CARB-X

Combating Antibiotic Resistant Bacteria

Pre-IND Meeting—Why and How

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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.

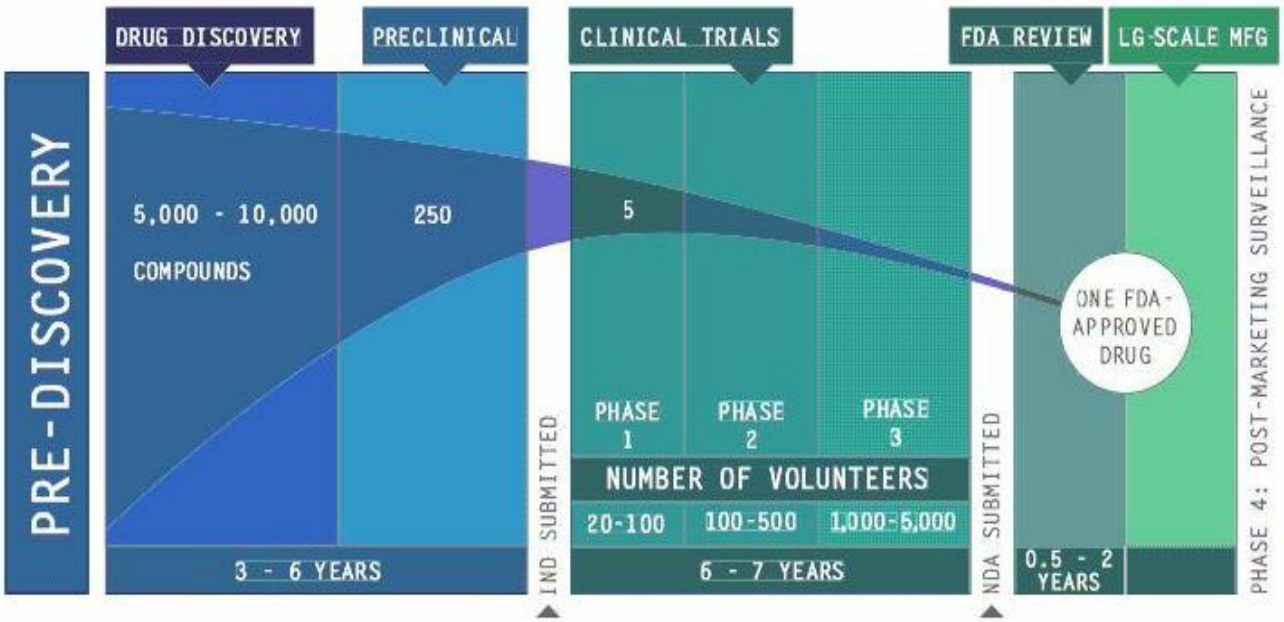
Pre-IND Meeting Overview
CDER and CBER

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!



https://www.slideserve.com/sybil/drug-development-takes-longer-than-it-did-in-the-past

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

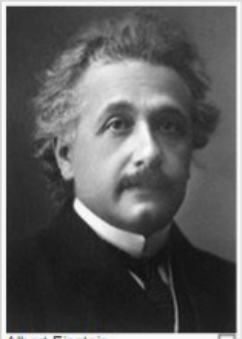
- The Sponsor may provide their notes to FDA a few days after the meeting
- FDA provides final comments within 30 calendar days after the meeting

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


Albert Einstein

"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

Pre-IND Meeting Briefing Document
CBER and CDER

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

Description		Example		
Product Description	Brief description and/or current product name	CTSI-001		
Mechanisms of Action (MoA)	The mechanism by which the product produces an effect on a living organism	Blocks the interaction between…		
Clinical Pharmacology	Pharmacokinetic information, distribution and pathways for transformation	▪ 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. ▪ The pharmacokinetic profile is roughly linear doses above 2 mg/kg and the mean half-life is around 28 days. ▪ 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.		
Indication	Target disease or manifestation of a disease and/or population	Moderate to severe patients inadequately controlled on inhaled corticosteroids		
Primary Efficacy Endpoints	The most important clinical outcome measure—ideally it should be easy to interpret and sensitive to treatment differences	***Optimistic***: >50% exacerbation rate reduction vs. inhaled corticosteroids	***Target***: 50% exacerbation rate reduction vs. inhaled corticosteroids	***Minimal***: 35% exacerbation rate reduction vs. inhaled corticosteroids
Secondary Efficacy Endpoints	Additional criteria that may be met during a clinical trial, but that are not required to obtain a successful positive clinical trial result	***Optimistic***: Four (4) months asthma control measured by Asthma Control Questionnaire	***Target***: Three (3) months asthma control measured by Asthma Control Questionnaire	***Minimal***: Two (4) months asthma control measured by Asthma Control Questionnaire

