



# **Doxycycline MedKit Regulatory Background**

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# Outline

- Doxycycline History
- Doxycycline MedKit
- Regulatory Issues
- Formulations
- Today's Agenda
- Committee Questions

# Doxycycline History

- Tetracycline-Class Antibacterial Drug
- First Approved in 1967 for a Variety of Infections
- Largely Replaced Use of Older Tetracyclines (Once or Twice Daily vs. Four Times Daily)
- FR Notice for Doxycycline and Penicillin G Procaine\*
  - Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*

\* 66 FR 55679 November 2, 2001

# Doxycycline MedKit

- Development Program Proposed by BARDA
  - 10-Day Supply of Doxycycline for Home Storage
  - For Sale by Prescription
  - Still in Early Development Stage
  - Private Manufacturer for Production/Distribution
- Pilot Study Conducted in St. Louis
  - CDC - IND Sponsor
- Emergency Use Authorization (EUA) in Postal Workers
  - Minnesota Department of Health

# Level of Evidence

- Standard Approval
  - Substantial Evidence of Safety and Effectiveness
  - Postmarketing Safety/Requirements
- EUA
  - Reasonable to Believe that the Product may be Effective in Treatment of Serious or Life-Threatening Condition
  - Known and Potential Benefits Outweigh Known and Potential Risks
  - No Adequate, Approved, and Available Alternative
  - Emergency Scenarios (Including Widespread Exposure)
  - Conditions of Use

# Previous FDA Advice

## Home MedKit Labeling and Packaging

- Information (Potentially from CDC Study)
  - Keep MedKit Intact and Unused
  - Location within the Household
  - Attitudes/Beliefs about the MedKit
- Labeling Comprehension
  - Refined Version
- Actual Use
- Public Service Announcements

# Previous FDA Advice

## Home Preparation ("Crushing") Instructions

- Consumer Friendly (Clear, Straightforward, Understood)
- Palatability of Mixtures with Food Substances
- Performance -- Studies to Evaluate:
  - (1) Laboratory Personnel
  - (2) Volunteers from the General Population
  - Adherence to Instructions, Dose Uniformity, Dose Recovery, and Stability
  - Studies would be used to determine whether revisions to the procedures and/or instructions are required.
- Bioequivalence/Bioavailability of the Doxycycline Preparations Using the Proposed Food Substances

# Formulations

- Doxycycline MedKit Contains 100 mg Tablets
- Multiple Oral Formulations of Doxycycline
  - Tablets, Capsules (50 mg, 75 mg, 100 mg)
  - Other Delayed Release and Extended Release Products
  - Doxycycline Calcium Syrup Oral Suspension (50 mg/5mL)
  - Doxycycline Monohydrate (Powder) for Suspension (25 mg/5mL)
- Considerations
  - Shelf-life and Storage
  - Palatability
  - Effective Dosing
- Alternatives?



# Today's Agenda

- FDA – Overview of Consumer Studies
- CDC and Minnesota Dept of Health
- Department of Homeland Security
- BARDA
- Perspectives from Invited Speakers
- Open Public Hearing

# Committee Questions

- Please comment on the public health implications of a prescription doxycycline MedKit intended for post-exposure prophylaxis for an anthrax counterterrorism event. Specifically address potential benefits and risks if a prescription MedKit were approved with the intention of home storage.

# Committee Questions

- Please comment on additions or modifications to the proposed and/or completed studies (e.g. label comprehension, palatability, simulated use, or additional studies) that would help assess the risks and benefits. What types of additional studies would be helpful to assess how users would behave in a real-life situation?
- What is a reasonable percentage of study subjects who should understand various components of the label and/or be able to refrain from using the product for other uses?

# Committee Questions

- The doxycycline MedKit proposal includes instructions for dosing children and adults who cannot swallow pills using the 100 mg tablets. Are the completed/proposed studies sufficient or are there any additional recommended studies to evaluate the dosing instructions in this population?
- Doxycycline is available in other dosages and as liquid formulations. Please discuss the pros and cons of the home preparation mixture versus other available formulations for use in a MedKit.

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# Consumer Studies Potentially Applicable to the Medkit Development Program

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# Objectives

- Provide an overview of four different types of consumer studies.
- Context for discussions on Medkit.

# Why Do We Need Consumer Studies?

- To make sure that a nonprescription drug can be used safely and appropriately by consumers without the involvement of an intermediary healthcare provider



# Nonprescription products as a focus of consumer research:

- Rx to OTC (over the counter) Switches.
- New OTC indications for an existing product.
- New OTC target market for an existing product.
- New ways of dosing an existing product.
- New products launched directly to OTC market.

# The Medkit Scenario

- Physician would prescribe for family members at their request— the empowered consumer.
- Product would be used in an emergency situation, where there may not be other extensive real time sources of information.
- Do they understand how/when to use the product?

# Key Research Questions:

- Can consumers accurately self-diagnose?
- Can consumers appropriately self-select?
- Can consumers correctly self-medicate in a home use setting?

