Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 4, 2009

Bioequivalence Recommendations for Oral Vancomycin Hydrochloride Products

Introduction

Colin Broom MD MRCP
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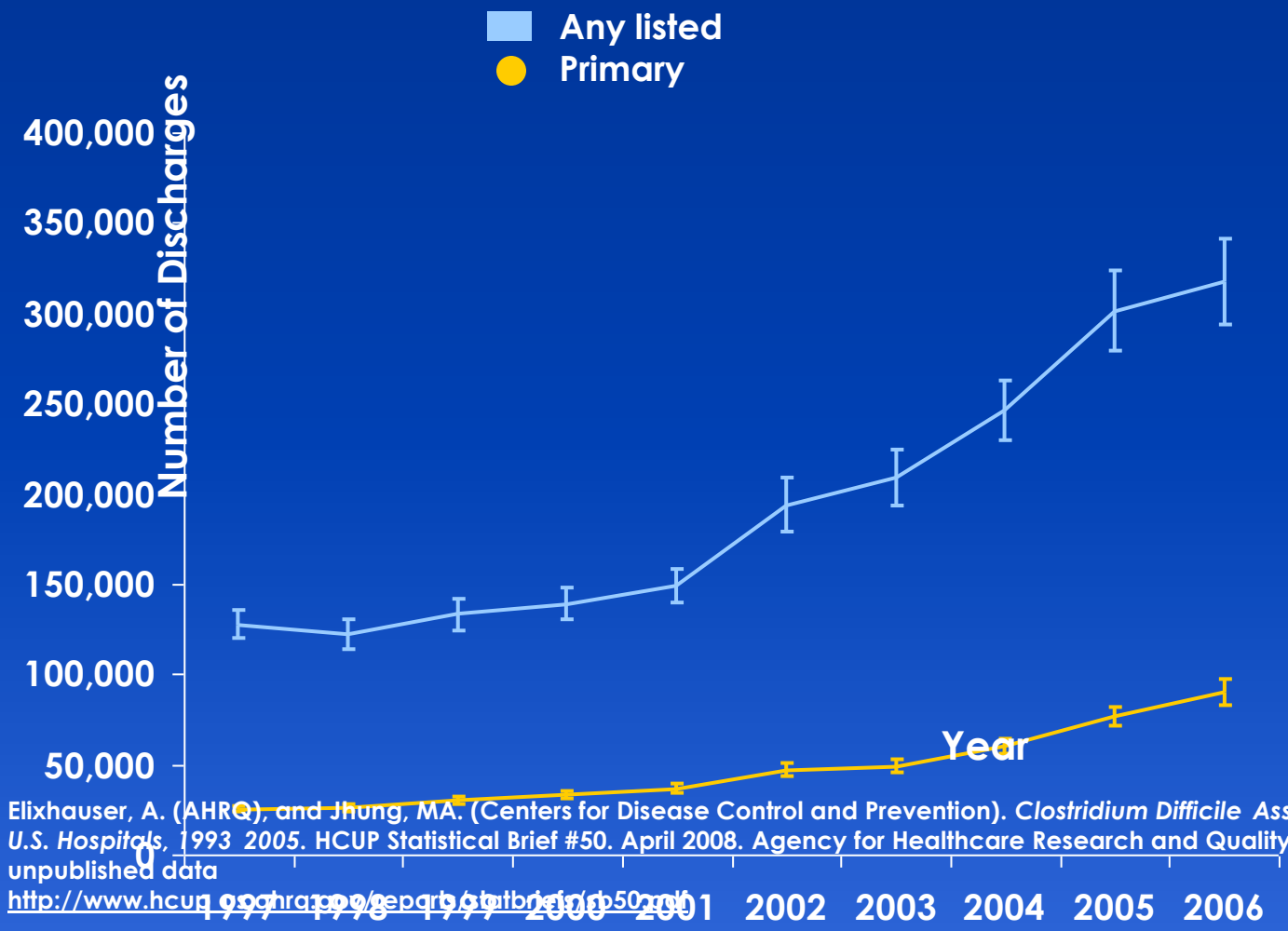
Oral Vancomycin Treatment of: *Clostridium difficile* Infection (CDI) *Staphylococcus aureus* Enterocolitis (SAE)

