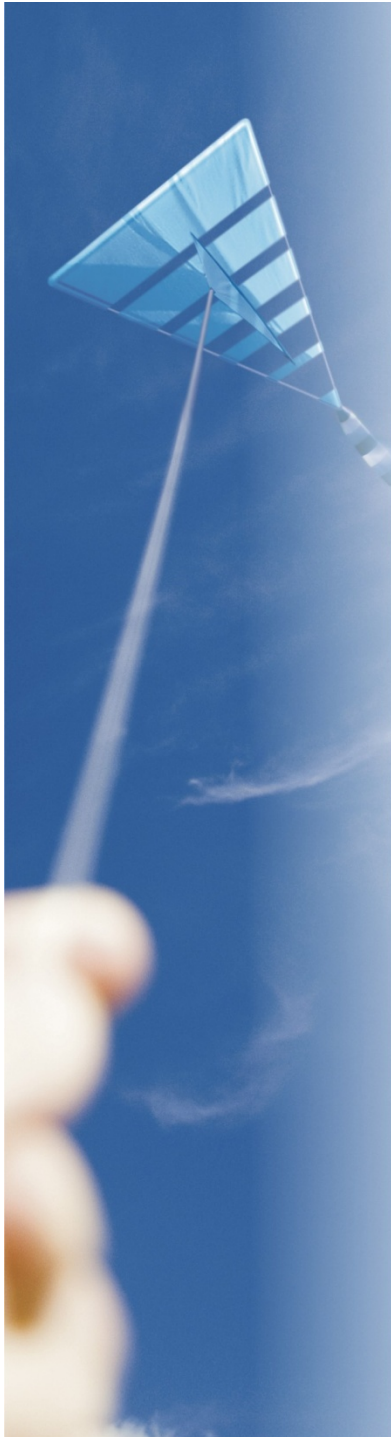
*Need for rat acute range-finding study will depend upon data availability to allow proper dose selection.

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Scientific Advice from the FDA



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The Pre-pre-IND Process



- Purpose – Enter into informal discussions of gene and cell therapy product development
- When – Early preclinical stage
- CBER’s Pharmacology/Toxicology Branch
- The sponsor provides a small package (approximately 25 pages) describing the intended clinical product along with a summary of any preclinical data and proposed study plans.
- Teleconference
- FDA will provide general advice on the preclinical development plan only

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The Pre-pre-IND Consultation

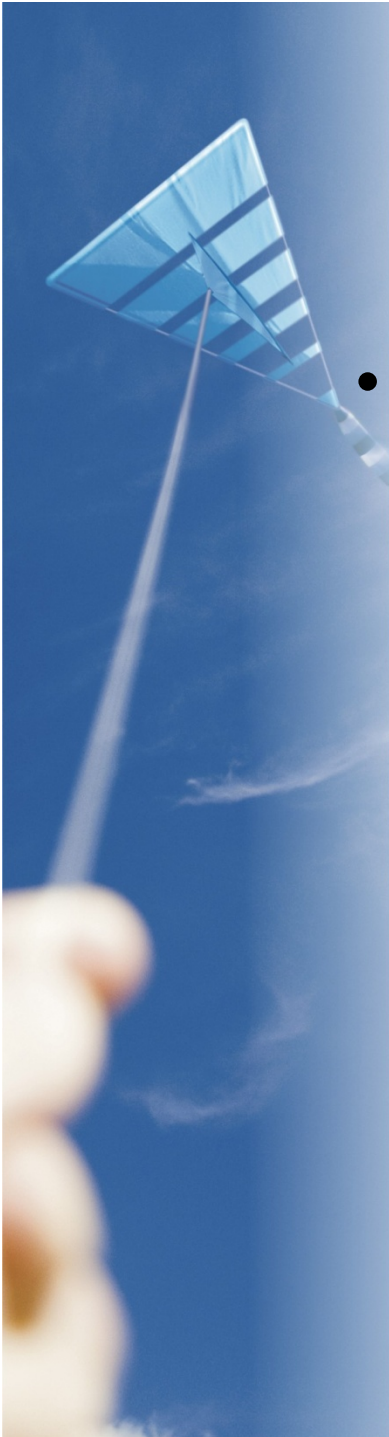


- Disease Group – Oncology
- Clinical Indication – Multiple Myeloma
- Product Type – novel gene therapy

