Pre-IND Meeting—Why and How

Carmella S. Moody, PhD
Regulatory Program Director
RTI International
Overview of Presentation

• Pre-IND meeting overview
• Specific suggestions for a meeting request letter and briefing document
• Feedback from a CARB-X development team about their experience with a pre-IND meeting
• Questions and answers
This presentation is provided for your consideration and is informational only. The presentation and information therein does not constitute legal or regulatory advice.
Pre-IND Meeting Overview
CDER and CBER
What Is a Pre-IND Meeting?

• A pre-IND meeting is a formal meeting, most frequently the first meeting with the FDA, where the specific division provides feedback to questions asked.

• It is a Type B meeting, which means FDA will schedule the meeting within 60 calendar days of a meeting request.

• FDA will grant most pre-IND meetings; however, they will generally only schedule one pre-IND meeting per application (e.g., investigational new drug [IND], new drug application [NDA], biologics license application [BLA])

• There is no charge for an FDA meeting
Why Have a Pre-IND Meeting?

• Gain agency feedback on Sponsor’s strategy for addressing development challenges.
• Focus and streamline the development program to save time and money!

What a Pre-IND Meeting Is Not

• The pre-IND meeting IS NOT the place TO PROVE TO FDA HOW WELL THE DEVELOPMENT IS GOING in the briefing document or show how much the Sponsor knows about development.

• The pre-IND meeting IS an opportunity to
  – present significant challenges that the Sponsor has encountered from a quality, nonclinical, clinical, or regulatory perspective.
  – gain agency feedback on the Sponsor’s plan to address these challenges.

• The IND is where the Sponsor PROVES to the FDA that they have implemented enough controls from a quality, nonclinical, or clinical perspective to proceed to human clinical trials.
When Does FDA Suggest a Pre-IND Meeting is Beneficial?

• When the product is intended to treat a serious or life-threatening disease
• When there is a novel indication
• When there are no current guidance documents
• When there are Sponsors new to drug development
• When there are questions from the Sponsor
• When there are pharmacologic or toxicologic signals of concern
• When the drug is a new molecular entity
FDA Perspective on Benefits of a Pre-IND Meeting

• Identifying and avoiding unnecessary studies
• Ensuring that necessary studies are designed to provide useful information
• Gaining FDA support for a proposed strategy
• Minimizing potential for clinical hold
• Providing opportunity for creative exchange of ideas
• Obtaining regulatory insight
• Minimizing costs
• Clearly defining endpoints and goals of the development program
• Allowing early interactions/negotiations with FDA
Will FDA Tell Us What to Do?

NO

- FDA will provide very thoughtful feedback on
  - Clinical trial design issues
  - Toxicity issues
  - Unique metabolites
  - Nonstandard or novel formulations
  - Dosing limitations
  - Species suitability
  - Immunogenicity
Is the FDA Feedback Binding?

• The Sponsor can choose to accept the feedback or use an alternative strategy. However
  – Remember that FDA’s guidance is generally based on knowledge of what most companies in the same field are doing and what FDA has required for other Sponsor’s products

• The FDA can decide when the IND is filed, and more data are available, that the guidance they initially provided at the pre-IND meeting is no longer valid
  – Pre-IND briefing document should, therefore, be very well written and accurate
Pre-IND Meeting Logistics
CDER and CBER
Preparation

• Submit the meeting request with the preferred meeting format:
  – Face to face
  – Teleconference/videoconference
  – Written responses

• Within 21 days of the meeting request:
  – FDA will contact the Sponsor to indicate meeting format
  – Schedule the meeting within 60 days of the initial request

• 30 days prior to the meeting the Sponsor must submit a briefing document with finalized questions and information to support FDA’s response to questions
FDA Preliminary Comments

• 24–72 hours before the meeting FDA will provide preliminary responses to the Sponsor’s questions
  – If preliminary responses answer all the Sponsor’s questions, the Sponsor may choose to cancel the meeting
  – If further clarification is needed for a question, the Sponsor notifies the FDA Regulatory Project Manager (RPM) about which specific questions need further discussion
  – Meeting will focus on only those questions
Meeting Conduct

• 1 hour is scheduled for the meeting
• The FDA RPM chairs the meeting
• Generally, no presentation is provided by the Sponsor to maximize time for discussing questions
• The first 5 minutes are introductions of FDA and Sponsor attendees
• The next 50 minutes are for discussion of the questions in the order requested
  – List the primary concern questions first when providing questions to the RPM, so if time runs out, these primary concerns have been discussed!
• The last 5 minutes are for a statement by the Sponsor of the agreements in the meeting
Post Meeting