- CDI
  - Primarily colon but can involve small bowel
  - Usually presents as diarrhea, abdominal pain, fever
  - Can progress rapidly to toxic megacolon, sepsis and death
  - Oral vancomycin used for severe disease
- SAE
  - Affects small bowel and colon, symptoms mimic CDI
  - Less common than CDI
- Most patients >65 years

National Estimates of US Short-Stay Hospital Discharges with *C. difficile* as First-Listed or Any Diagnosis, National Inpatient Sample



Elixhauser, A. (AHRQ), and Jhung, MA. (Centers for Disease Control and Prevention). *Clostridium Difficile Associated Disease in U.S. Hospitals, 1993 2005*. HCUP Statistical Brief #50. April 2008. Agency for Healthcare Research and Quality, Rockville, MD. And unpublished data

http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf

Vancocin BE Regulatory Overview

- 1986 Approval
  - Safety and efficacy assumed based on healthy subject PK data
- 1996 BE Standard was clinical endpoint study
- 2006 BE Letters: Rapidly dissolving BCS class 1
- 2008 BE Guidance
  - Assumed in solution "hours before" reaching site of action
  - Q1Q2 "identical"

Three Key Points

- The proposed in vitro test does not consider the relevant in vivo environment
- Q1Q2 is inadequate given formulation and critical manufacturing process controls
- Precedent setting approach – patient risk must be considered

Proposed Guidance is a Precedent Setting Paradigm Shift

- Clinical endpoint BE studies required
  - Topicals
    - Intranasal steroids; antifungal agents
  - Locally-acting GI drugs
    - Sucralfate; mesalamine products
- No biowaiver ever granted to locally-acting GI agent
  - Cholestyramine and acarbose do not treat GI disease

Speakers

Introduction	Colin Broom MD MRCP ViroPharma Incorporated
In Vivo GI Conditions in Patients	Ciarán Kelly MD Harvard Medical School
Biopharmaceutical Limitations	Patrick K. Noonan PhD Virginia Commonwealth University; PK Noonan and Associates, LLC
Risk Analysis and Conclusions	Ciarán Kelly MD Harvard Medical School

In Vivo GI Conditions in CDI and SAE

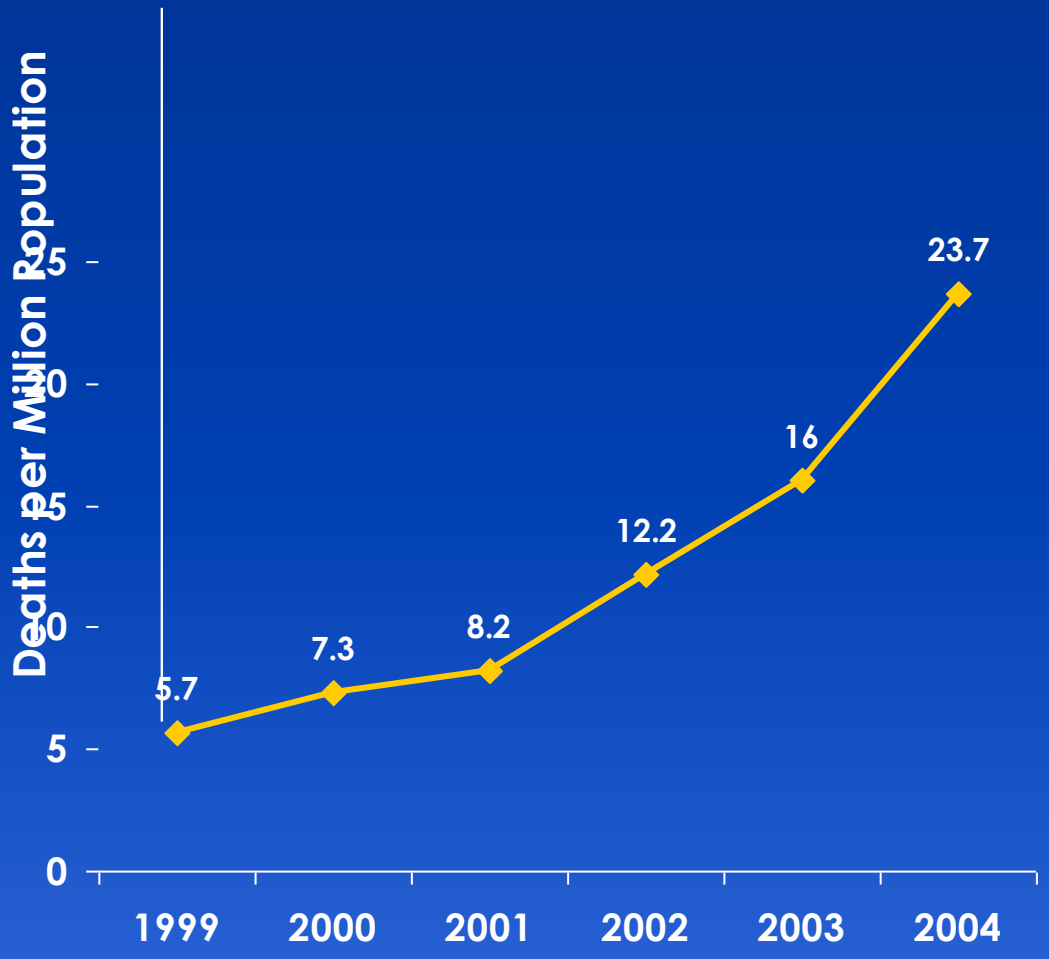
Ciarán Kelly MD
Professor of Medicine Harvard Medical School
Beth Israel Deaconess Medical Center
Boston

