Welcome to the American College of Toxicology's Signature Webinar Series

Preparing for Regulatory Interactions: How Much is Enough?

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ToxStrategies, Inc.

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ToxStrategies

Outline

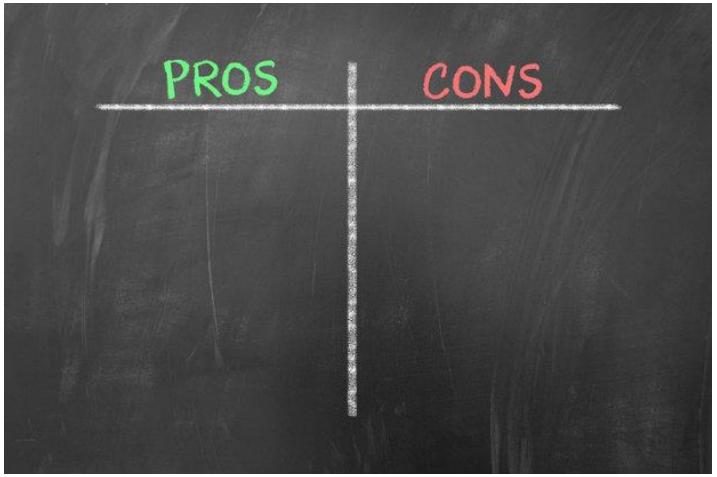
- Is a meeting essential?
  - What key issue(s) need to be discussed/agreed to with the regulatory authority?
- What kind of meeting: face-to-face, teleconference or written responses?
- Timeline
- Preparation
- Briefing book
  - Are new studies or data needed prior to the meeting?
- During and after the meeting
- Examples

Deciding on a Meeting

- Is a meeting needed?
- Is regulatory feedback necessary to move forward with clinical development?
- Examples, agreement needed on:
  - Alternative or non-standard toxicology package (fewer studies or alternative studies)
  - Juvenile toxicology plan and juvenile toxicology protocol
  - No relevant animal model (biologics)
  - First-in-human (FIH) dosing rationale
- Or can a sponsor proceed without a meeting (at a low level of risk)?

What Meeting Type?

- Each meeting type has its own pros and cons:
  - Face-to-face meeting
  - Teleconference
  - Written responses



- Face-to-face meeting if:
  - A complex topic without one clear path
  - Requires back-and-forth dialogue
  - Time sensitive
- Teleconference if:
  - Topic can be explained/understood by phone
  - Travel is cost- and/or time-prohibitive
- Written responses if:
  - Straightforward issue that requires formal agreement

Timeline Considerations

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Rachel Kichline at 301-796-0319 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Procedural

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12/18/2017

Table A: Meeting Management Procedural Goals

Meeting Type	FDA Response to Request	FDA Receipt of Meeting Package	FDA Preliminary Responses to Requester (if applicable†)	Requester Response to FDA Preliminary Responses (if applicable†)	FDA Scheduled Meeting Date (days from receipt of request)	FDA Meeting Minutes to Requester (if applicable†)
A	14 days	With meeting request	No later than 2 days before meeting	--	Within 30 days	30 days after meeting
B	21 days	No later than 30 days before meeting	No later than 2 days before meeting	--	Within 60 days	30 days after meeting
B (EOP)*	14 days	No later than 50 days before meeting**	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 70 days	30 days after meeting
C	21 days	No later than 47 days before meeting***	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 75 days	30 days after meeting

FDA PreIND Timeline Example

Activity	# Days Relative to Meeting
Meeting Request Letter	-60
Briefing Book Submission	-30
Rehearsals	-30
Preliminary Response	-2
Meeting	0
Draft Minutes	15
Final Minutes	30

Meeting Request

- Purpose of meeting: objectives, agenda
- Attendees
- Questions to be discussed and addressed
- Suggested dates for meeting
- Meeting request used to schedule meeting and determine attendees

7 March 2018

Head at FDA, MD
Director, Division of XYZ Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: BB-IND XYZ
Amazing Product XYZ
SN0XYZ
[Nonclinical Request for Meeting]

Attn: Super Smith, PhD, Regulatory Project Manager

Dear Dr. XYZ:

Please refer to our BB-IND XXX for the development of Amazing Product XYZ as a treatment for rheumatoid arthritis.

