

Lessons from Carraguard™

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Population Council

Microbicides 2002 - Antwerp, Belgium

Product Development

Laboratory Bench



Pharmaceutical

Pre-clinical file → IND ← Manufacturing



Clinical trials





FDA Microbicide Requirements

- Efficacy
 - in vitro and in vivo
- Stability
 - primary and production batches
- Pharmacology
 - absorption, distribution, metabolism and excretion
- Toxicology
 - irritation, teratology, mutagenicity, carcinogenicity, fertility and reproductive
- Microbiology
 - preservative and vaginal flora
- Chemistry
 - identification, validation, impurities, and monograph
- Manufacturing
 - primary, scale-up, and final market product, GMP for pharmaceuticals
- Controls
 - lot and batch consistency, in-process and final accept/reject

Pre-clinical Lessons

- Carrageenan
- Industry
- Placebo
- Safety
- Stability
- SOPs

Carrageenan

- History
 - Used for hundreds of years for medicinal and dietary purposes
- In 1972
 - FDA classified carrageenan as “GRAS” (generally recognized as safe)
 - WHO declared “no limit on daily intake”

Food Additive

- Emulsifier, thickener, and stabilizer
- Fiber and low-fat enhancer
 - dairy products: ice cream, chocolate milk, pudding, infant formula, and cheese
 - bakery products: cookies, pies and cakes, filling and frosting, and marshmallows
 - soup, salad dressing
 - whole-muscle and processed meats and poultry
 - dog and cat foods

Cosmetics and Toiletries

- Emulsifier, thickener and stabilizer
 - creams, lotions, beauty liquid, foundation, lipstick, eye liner and shadow, mascara, cheek blush
 - shampoo, hair cream and conditioner
 - toothpaste

Pharmaceutical Excipient

- Solid dose forms
- Water dispersible hydrocolloids
- Vehicle for pharmaceutical suspensions
 - pill coating
 - tablets binder, disintegrant, chewables
 - oral liquids and nasal sprays

FDA Carraguard™ Requirements

GRAS → API

(Active Pharmaceutical Ingredient)

- Efficacy
- Microbiology
- Pharmacology
- Toxicology
- Stability
- Chemistry
- Manufacturing
- Controls

Lesson Learned

- There are no exceptions to the rules when it comes to developing a pharmaceutical

FMC BioPolymer

- Long-time experience with carrageenans
- Experienced with pharmaceutical grade
- Extensive CONFIDENTIAL chemical, safety, and stability profiles on carrageenan

Developmental Strategy

- Identification of specific carrageenans for pharmaceutical activity
 - Development of API pre-clinical file
 - Seek FDA approval as API
- ↓
- New market for carrageenan
 - Open research for other pharmaceutical indications
 - New division within Corporation

Chemical Identity

- Establish analysis to distinguish between different carrageenans
 - Analysis of impurities
 - Molecular weight distribution
- ↓
- Development of official monographs
(USP, EP, and JP)

Lesson Learned

- A large pharmaceutical company might not be the only industrial entity for a productive collaboration