Assumptions:

- Clinical trial would be supported by 4-week toxicology study in advanced stage cancer patients
- One species would be sufficient
- Dose groups would consist of only one control and the dose-response for the product (i.e., 4 dose groups = control, low-, mid-, high-dose)
- Immunogenicity to consist of quantitation of anti-drug antibodies

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The Pre-pre-IND Consultation



- Meeting Outcome:
 - Two repeat-dose toxicology studies may be necessary
 - Rodent
 - Nonrodent; justification for not using a nonrodent species would be needed in the pre-IND package
 - Two control groups (negative and positive)
 - Dose group containing the rodent-specific sequence
 - Single dose toxicity with biodistribution assessment study strongly recommended

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The IND



- The IND (investigational new drug application) is the vehicle through which a sponsor advances to clinical trials (human trials).
- The IND will contain information in 3 broad areas:
 - Animal Pharmacology and Toxicology Studies
 - Manufacturing Information
 - Clinical Protocols and Investigator Information

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Purpose of Nonclinical IND Safety Studies



- Assess the safety of first in human (FIH) administration in studies of pharmacodynamics, pharmacokinetics, toxicity and their relationships
- Goals of the toxicology studies
 - Identify starting dose
 - Identify organ toxicities and reversibility
 - Guide dosing regimens and escalation schemes

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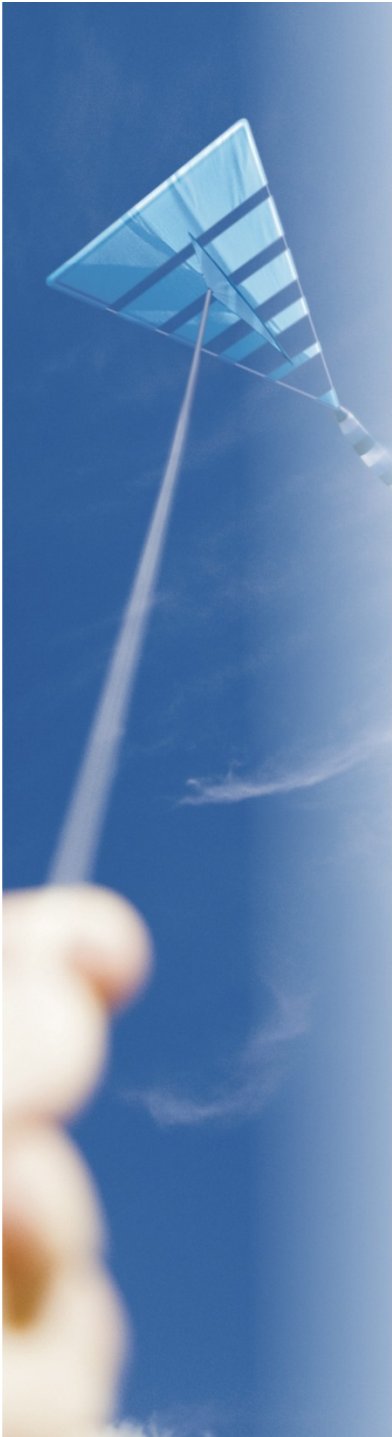


The IND Process



- Draft, unaudited toxicology study reports are acceptable for initiation of IND, however, audited final study reports should be available within 120 days of submission of IND
- Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials.

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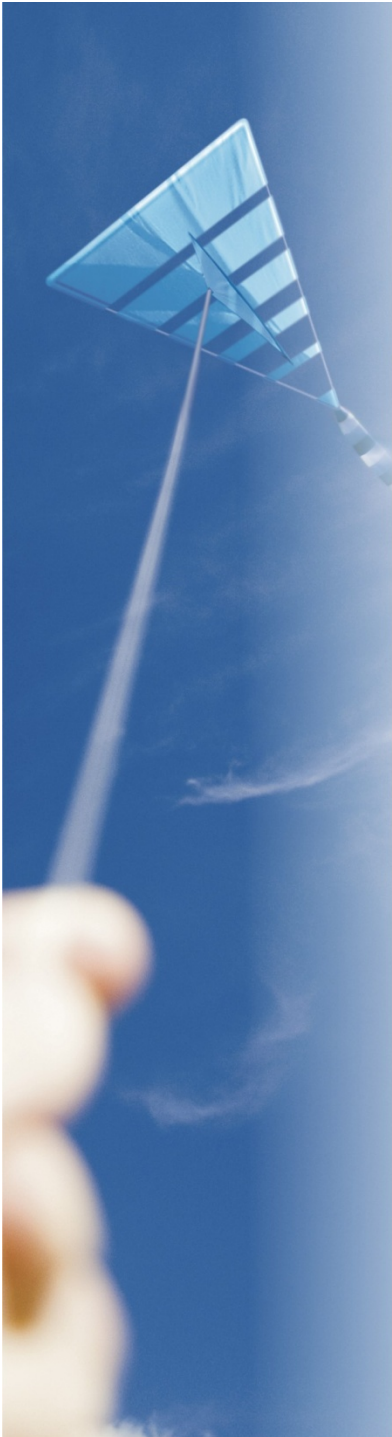