The purpose of this meeting is to get agreement on the nonclinical plan for Amazing Product XYZ. The proposed list of questions is provided below along with a list of attendees.

We plan to provide a briefing book and reports for X studies in the meeting package.

Preliminary questions to the Division include the following:

Question 1. The Sponsor proposes to conduct repeat dose studies in rats and dogs. Does the Agency agree that these species are acceptable?

Question 2. The Sponsor proposes to conduct reproductive toxicology studies in rats and rabbits. Does the Agency agree these species are adequate?

Question 3. Does the Agency agree that a waiver of carcinogenicity studies for Amazing Product XYZ is appropriate?

We request a meeting or teleconference with the Division to discuss the above questions.

If you have any questions about this or any other submission to this IND, please feel free to contact me at phone number (000) 000-0000, Fax: (000) 000-0000, email: superdrug@XYZ.com, or at the mailing address XYZ.

Sincerely,

Super Drug, PhD

Meeting Questions

- What questions do you need answered?
- Provide all questions prior to meeting.
- Helps a regulator prepare and review the briefing book in the context of the questions.

Meeting Agenda

- How much time do you have?
- Usually 1−1.5 hours
- Are slides really needed?
- Who will be attending?
- Determine how much time per question is needed.

Meeting Agenda Example

Agenda depends on goal of meeting, questions, contents of briefing book, and stage of development.

- Introductions (5 min)
- CMC Questions (10 min)
- Nonclinical Questions (15 min)
- Clinical Questions (20 min)
- Recap, Action Items and Minutes (5 min)

Briefing Book

- Briefing book (BB) content depends on type of meeting and topics to be covered
- For comprehensive meetings like pre-IND, pre-NDA/BLA, briefing book should have summary of entire program across disciplines
- For more focused meetings, content should be based on questions to be answered
- BB should be concise and clear

Common Technical Document:

2.6 Nonclinical written and tabulated summaries

- 2.6.1 Introduction
- 2.6.2 Pharmacology written summary
- 2.6.3 Pharmacology tabulated summary
- 2.6.4 Pharmacokinetic written summary
- 2.6.5 Pharmacokinetic tabulated summary
- 2.6.6 Toxicology written summary
- 2.6.7 Toxicology tabulated summary

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R4_Organisation/M4_R4__Granularity_Document.pdf

Briefing Book (continued)

2.6.6 Toxicology Written Summary

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2.6.6 Toxicology Written Summary

1. BRIEF SUMMARY

Superdrug XYZ is a novel inhibitor of XYZ kinase being developed for XYZ in adult patients. The mechanism of action of Superdrug XYZ is…. .

The initial nonclinical toxicology studies for Superdrug XYZ were designed to enable the proposed Phase 1/2 Study in patients. The rat and dog were selected for the toxicology studies as pharmacologically relevant nonclinical species to characterize the nonclinical safety profile of Superdrug XYZ because of in vitro and in vivo data that show XYZ.

The same batch of material (Lot No. XXX) was used in all of the GLP IND-enabling studies and is representative of the clinical batch of material to be used in Phase 1/2 trials (Module 3, XXX).

The completed nonclinical safety studies are shown in Table 1 below and include repeat dose toxicology studies in rats and dogs. The subcutaneous route of administration was used for the nonclinical safety studies because it is the proposed clinical route.

Safety pharmacology studies were completed in the rat and dog.

A full battery of in vitro genetic toxicity studies was completed to support Phase 1/2.

Pivotal studies were conducted in compliance with United States Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations (21 CFR Part 58). Development of Superdrug XYZ also followed applicable ICH and FDA guidance documents.