# Consumer Studies

- Label Comprehension
- Human Factors
- Self-Selection
- Actual Use



# Label Comprehension Studies

# 21 CFR 330.10 (a)(4)(v)

- OTC labels must:

“ . . . be likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.”

# Label Comprehension Studies

- Ideally the first consumer study in a nonprescription drug development program
- Determines if a label – including consumer package inserts - communicates important information about drug to consumers



## ***Drug Facts***

***Active ingredient(s)***

***Purpose***

***Use(s)***

***Warnings***

Do not use

Ask a doctor before use if you have

Ask a doctor or pharmacist before use if you are

When using this product

Stop use and ask a doctor if

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

***Directions***

***Other information***

***Inactive ingredients***

***Questions or comments?***



# Label Comprehension Studies

- Endpoints are based on the key communication elements on the label that need to be understood.
- Both the endpoints and the predetermined thresholds of success are grounded in clinical rationale.

# Label Comprehension Studies

- Test comprehension...not behavior!

# Label Comprehension Studies

- Target population:
  - Generally representative sample of U.S. population – all comers.

# Label Comprehension Studies

- Questionnaire
  - Primary data collection tool
  - Scripted interviews
  - Types of questions:
    - Open-ended
    - Closed-ended
    - Scenario

# Label Comprehension Studies

- Scenario based question:
  - hypothetical medical situation
  - tests ability of the respondent to apply information from the label

# Label Comprehension Studies

- Example scenario question:
  - Janet is a 38-year-old with diabetes who has a headache (scenario)
    - Is it ok or not ok for her to take medication X? (closed-ended question)
    - Why do you say that? (open-ended probing question)

# Label Comprehension Studies

- Questions/Issues
  - Will consumers understand key aspects of the label related to indication, dosing, length of therapy and warnings?
  - Will consumers understand that this is just a starter dose and that they need to visit a public dispensing center to obtain the full course of therapy?

# Human Factors Studies

- Can be part of label comprehension or a separate study.
- Typically conducted when a product brings a new way of dosing administration to the OTC arena.
- Testing assesses whether consumers can follow directions in preparing the product for use.
- Active ingredient is not administered.



# Human Factor Studies

- Questions/Issues
  - Will consumers be able to demonstrate that they understand the instructions for preparing the mix for children and those who cannot swallow pills?



# Self-Selection Studies

# Self-Selection Studies

- Objective: to determine if consumers appropriately self-select or not select to use an OTC product.
- Assess the ability of consumers to apply drug labeling information to their own personal health situation.

# Self-Selection Studies

- Examples of when they may be required:
  - New OTC target population
  - Contraindicated for a select population (e.g., women of childbearing age) – to be certain that they won't use the product.

# Self-Selection Studies

- Target population
  - Generally representative sample of U.S. population
    - Potential product users and nonusers and/or:
  - Populations of interest only
    - Population who should not select to use the medication

# Self-Selection Studies

- Testing procedure:
  - Participant reads the label
  - A typical self-selection question might be:
    - “Is this product o.k. for you to use?”
    - “Why did you say that?”
  - Demographic information and medical history is collected

# Self-Selection Studies

- Correct self-selection is usually based on self-reported information.
- Success threshold based on clinical rationale determined a priori.

# Self Selection Studies

- Potential research questions:
  - Will consumers want to open the Medkit if they suspect a tick bite?
  - Will consumers want to use the Medkit if there is an anthrax attack in another part of the world?
  - Will consumers want to use the Medkit in the event of an unrelated attack?





# Actual Use Studies

# Actual Use Studies

- Simulate use of product in a “real-world” setting.
- Objectives:
  - Primary:
    - Adherence to labeled directions and warnings
  - Secondary:
    - Provide safety data for the product in an unsupervised setting

# Actual Use Studies

- Examples of when are they required:
  - New or complicated dosing regimen
  - New method of use for an OTC drug
  - New OTC medical follow-up requirements/recommendations

# Actual Use Studies

- Sample:
  - Ideally all consumers who may have an interest in the product
  - Populations of interest only (e.g., adolescents)

# Actual Use Studies

- Study length
  - Varies depending upon the labeled duration of use
- Success thresholds determined a priori
  - Based on clinical rationale

# Actual Use Studies

- Consumers go to drugstore to pick up product.
- Record actual use in either electronic or paper diary, along with symptoms.
- Consumers return diary and unused product at end of study.

# Actual Use Studies

- Questions/Issues
  - Measurement of *non actual use* (i.e., whether consumers leave the Medkit intact if there is no anthrax event)
  - Actual Use - Do they use it for potential Lyme disease or to self-medicate for presumed bacterial infections?
  - “Actual Use” – can they locate the kit and do they have all necessary ingredients on hand in a simulated emergency?

# Consumer Studies

- Label Comprehension
- Human Factors
- Self-Selection
- Actual Use