The Pre-IND Meeting



- Not required by FDA but highly recommended, particularly for unique products/questions
- Timing is often 6 months to one year prior to submission
- Purpose is to get feedback from the Division as to the appropriateness of the initial development plan
 - The design of nonclinical pharmacology, toxicology, and drug activity studies
 - Nonclinical safety study issues
- Not a full data review

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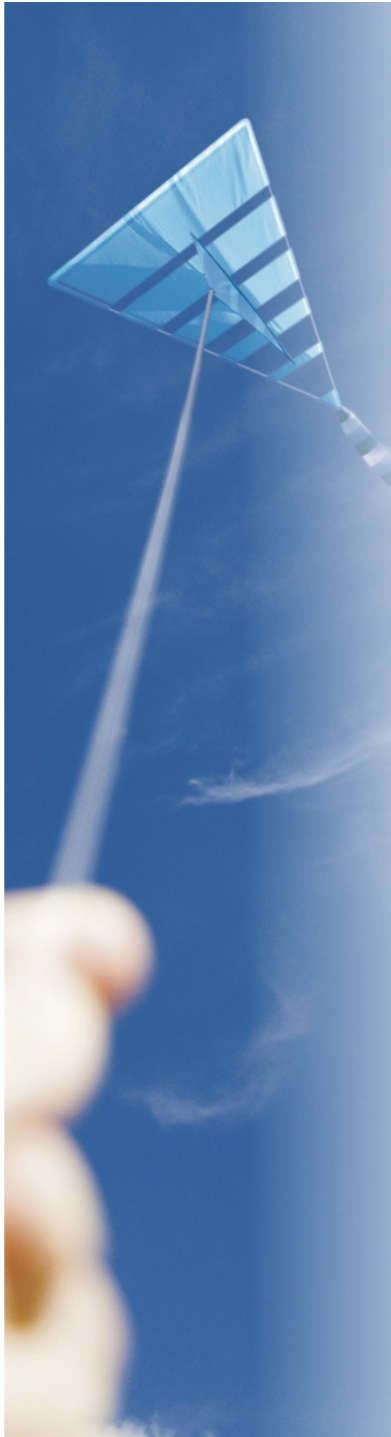


Case 1 – Pre-IND Review



- Compound – gene therapy product with two active components
- Proposed indication for advanced cancer
- Pre-IND meeting requested
- FDA granted meeting request
- Assumptions:
 - Rationale for conducting pivotal toxicology study in one species acceptable
 - Four-week repeat-dose toxicology study sufficient to support extended