Table 1: Superdrug XYZ Nonclinical Safety Studies

Species / Test System	Study Description Duration (weeks)	Route of Administration	GLP Status	Study Number
Rat	1-month with 1-month recovery	SC	GLP	XYZ
Dog	1-month with 1-month recovery	SC	GLP	XYZ
Rat	Safety Pharmacology - Neurobehavior	SC	GLP	XYZ
Rat	Safety Pharmacology - Respiratory	SC	GLP	XYZ
Dog	Safety Pharmacology - Cardiovascular	SC	GLP	XYZ

Revise Agenda Based on Preliminary Response

Revised Agenda (no CMC comments from regulatory authority):

- Introductions (5 min)
- ~~CMC Questions (10 min)~~
- Nonclinical Questions (20 min)
- Clinical Questions (25 min)
- Recap, Action Items and Minutes (5 min)

Face-to-Face Meeting

- Pros
  - Real-time dialogue
  - Decision can be made quickly
  - Body language and non-verbal cues
  - Negotiation/discussion with regulatory authority may lead to other positive outcomes
  - Build relationship/partnership
- Cons
  - More preparation to ensure participants are on the same page – goals, messages, talking points
  - Can go off-topic – one person should drive/direct conversation on each side
    - Usually regulatory affairs lead who can intervene if conversation goes off-track
  - Travel and time

Face-to-Face Meeting Preparation

- Outline key questions
- Prepare draft responses
- Practice/rehearse with colleagues
- Is issue being discussed complex, and is a decision tree needed?
- Determine who will address specific types of questions (CMC, clinical, nonclinical)
- Ensure each team member is prepared to address potential issues/questions that may arise
- Prepare slides if needed
- Have copy of briefing book readily available at meeting

General Advice and What Not To Do

- Attitude matters – be positive
- Appearance – professional
- Limit use of laptops during F2F meetings
- Make eye contact
- Take notes!
- What NOT to do:
  - Generally, do not ask regulator what you should do. Usually, it is best to provide your proposed plan or path forward and ask if they agree.
  - Do not get angry or be rude.
  - Do not ask about something not described or supported in the briefing package.

Teleconference

- Pros
  - Travel not necessary; overall time and cost savings
  - Sponsors – can go on “mute” and discuss regulatory feedback with colleagues before responding
  - Similar to F2F, can get feedback real-time and negotiate or discuss complex issues

- Cons
  - Preparation similar to F2F
  - Can’t see body language
  - Relationship building not as direct as F2F meeting

Teleconference Meeting Preparation

- Outline key questions
- Prepare draft responses
- Practice with colleagues
- Determine who will address specific types of questions (CMC, clinical, nonclinical)
- Ensure each team member is prepared to address potential issues/questions that may arise
- Have copy of briefing book available

During and After the Meeting

- Take notes during the meeting
- Recap with regulatory authority at the end of the meeting to ensure capture of key points and action items
- Meet with colleagues afterward to discuss
  - Meeting impressions
  - Lessons learned
  - Does everyone agree on what was discussed and decided?
  - Next steps
    - Provide regulatory authority with any further information they need
    - Prepare and submit meeting minutes by the due date

Meeting Minutes for F2F and Teleconferences

- Regulatory authorities usually want minutes from sponsor
- Regulatory authority will either review and comment on sponsor minutes or create own version of minutes; used as official record of meeting for FDA
- Submit sponsor minutes in timely fashion (usually within 1-2 weeks) while issues are fresh in everyone's minds
- If there are any issues or disagreements to resolve (e.g., disagreement between sponsor and regulatory body), be sure to address them ASAP

Written Responses

- Pros
  - Travel not necessary; overall time and cost savings
- Cons
  - May not receive clear and/or definitive response
  - Cannot discuss issues in real time with regulator; however, may be able to follow up to clarify issues

Written Responses Preparation

- Ensure briefing book is simple, clear, and easy to interpret.
- Present all critical data sets, because there is no back-and-forth on the data.
- Determine what questions a regulator could ask on package – make sure questions can be answered with data provided.