- The Sponsor may provide their notes to FDA a few days after the meeting
- FDA provides final comments within 30 calendar days after the meeting
Pre-IND Meeting Request
CBER and CDER
Information to Include in Pre-IND Meeting Request

• Meeting objective
• Proposed agenda, including estimated times needed for each agenda item
• List of specific questions (proposals and questions) categorized and grouped by discipline (e.g., chemistry, manufacturing, and controls [CMC], pharmacology/toxicology, clinical pharmacology and biopharmaceutics, and clinical investigations)
• List of Sponsor participants
• List of requested participants from CDER or CBER and if a drug/device combination, CDRH
• Quantitative composition (all ingredients by percent composition) of the drug or biologic proposed for use in the study to be discussed
• Proposed indication
• Dosing regimen, including concentration, amount dosed, and frequency and duration of dosing if known
• Proposed meeting date (propose 6–8 weeks in the future)
• When the background packet will be available (at least 4 weeks before the proposed meeting date)
Questions for FDA

“If I had an hour to solve a problem and my life depended on the solution, I would spend the first 55 minutes determining the proper question to ask, for once I know the proper question, I could solve the problem in less than five minutes.”

Albert Einstein (1879 - 1955) Physicist & Nobel Laureate
Information to Include in a Briefing Document

• There is no specific FDA mandate for information to include in briefing document, however, information usually presented is:
  – Information to demonstrate to FDA that Sponsor understands its product
  – Finalized questions
  – Background information to give FDA enough information to answer the questions asked

• Data should be summarized and succinct
• Generally, no new information may be presented after the pre-meeting briefing document is submitted or during the meeting, however, on occasion there may be discussion of matters not addressed in the questions.
# Target Product Profile

<table>
<thead>
<tr>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Description</strong></td>
<td>Brief description and/or current product name</td>
</tr>
<tr>
<td><strong>CTSI-001</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanisms of Action (MoA)</strong></td>
<td>The mechanism by which the product produces an effect on a living organism</td>
</tr>
<tr>
<td><strong>Blocks the interaction between...</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Pharmacology</strong></td>
<td>Pharmacokinetic information, distribution and pathways for transformation</td>
</tr>
<tr>
<td><strong>Intravenous (IV) administration of CTSI-001 to subjects was well tolerated in the ascending single-dose (0.002–10 mg/kg) and multiple-dose (0.5–5 mg/kg) studies.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>The pharmacokinetic profile is roughly linear doses above 2 mg/kg and the mean half-life is around 28 days.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Safety and PK profiles from the subcutaneous tolerability study are expected to be comparably to that seen in IV studies and PK/PD profile in treatment population will be supportive of monthly dosing regimen.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Target disease or manifestation of a disease and/or population</td>
</tr>
<tr>
<td><strong>Moderate to severe patients inadequately controlled on inhaled corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Efficacy Endpoints</strong></td>
<td>The most important clinical outcome measure—ideally it should be easy to interpret and sensitive to treatment differences</td>
</tr>
<tr>
<td><strong>Optimistic</strong>: &gt;50% exacerbation rate reduction vs. inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td><strong>Target</strong>: 50% exacerbation rate reduction vs. inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal</strong>: 35% exacerbation rate reduction vs. inhaled corticosteroids</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Efficacy Endpoints</strong></td>
<td>Additional criteria that may be met during a clinical trial, but that are not required to obtain a successful positive clinical trial result</td>
</tr>
<tr>
<td><strong>Optimistic</strong>: Four (4) months asthma control measured by Asthma Control Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>Target</strong>: Three (3) months asthma control measured by Asthma Control Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal</strong>: Two (4) months asthma control measured by Asthma Control Questionnaire</td>
<td></td>
</tr>
</tbody>
</table>

Source: Launchpad.ucsf.edu
Clinical

- Clinical study synopsis/draft protocol for IND opening clinical study
  - Route of administration
  - Proposed treatment regimen
  - Patient population or healthy normal controls
  - Blinding strategy
  - Inclusion and exclusion criteria
  - Stopping rules

- Synopsis for follow-on to first IND study
### Clinical Microbiology

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Preferred</th>
<th>Minimum Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MIC on drug-sensitive clinical isolates (n=25–30)</strong></td>
<td>&lt; 0.1 µg/mL</td>
<td>&lt; 2 µg/mL</td>
</tr>
<tr>
<td><strong>MIC on drug-resistant clinical isolates</strong></td>
<td>&lt; 0.1 µg/mL</td>
<td>&lt; 2 µg/mL</td>
</tr>
<tr>
<td>Efficacy in in vivo model</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compound mechanism of action</strong></td>
<td>Confirmed MOA</td>
<td>Consistent with proposed MOA, active on resistant strains</td>
</tr>
<tr>
<td>PK/PD predictors of efficacy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nonclinical Information