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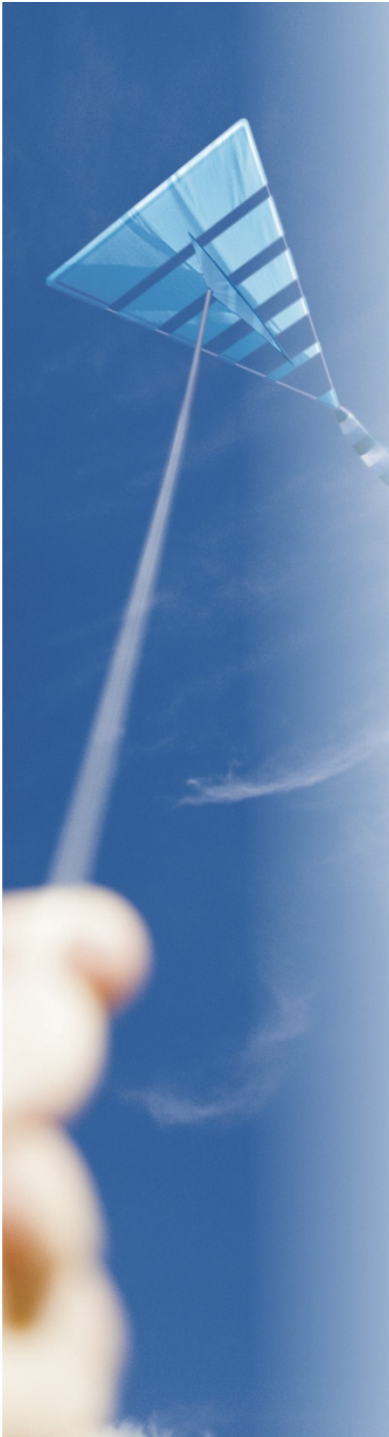


Case 1 – Pre-IND Review



- Preclinical Issues Identified
 - Repeat-dose toxicology studies in two species
 - Repeated-dose toxicology study in the rodent to consist of 8 dose groups; only 3 dose groups in nonrodent (one in the most biologically relevant species [rodent] and the other study in a large animal to evaluate toxicity of large volume administrations)
 - Duration of the toxicology studies to be equivalent to the clinical trial duration (i.e. 6 weeks)
 - Biodistribution assessment only in the most relevant species (rodent)

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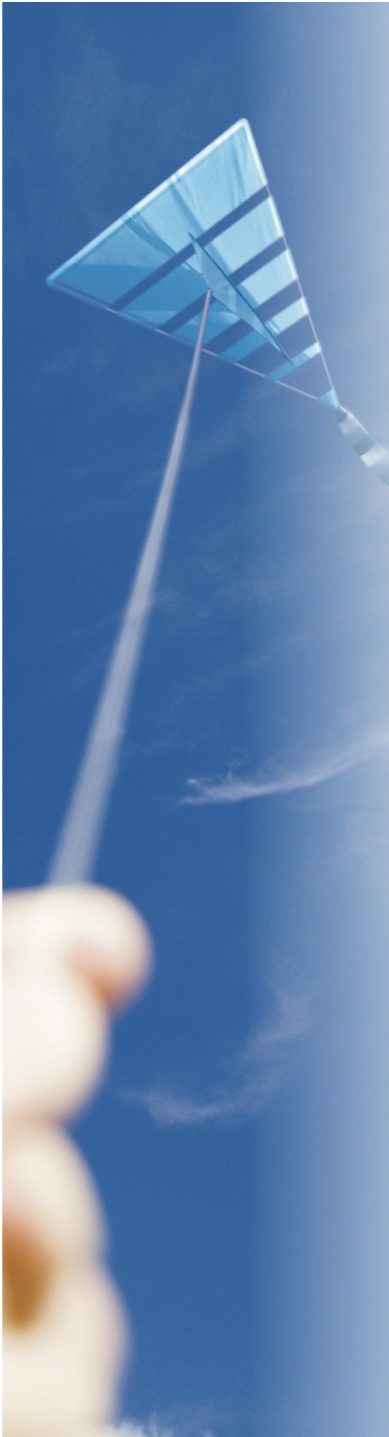


Case 1 – Pre-IND Review



- Preclinical Issues Identified (continued)
 - T-cell response to be investigated as part of the immunogenicity assessment
 - Acute toxicology arm only in the most relevant species (rodent)
- Post pre-IND meeting activity
 - FDA's Pharm/Tox reviewer worked directly with sponsor to design both pivotal toxicology studies

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Case 2 – Pre-IND Review



- Compound – a targeted peptide-protein conjugate
- Indication for treatment of intractable chronic pain in terminally ill patients.
- Phase 1/2 clinical trial will consist of a single intrathecal injection
- Assumptions:
 - GLP toxicology studies with CRD1 would support clinical trials.
 - Rationale = CRD1 – the peptide is linked to the protein with an N-terminal cysteine linker, CRD2 – the peptide is linked to the protein with a more stable linker.
 - Nonclinical safety studies with CRD1 consisted of
 - 1) GLP single-dose toxicity study in rat with 1-month and 6-month recovery
 - 2) GLP single-dose toxicity study in dog with 1-month and 3-month recovery

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Case 2 – Pre-IND Review



Sponsor Question: Does the Division agree that the current nonclinical safety studies conducted with CRD1 in rats and dogs are sufficient to support the proposed Phase 1/2 study in terminally ill cancer patients with intractable chronic pain?