Typical *C difficile* Patient

- Mean age = 67 years
- Acutely ill
- Multiple comorbidities
  - Mean Charleston Score = 3.3
- Multiple medications
  - Acid antisecretory drugs in 75%
- CDI-related in-hospital mortality = 12%
  - CDI as primary cause = 4%
  - CDI as contributing cause = 8%

Cloud J. et al; *Clinical Gastroenterology and Hepatology*, 2009

Increasing CDI-Related Mortality based on Listings on U.S. Death Certificates

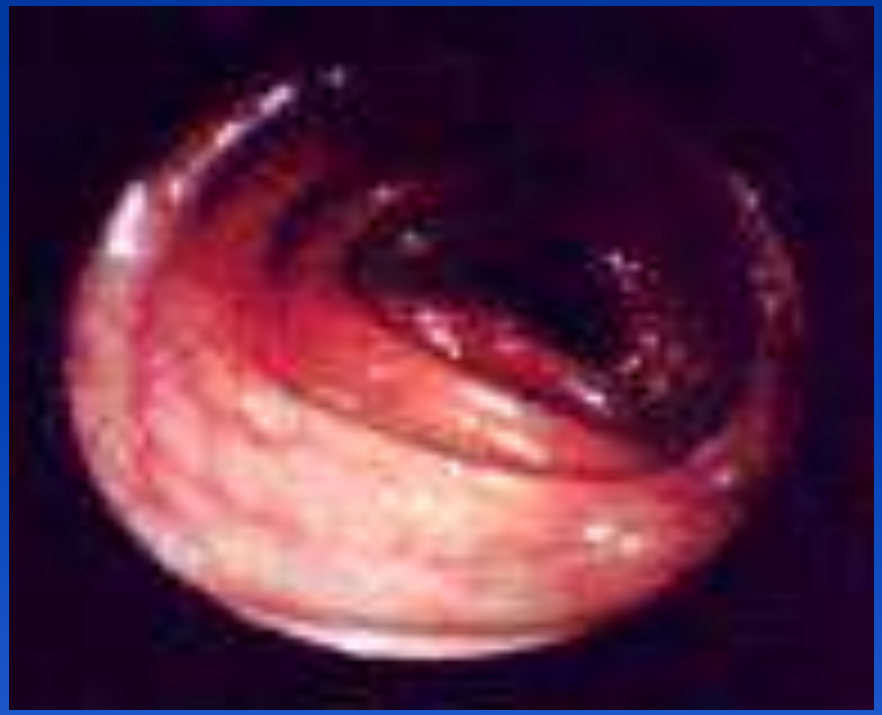


Age Adjusted Mortality Rate (%)	
Age 55-64	6.0%
Age 65-74	16.0
Age 75-84	38.0
Age ≥85	37.1