Resolving Issues with Regulators

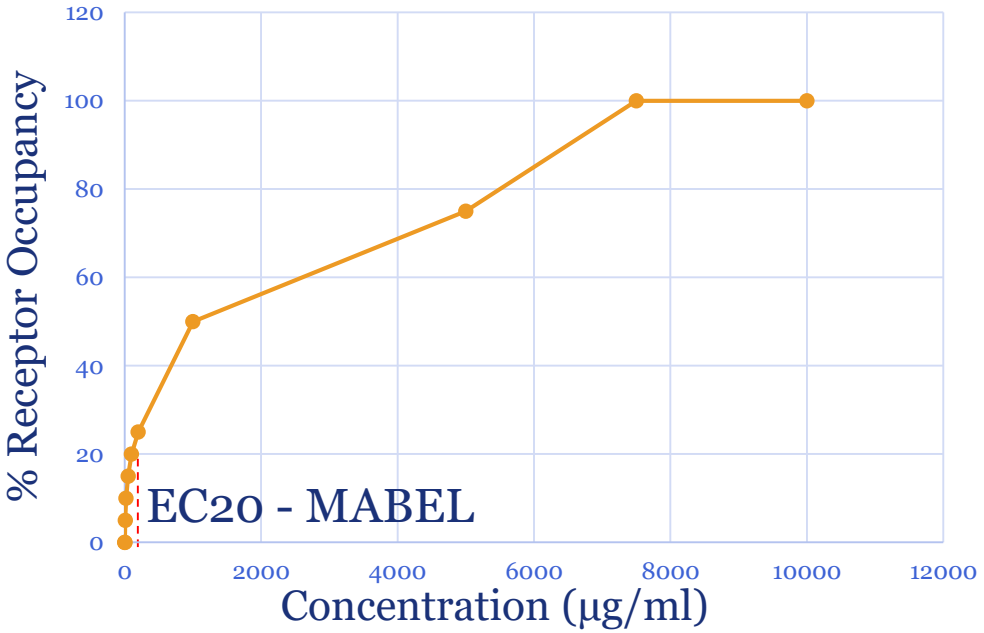
- Potential issues
  - Lack of clarity after meeting
  - No path forward determined
- First try to address the issue directly, follow up phone call with contact at regulatory authority in order to discuss issue and determine options
- Dispute resolution
- Ombudsman

F2F Meeting Example

- Meeting Type: Pre-IND/Scientific Advice Meeting
- Product: Novel target and biologic product
- Background:
  - No relevant species
  - Literature and *in vitro* studies in human cells used to characterize target and determine FIH dose
  - Minimally anticipated biologic effect level (MABEL) as basis for FIH dose
- Question to Regulator: Are the proposed studies and MABEL approach adequate to support the proposed Phase 1 and FIH dose?

F2F Example (Continued)

- Briefing book:
  - Nonclinical data show no relevant species
  - Summary of all in vitro data used to characterize molecule
  - Details on study/assay used to determine the MABEL
  - Provide justification for FIH dose (e.g., EC20 and conversion to ug/kg dose) based on understood mechanism of action, pharmacology and potential toixicity.



Teleconference Example

- Meeting Type: End of Phase 2
- Product: novel small molecule to target that has been characterized in the literature
- Background:
  - Adequacy of nonclinical plan to support a New Drug Application (NDA)
  - No reproductive toxicology or carcinogenicity studies planned, because hazard identified for target in the literature
- Question to Regulator: Can literature be used to define potential reproductive toxicity and carcinogenicity hazards, and for labeling?

Teleconference Example (Continued)

- Briefing book:
  - Summary of available literature data across species, findings
  - Was a hazard identified? At what dose relative to the proposed clinical dose?
  - Scientific rationale for why literature are sufficient to define carcinogenic and reproductive risk in patients and additional studies are not needed.

Written Response Example

- Meeting Type: Type C
- Product: small molecule previously developed in adults.
- Background:
  - Agreement on nonclinical plan and study design for juvenile toxicology studies
  - Provide juvenile toxicology protocol and overall nonclinical plan for clinical development
- Question to Regulator: Does the regulatory authority agree that the juvenile toxicology study design will support the proposed Phase 1 clinical trial in pediatric patients?

Written Response Example (continued)

- Briefing book:
- Detailed juvenile toxicology study design and rationale.
  - Species
  - Is species relevant and predictive?
  - Duration of dosing
  - Does duration support proposed pediatric clinical trial and allow for potential toxicity to be observed?
  - Study endpoints
  - Dose rationale relative to proposed clinical doses
  - Post-natal day age at start and end of dosing