Agency Response : No. Toxicology data for CRD2 in two species will be required for the IND.

Sponsor Request: Conduct a CMC bridge between CRD1 and CRD2 in lieu of conducting toxicity studies in rat and dog.

Agency Response: Agreed with CMC bridge; however, a single-dose toxicity study in dog with 90-day recovery would still be needed.

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End-of-Phase 2 Meeting



- The EOP2 will help to ensure that meaningful and adequate data are generated during Phase 3 studies and to get FDA input of marketing requirements
- Discuss and agree on plans/protocols
- Identify safety issues, scientific issues and/or potential problems and address/resolve them prior to initiating Phase 3 studies
- Identify potential roadblocks that could affect review of marketing application

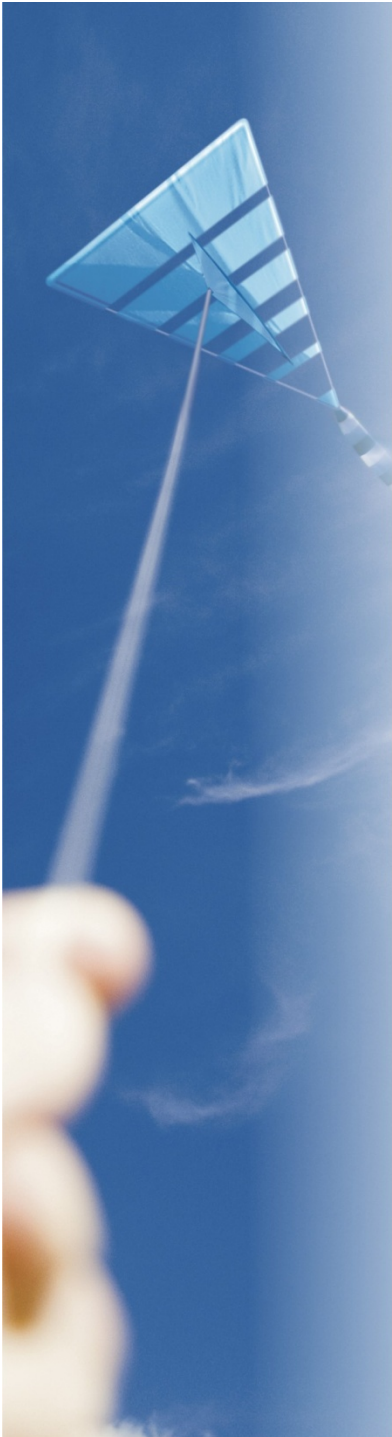
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The NDA Process



- The NDA application is the vehicle through which sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.
- Goals of the NDA
 - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
 - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
 - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

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The Pre-NDA Meeting



- General focus
 - Filing and format issues at least 6 months prior to NDA submission
 - Discussion of any problems that can lead to refuse-to-file recommendation or hinder the review process.