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

Criterion	Preferred	Minimum Acceptable
MIC_{90}		
MIC on drug-sensitive clinical isolates (n=25–30)	< 0.1 µg/mL	< 2 µg/mL
MIC on drug-resistant clinical isolates	< 0.1 µg/mL	< 2 µg/mL
Efficacy in in vivo model		
Compound mechanism of action	Confirmed MOA	Consistent with proposed MOA, active on resistant strains
PK/PD predictors of efficacy		

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

Criterion	Preferred	Minimum Acceptable
$T_{1/2}$ in human microsomes	> 1.5h	
Non-rodent IV/PO PK	%F > 50%, t½ > 4hr	
P450 Inhibition	< 10% @ XX µM	
CYP metabolism phenotype	< 30% of metabolism predicted via CYP3A4/5 in HLM	
CYP 3A4/5 induction	No induction in hepatocytes (3 donors, mRNA & enzymes)	Minimal induction in hepatocytes (< 25% rifampin)
Cross-species metabolism	No human unique metabolite (LM & Hepatocyte incubation)	Circulating metabolite without safety liability
Absorption/permeability	Caco2 > $5x10^{-6}$ cm/s	Caco2 > $1x10^{-6}$ cm/s
Drug transporter P-gp	Not a P-gp substrate or inhibitor	BA/AB ratio < 5 if substrate
Projected human dose	< 200 mg qd	

Safety/Toxicology

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

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

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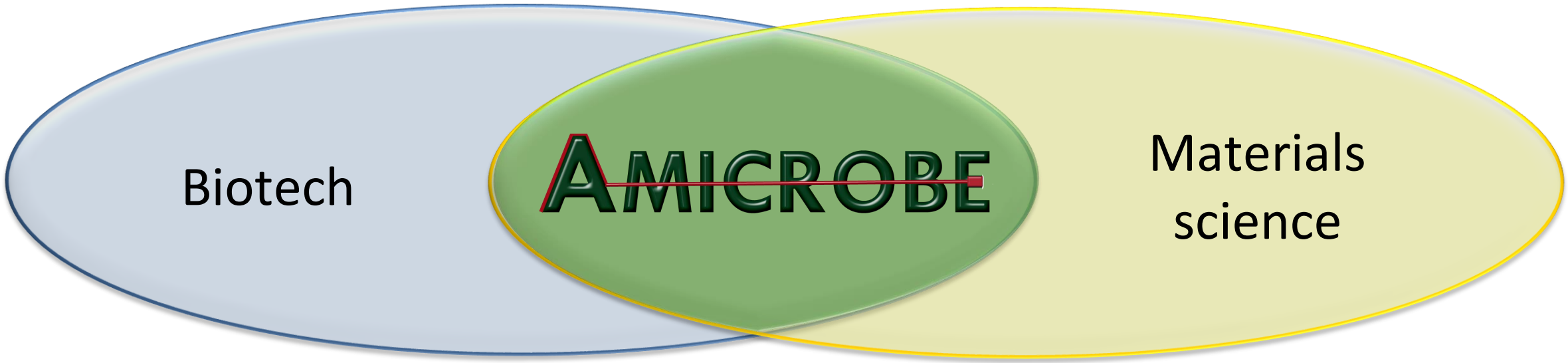
AMICROBE

Keeping safe in the era of antibiotic resistance

Some lessons learned on “non-traditional” products: Amicidins

May 28, 2020

What we do



PREVENT
Amicidin-α
Surgical Gel
PIND 140908

TREAT
Amicidin-β
Solution
PIND 146007

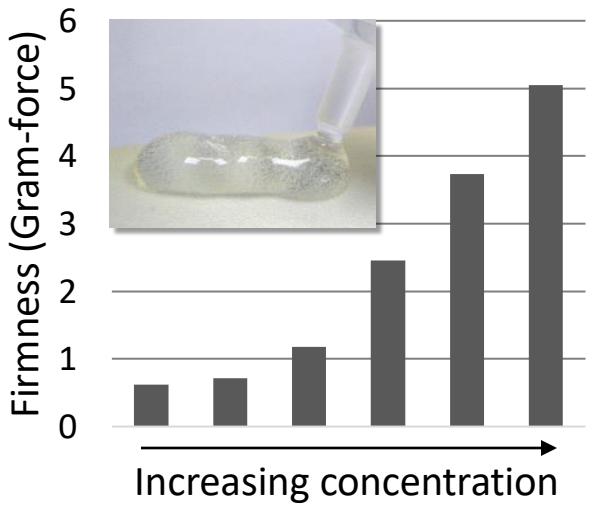
To prevent and treat life-threatening infections