Juvenile Toxicology Study Design

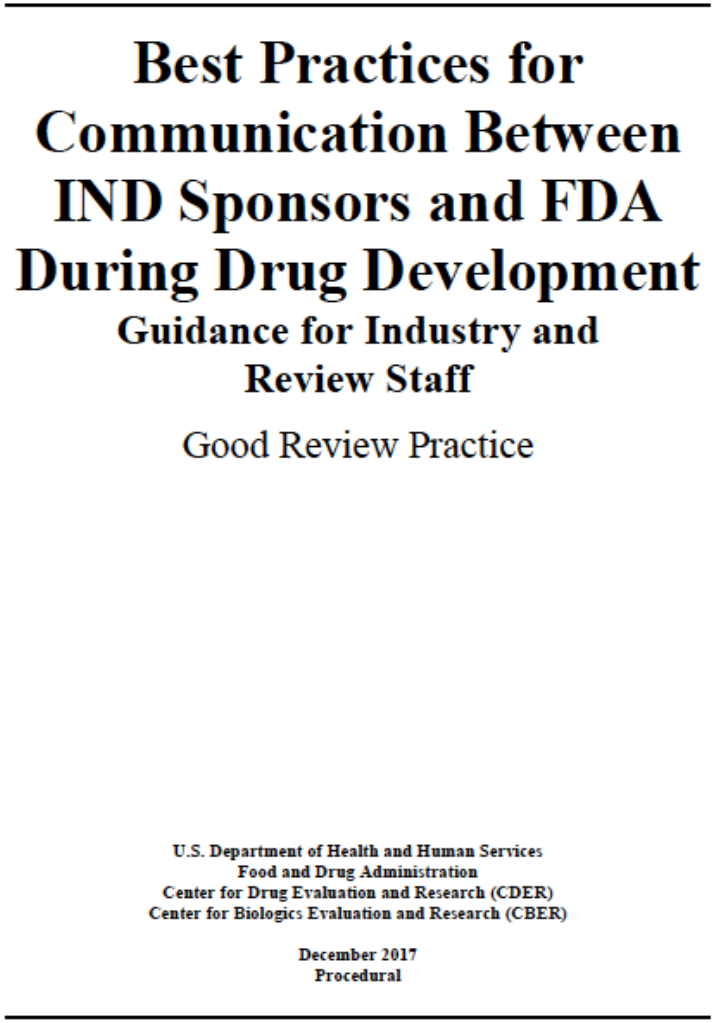
Group	Test Article	Dose Level (mg/kg)	Dose Volume (ml/kg)	Main Study # (M/F)	TK # (M/F)	Recovery Study # (M/F)
1	Vehicle	0	2	10/10	9/9	10/10
2	TA-X	5	2	10/10	9/9	10/10
3	TA-X	10	2	10/10	9/9	10/10
4	TA-X	50	2	10/10	9/9	10/10

- Species Rationale: rat showed activity (binding, in vitro and/or in vivo)
- Dose and Route Rationale: dosing to MTD or MFD, or target saturation, use clinical route of administration
- Duration Rationale: support pediatric population and development of potential target organs; equivalent post-natal day in rat vs. human (PND 21 in rat is 2 years in human)
- Special Endpoints: neurobehavior, pharmacodynamic markers, histopathology, fertility

Summary and Conclusions

- In summary, regulatory meetings are time- and resource-intensive for both parties – sponsor and regulatory authority.
- Ensure briefing package presents all necessary data for decision making. May be worthwhile to delay meeting for additional data.
- Propose the meeting type that is necessary and appropriate for the questions at hand.
- Prepare and rehearse for meetings.
- Take notes during meeting, and recap at the end of the meeting.
- Minutes are critical for ensuring agreement and documentation.

Guidance on Best Practices



Best Practices for Communication Between IND Sponsors and FDA During Drug Development

Guidance for Industry and Review Staff

Good Review Practice

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Procedural

Resources

- Food and Drug Administration (FDA) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM475586.pdf
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf
- European Medicines Association (EMA) http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143121.pdf
- Pharmaceuticals and Medical Devices Agency (PMDA) https://www.ich.org/fileadmin/Public_Web_Site/Training/GCG_-_Endorsed_Training_Events/APEC_LSIF_FDA_prelim_workshop_Bangkok__Thailand_Mar_08/Day_1/PMDA_and_Applications.pdf
- Medicines and Healthcare products Regulatory Agency (MHRA) https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

Questions?

Please feel free to contact Janice Lansita – jlansita@toxstrategies.com with questions.