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The Pre-NDA Meeting



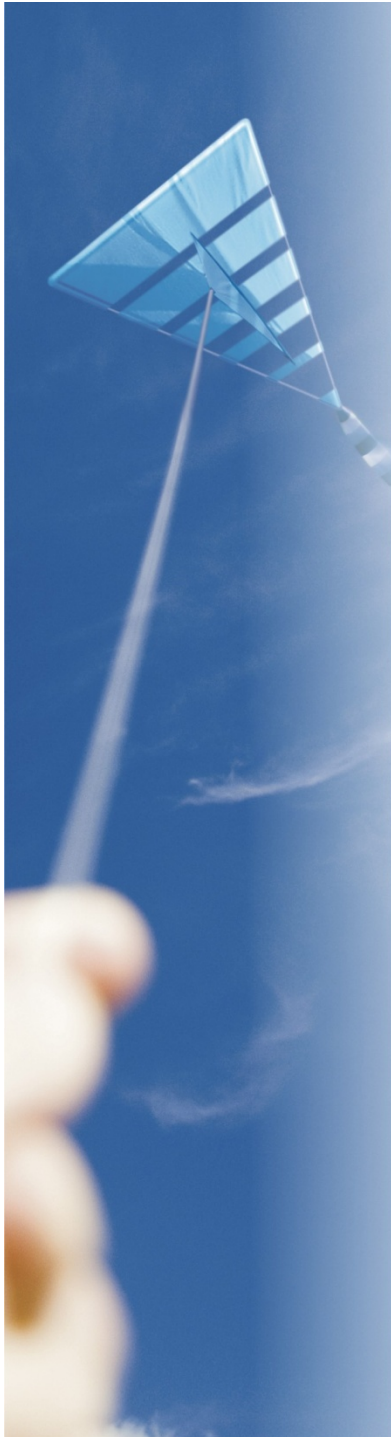
- **Compound:** previously approved small molecule
- **Indication:** Palliative Treatment of Advanced Prostrate Cancer
- **Next Milestone:** NDA
- **Sponsor Question:** Does the Division agree that the toxicology information, as archived in the original NDA submission, can be referenced in lieu of re-submitting this information?
- **FDA Response:** If you are planning to submit the NDA electronically, we suggest that you re-submit the study reports. Please note that for the proposed indication, results of embryo-fetal toxicology study(ies) will be needed with the NDA. For a 505(b)(2) NDA, information available from labels of approved products may be used.

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The Pre-NDA Meeting

- **Sponsor Request:** Based on the proposed indication and clinical use of this product in men and women for numerous indications, Sponsor requests a waiver.
- Sponsor is willing to accept the Category X labeling associated with other marketed products.

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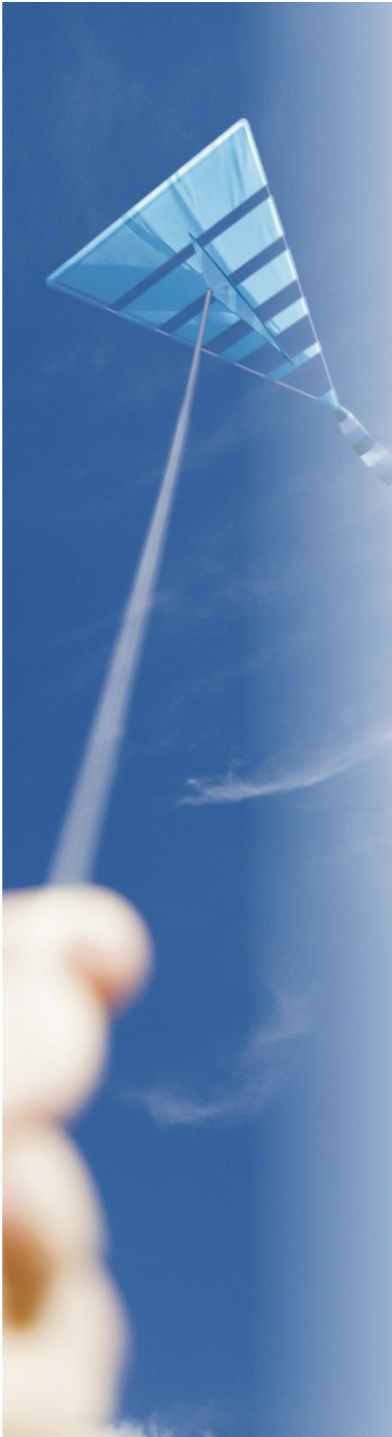
The Pre-NDA Meeting

Rationale for Waiver of Embryo-fetal Toxicology Study



- Based on ICH S9 guidance 'Nonclinical evaluation for anticancer pharmaceuticals', embryo-fetal toxicity studies are not considered essential to support clinical trials intended for the treatment of patients with late stage or advanced cancer.
- Previously approved drug product:
 - **Approval Status:** Approved January 2002
 - **Treatment Area:** Advanced prostate cancer
 - **Label of the marketed product:** *Pregnancy, Teratogenic Effects:* Pregnancy category X.
 - **Nonclinical studies based on marketed product**

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The Pre-NDA Meeting



- FDA Response :
 - Conduct the required embryo-fetal toxicology studies or change the designation of the application to 505(b)(2).