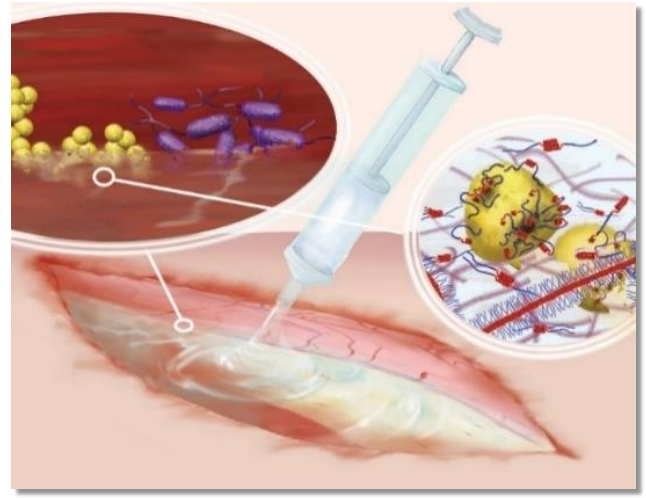
especially in surgery and trauma

PREVENT Amicidin-α Surgical Gel

Dual mode of action – Barrier and microbicide

For application to clean tissues exposed during surgical procedures…





Physical barrier

like keratins & collagens

+

Microbicidal activity

like cathelicidins & defensins

=

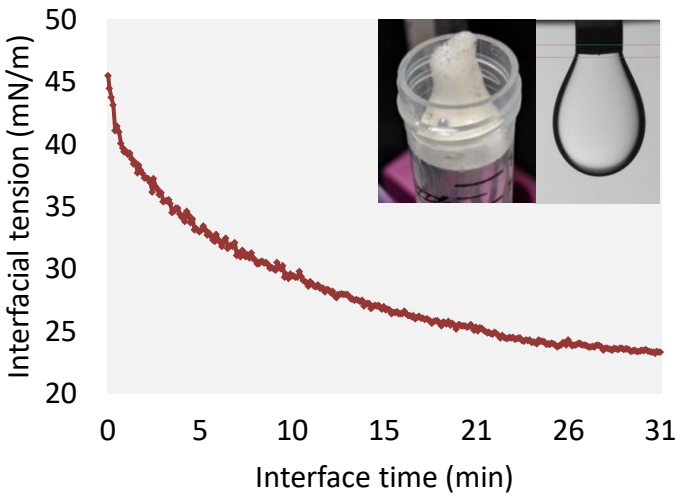
Dual MOA
"Block and Kill"

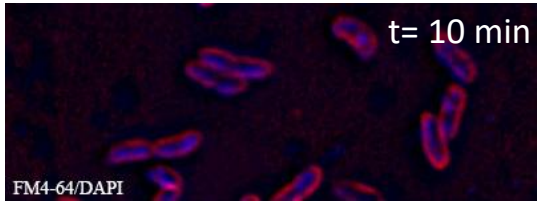
…to protect against microbial contamination and reduce post-operative infection.

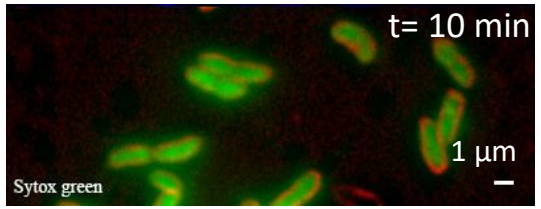
TREAT Amicidin-β Solution

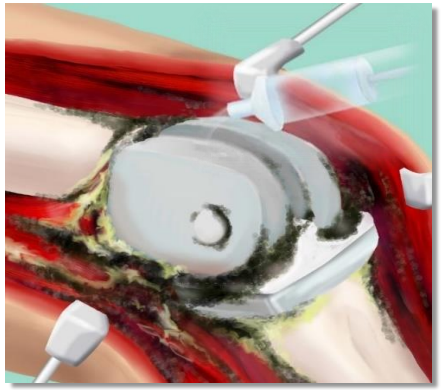
Dual mode of action – surfactant & microbicide