• Summary data for nonclinical studies to support the drug and the indication
  – Dose range finding study(s) data (4- to 14-day duration), 1 or 2 species
  – Non-GLP single dose PK data in 1 or 2 species
  – In vitro cross-species metabolism
  – Safety pharmacology studies, if available, or strategy for safety pharmacology studies, especially hERG if CV issues for class
  – Preliminary information on genetic toxicology
  – Draft study outlines for pivotal toxicology studies
## Distribution, Metabolism, Pharmacokinetics

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Preferred</th>
<th>Minimum Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$ in human microsomes</td>
<td>$&gt; 1.5h$</td>
<td></td>
</tr>
<tr>
<td>Non-rodent IV/PO PK</td>
<td>$%F &gt; 50%, t\frac{1}{2} &gt; 4hr$</td>
<td></td>
</tr>
<tr>
<td>P450 Inhibition</td>
<td>$&lt; 10% @ XX \mu M$</td>
<td></td>
</tr>
<tr>
<td>CYP metabolism phenotype</td>
<td>$&lt; 30%$ of metabolism predicted via CYP3A4/5 in HLM</td>
<td></td>
</tr>
<tr>
<td>CYP 3A4/5 induction</td>
<td>No induction in hepatocytes (3 donors, mRNA &amp; enzymes)</td>
<td>Minimal induction in hepatocytes ($&lt; 25%$ rifampin)</td>
</tr>
<tr>
<td>Cross-species metabolism</td>
<td>No human unique metabolite (LM &amp; Hepatocyte incubation)</td>
<td>Circulating metabolite without safety liability</td>
</tr>
<tr>
<td>Absorption/permeability</td>
<td>Caco2 $&gt; 5 \times 10^{-6}$ cm/s</td>
<td>Caco2 $&gt; 1 \times 10^{-6}$ cm/s</td>
</tr>
<tr>
<td>Drug transporter P-gp</td>
<td>Not a P-gp substrate or inhibitor</td>
<td>BA/AB ratio $&lt; 5$ if substrate</td>
</tr>
<tr>
<td>Projected human dose</td>
<td>$&lt; 200$ mg qd</td>
<td></td>
</tr>
</tbody>
</table>
## Safety/Toxicology

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Preferred</th>
<th>Minimum Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutagenicity (Ames Test)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Clastogenicity in vitro (CHO cells)</td>
<td>Negative</td>
<td>Positive (negative in vivo)</td>
</tr>
<tr>
<td>Clastogenicity in vivo (mouse micronucleus)</td>
<td>Negative</td>
<td>Negative if positive in vitro</td>
</tr>
<tr>
<td>Receptor/Enzyme/Channel Off-target binding</td>
<td>No hit (&lt;50% inhibition at 10 µM)</td>
<td></td>
</tr>
<tr>
<td>NOAEL (rats and higher species, 14-day dose ranging toxicity)</td>
<td>&gt; 10-fold over efficacious exposure</td>
<td>&gt; 3-fold over efficacious exposure</td>
</tr>
</tbody>
</table>
Quality/CMC

• Brief description of the manufacturing scheme for the active molecule and formulation for clinical study
• Brief assay descriptions
• Flowcharts for drug substance and drug product manufacturing processes (actual or proposed for clinical trials)
• Batch release tests proposed for drug substance and drug product
• May include specifications for batch release tests; however, FDA will generally indicate the specifications are a review issue for IND
• Comparability protocol plans
How Can the CARB-X Program Help?

• Development of a regulatory strategy

• Provision of templates for
  – Pre-IND briefing document
  – Target product profile
  – Clinical synopsis
  – Clinical protocols

• Review and guidance on content
  – CARB-X and BARDA strongly suggest Sponsors consult with them on preparation of the meeting request and briefing book
  – CARB-X and BARDA will review draft clinical protocols but require 15 days to review
Helpful Links

• 21 Code of Federal Regulations-Part 312.47 Meetings

• Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products-Guidance for Industry

• CDER-Small Business and Industry Assistance: Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting
Development Team Perspective from Pre-IND Meeting
Some lessons learned on “non-traditional” products:
Amicidins

May 28, 2020
What we do

To prevent and treat life-threatening infections especially in surgery and trauma

Amicidin-α
Surgical Gel
PIND 140908

Amicidin-β
Solution
PIND 146007
For application to clean tissues exposed during surgical procedures...