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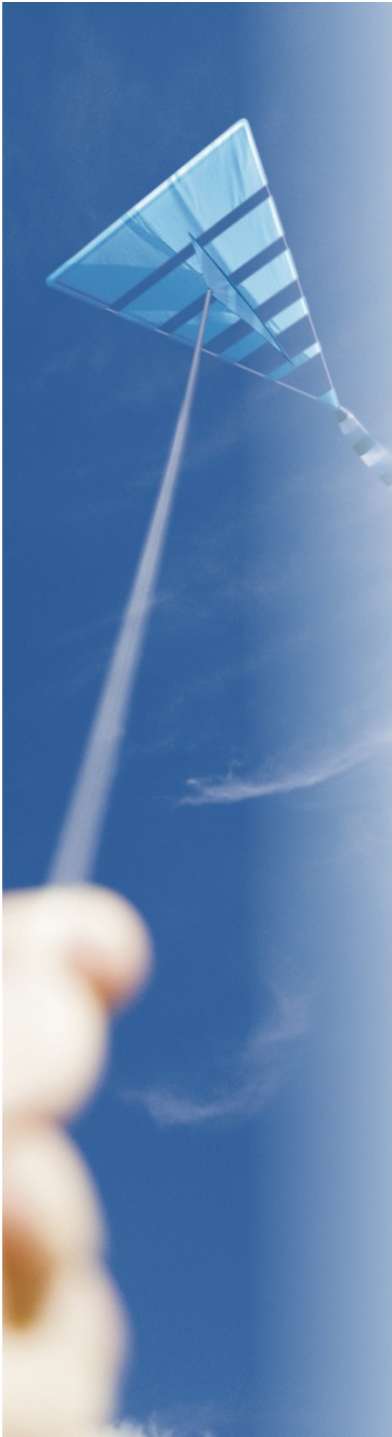


The Pre-NDA Meeting Conclusion



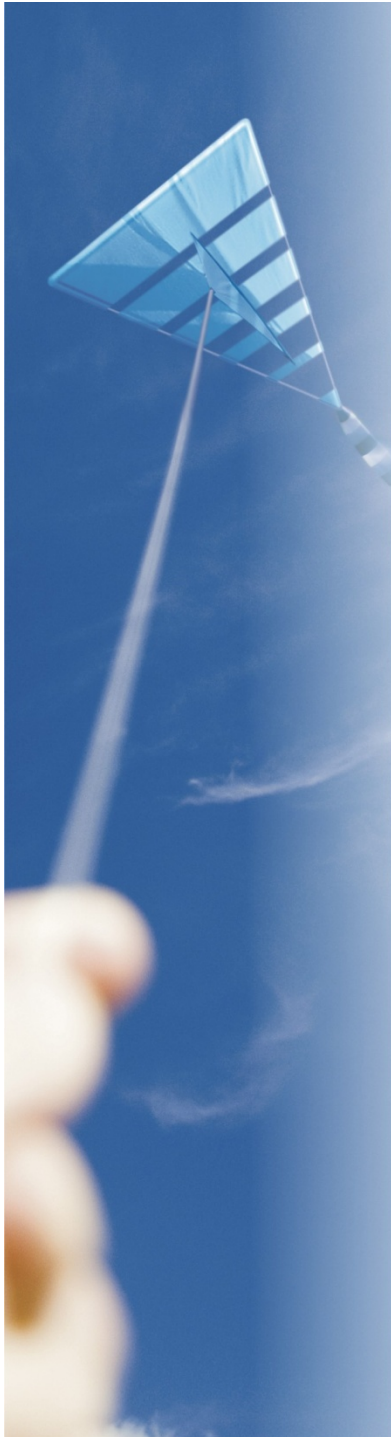
- Sponsor proposes an embryo-fetal toxicity study be conducted in one species only, i.e., rabbit
- Rationale based on ICH S9 guidance
 - “in cases where there is positive data for embryo-fetal developmental toxicity in one species, a second species is not warranted”
 - Marketed Label - Major fetal abnormalities were observed in rabbits but not in rats after administration throughout gestation.
- FDA agreed to proposal

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Questions?

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Approach to Toxicology Studies: General Remarks



- Toxicity studies should be conducted in compliance with Good Laboratory Practices (GLP) as specified in 21 CFR 58. Area(s) of noncompliance should be defined and reason included (21 CFR 312).
- Test articles used in GLP studies should be from lots manufactured with the same production process, formulation, and release specifications as the lots intended for clinical use. Supporting stability data should be available.

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