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









Surfactant properties

to cleanse tissues

+

Microbicidal activity

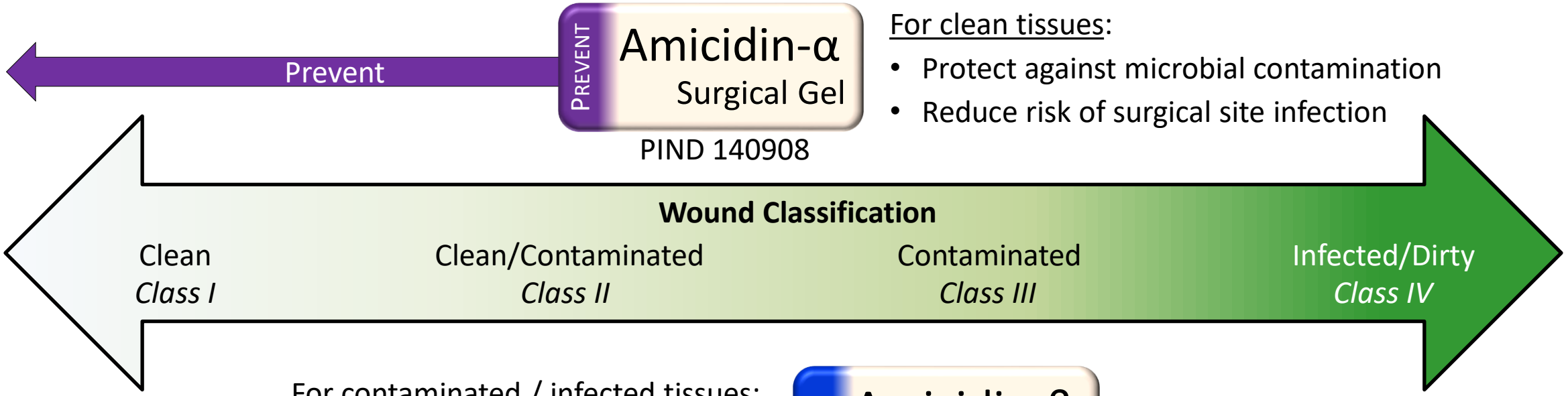
to kill microbes

=

Dual MOA
"Clean and kill"

…to cleanse, reduce microbial load, & provide infection source control.

Amicidin-α and Amicidin-β: New adjuncts for surgery & trauma



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 <u>exposed</u> 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

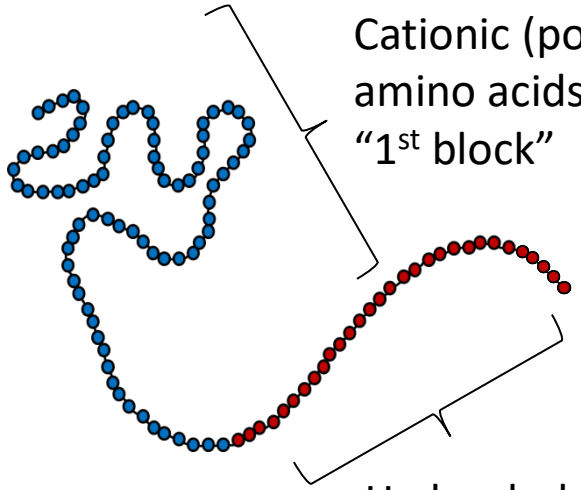
Amicidins are chemically synthesized long-chain amino acid polymers

Scalable and cost-effective

One-pot polymerization

1st Monomer
Initiator
Solvent
2nd Monomer

Amicidins

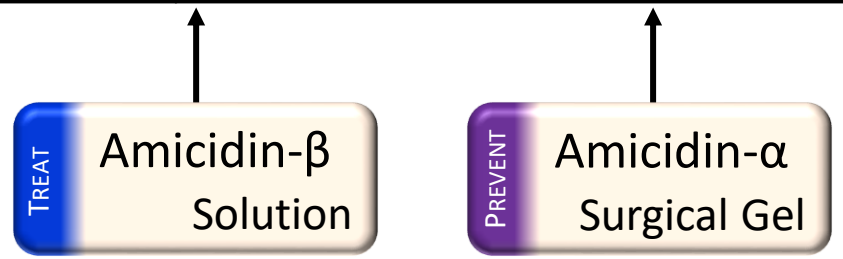


Cationic (positively-charged) amino acids
"1st block"

Hydrophobic (water-hating) amino acids
"2nd block"

Drug or biologic?

Peptide	Polypeptide or protein	Protein
1-40 amino acids	41-99 amino acids	100+ amino acids
Drug [505(b)]	It depends	Biologic [351(a)]



*"…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

FDA supports “non-traditional” products in infection

Amicrobe’s experience

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

AMICROBE

Keeping safe in the era of antibiotic resistance

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