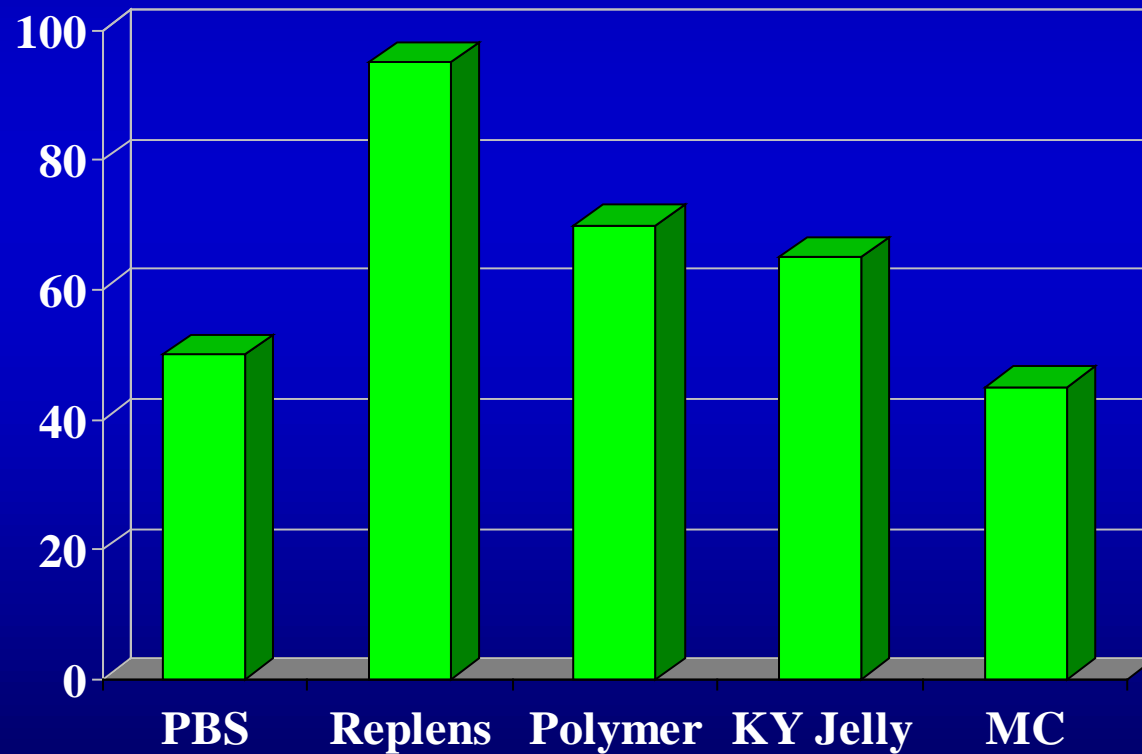
Placebo

- In 1785
 - “a commonplace method or medicine”
- Two editions later
 - “make-believe medicine,” allegedly inert and harmless

The MERCK Manual, Sixteenth Edition

Placebo (In)activity (?)

HSV-2 / Mouse System



Lesson Learned

“We now know that placebos may have profound effects, both good and bad.”

» The MERCK Manual, Sixteenth Edition

- What you think is a placebo might be an active formulation.

Safety, Safety, and Safety

- Microbiology
 - preservative effectiveness and vaginal flora
- Toxicology
 - irritation, teratology, mutagenicity, carcinogenicity, fertility and reproductive
- Pharmacology
 - absorption, distribution, metabolism and excretion
 - condom integrity

Lesson Learned

- Any adverse effects even the most minor are unacceptable to the FDA

Stability

- Challenge with aqueous solutions
- Prescription drug
 - 2 to 3 years, sensitive to extreme conditions
- Over-the-counter (OTC) drug
 - 5 years, resistant to extreme conditions
- Impact on product pricing

Lesson Learned

- For an OTC microbicide long-term stability under extreme conditions of an aqueous formulation is essential

The World of SOPs

Essential for maintaining the safety and effectiveness of a pharmaceutical, and FDA required!!!

- Legitimize laboratory testing (32)
- Validation of analytical instrumentation (16)
- Controls production process (68)
- Decreases time-to-start-up and time-to-market

Lesson Learned

- It saves a lot of time and money if SOPs are written, followed, and kept current from the beginning

Manufacturing Lessons

Applicator Needs

Phase I study	500
Phase II study	150,000
Phase III study	2,000,000

Clean Chemical Sweden AB



Clean Chemical Sweden AB

- Advantages
 - produces small and large production runs
 - not reliant on Carraguard™ project
 - extremely interested in project
 - EU approved pharmaceutical producer
 - allow direct interaction with production personnel

Clean Chemical Sweden AB

- Disadvantage
 - located in the north of Sweden where it's cold and dark

Production Scale-up

Laboratory scale	1 liter
Phase I study	15 liters
Phase II study	1,500 liters
Phase III study	20,000 liters

Production Scale-up

Difficult under the most optimal conditions

- Disadvantages
 - new production technology
 - two different production processes
 - disrupts routine production operation
- Advantages
 - straightforward production (no synthesis)
 - establishes FDA compliance

Lesson Learned

Validation of Murphy's Law

Lesson Learned Summary

Lesson #1 – There are no exceptions to the FDA rules

Lesson #2 – “Large Pharma” might not rule

Lesson #3 – placebos have no rules

Lesson #4 – Safety, stability and SOPs are all rules

Lesson #5 – Murphy’s Law rules!