Dual mode of action – Barrier and microbicide

**Physical barrier**
*like keratins & collagens*

**Microbicidal activity**
*like cathelicidins & defensins*

...to protect against microbial contamination and reduce post-operative infection.

Dual MOA “Block and Kill”
Amicidin-β
TREAT
Solution

Dual mode of action – surfactant & microbicide

For application to contaminated or infected tissues (including biofilms)...

Surfactant properties
- to cleanse tissues

Microbicidal activity
- to kill microbes

Dual MOA
“Clean and kill”

...to cleanse, reduce microbial load, & provide infection source control.
Amicidin-α and Amicidin-β: New adjuncts for surgery & trauma

For clean tissues:
- Protect against microbial contamination
- Reduce risk of surgical site infection

For contaminated / infected tissues:
- Cleanse & debride
- Reduce microbial load
- Infection source control

Locally applied in surgical procedures and traumatic injuries
Amicidins raised some interesting regulatory questions

With surprising differences of opinion amongst Amicrobe consultants

1. Dual mode of action – Physical (barrier, cleanser) and chemical (microbicide)

   Device or therapeutic?

2. Chemically synthesized long-chain amino acid polymer

   Drug or biologic?

3. Locally applied to exposed tissues (not exactly a “topical”, not a systemic)

   IND-enabling microbiology? GLP tox? Patient populations? Outcome measures?
Device or therapeutic?

1. Amicrobe consultants had differing opinions
2. Early in preclinical development, we filed pre-IND documents with FDA Office of Antimicrobial Products, CDER
3. Granted pre-IND face-to-face meetings for both investigational products

Both Amicidins are therapeutics –
the Agency seemed to have no doubts

Non-traditional lesson learned: Go to the Agency early and focus on a few questions
Amicidins are chemically synthesized long-chain amino acid polymers.

Scalable and cost-effective

One-pot polymerization

1st Monomer
Initiator
Solvent
2nd Monomer

Amicidins

Cationic (positively-charged) amino acids
“1st block”

Hydrophobic (water-hating) amino acids
“2nd block”
## Drug or biologic?

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Polypeptide or protein</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-40 amino acids</td>
<td>41-99 amino acids</td>
<td>100+ amino acids</td>
</tr>
<tr>
<td>Drug [505(b)]</td>
<td>It depends</td>
<td>Biologic [351(a)]</td>
</tr>
</tbody>
</table>

“...more than 99 amino acids would have... **a level of structural and functional complexity**...that makes regulating such a protein under the same statutory authority as the majority of proteins more appropriate.”

- Definition of the Term “Biological Product” (FDA proposed amendment; 21 CFR Part 600 RIN 0910-AH57)

Both Amicidins are biologics (synthetic proteins)

*Non-traditional lesson learned: Read the guidance documents carefully (yourself)*
Amicidins are locally applied to exposed tissues

*Not exactly a “topical”, not a systemic – a lot of non-clinical & clinical trial design questions*

**Non-clinical development**

1. IND-enabling microbiology – type of assay(s) and number of isolates?
2. GLP toxicology – how many models (tissues & applications), dose by volume vs. concentration (viscosity?), and systemic tox of locally applied product (location matters)?

**Clinical development**

1. Is incidence of post-op infection the only acceptable outcome measure?
   a. Difficult in certain clinical settings / procedures, especially prevention
   b. Range from easily managed incisional infection to sepsis/death
2. Role of intrawound microbiology (e.g., microbe type vs number)?
3. Role of surrogate markers in blood (e.g., CRP)?
4. Multiple outcomes & antibiotic use analyzed by DOOR/RADAR?

*Non-traditional lesson learned: Work with the Agency – they are smart and can be very helpful*
1. Public conferences / presentations / interactions
   - Duke Margolis – Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics (June 14, 2018)
   - Development of Non-Traditional Therapies for Bacterial Infections (August 21-22, 2018)
   - ASM/ESCMID 2019 Annual Conference / CARB-X meeting (September 3-6, 2019)

2. Pre-IND face-to-face meetings

3. Helpful feedback and guidance
“Non-traditional” lessons learned by Amicrobe

For pre-IND meetings

1. Go to the Agency early and focus on a few questions
2. Read the guidance documents carefully (yourself)
3. Work with the Agency – they are smart and can be very helpful

Product developers and regulators are in this together
Keeping safe in the era of antibiotic resistance

Michael P. Bevilacqua, MD, PhD
Chief Executive Officer / Chief Scientific Officer
mpb@amicrobe.com

Daniel J. Huang
Vice President of Operations
dhuang@amicrobe.com