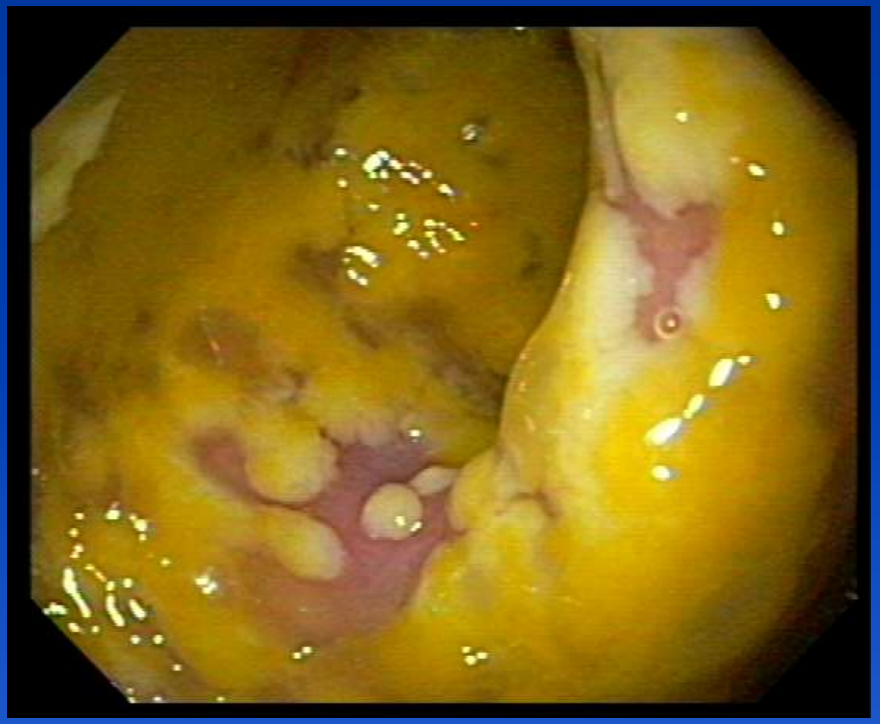
Redelings MD, et al. Emerg Infect Dis 2007;13:1417–1419.

Clostridium difficile Infection (CDI)

Normal Colon



Colon in CDI Covered by Pseudomembranes

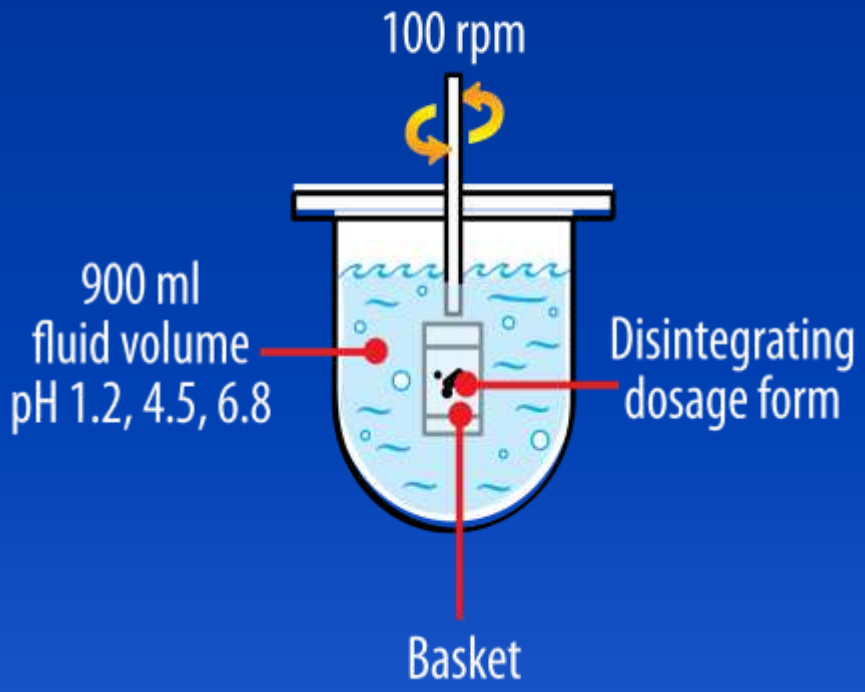


ENTIRE GI TRACT Abnormal in CDI Patients

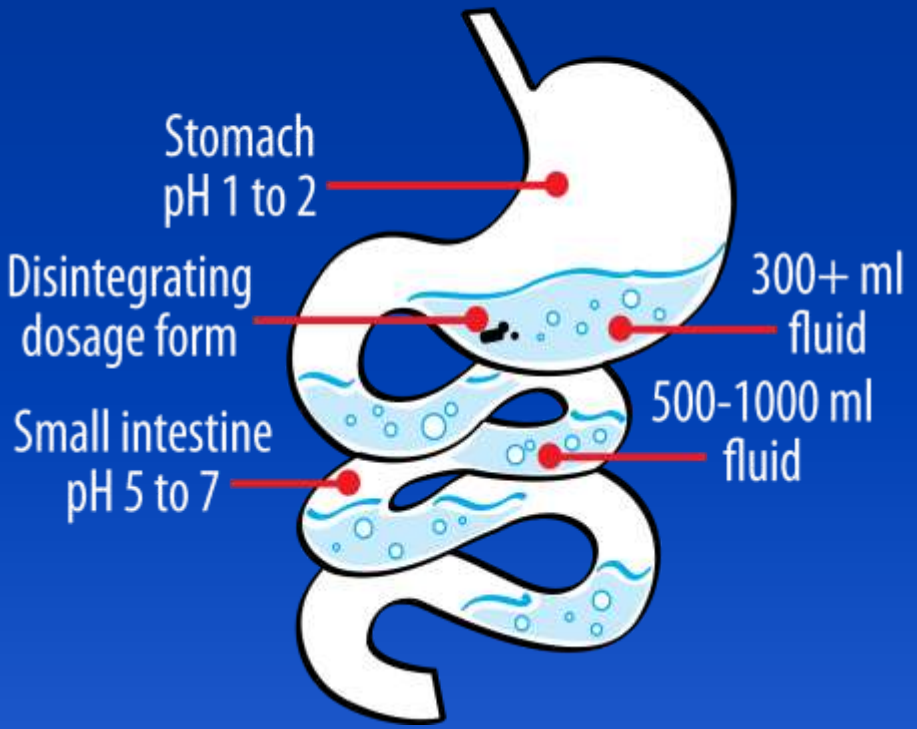
- Stomach
  - Aging factors, high pH, PPIs, low volume
- Small intestine
  - Low volume
  - Variably motility
  - Site of disease in SAE and some patients with CDI
- Colon
  - Primary site of CDI
  - Inflammatory mediators abnormal fluid constituents

GI Tract of Healthy Subjects

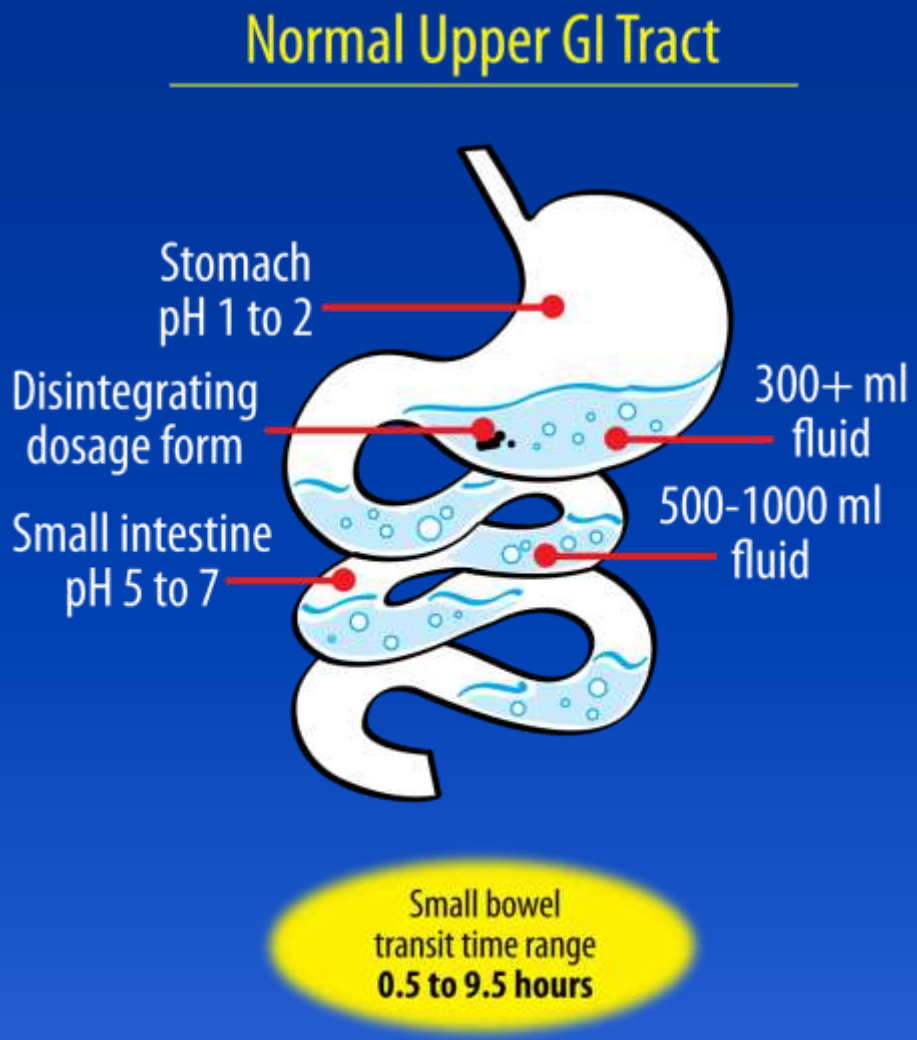
Dissolution Apparatus 1

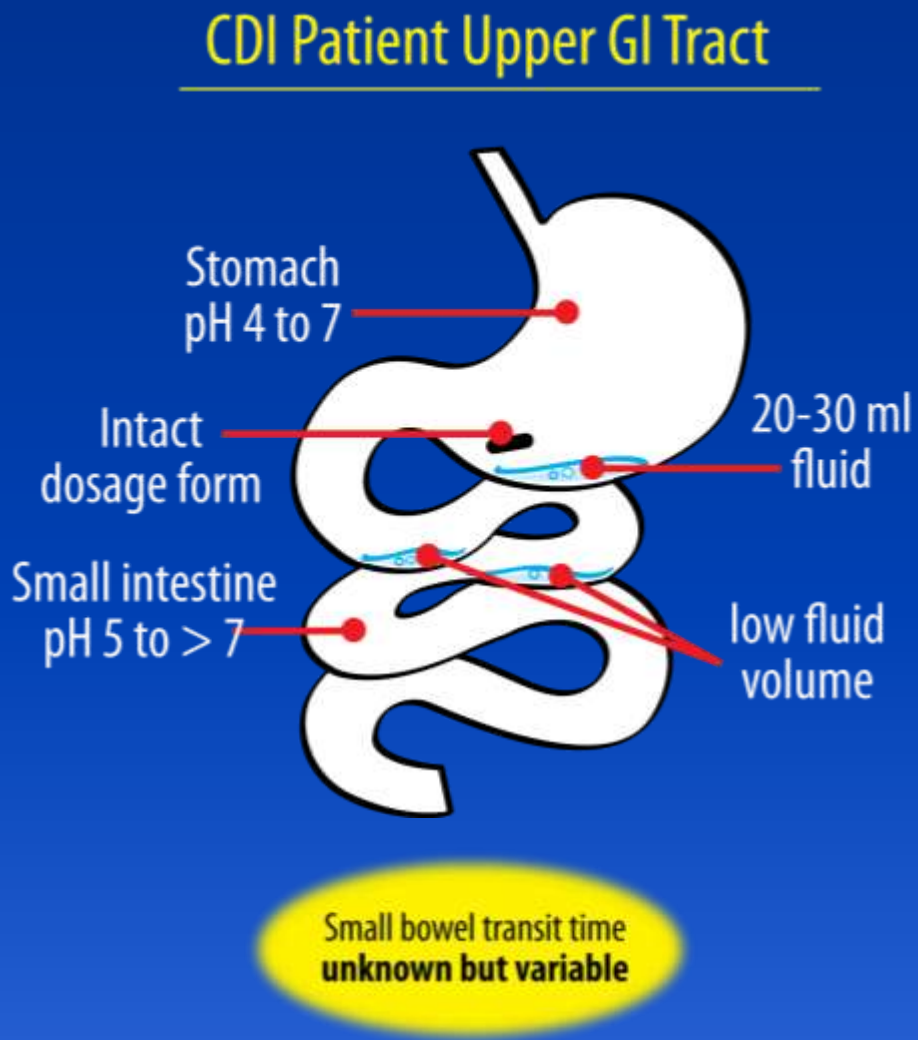


Normal Upper GI Tract



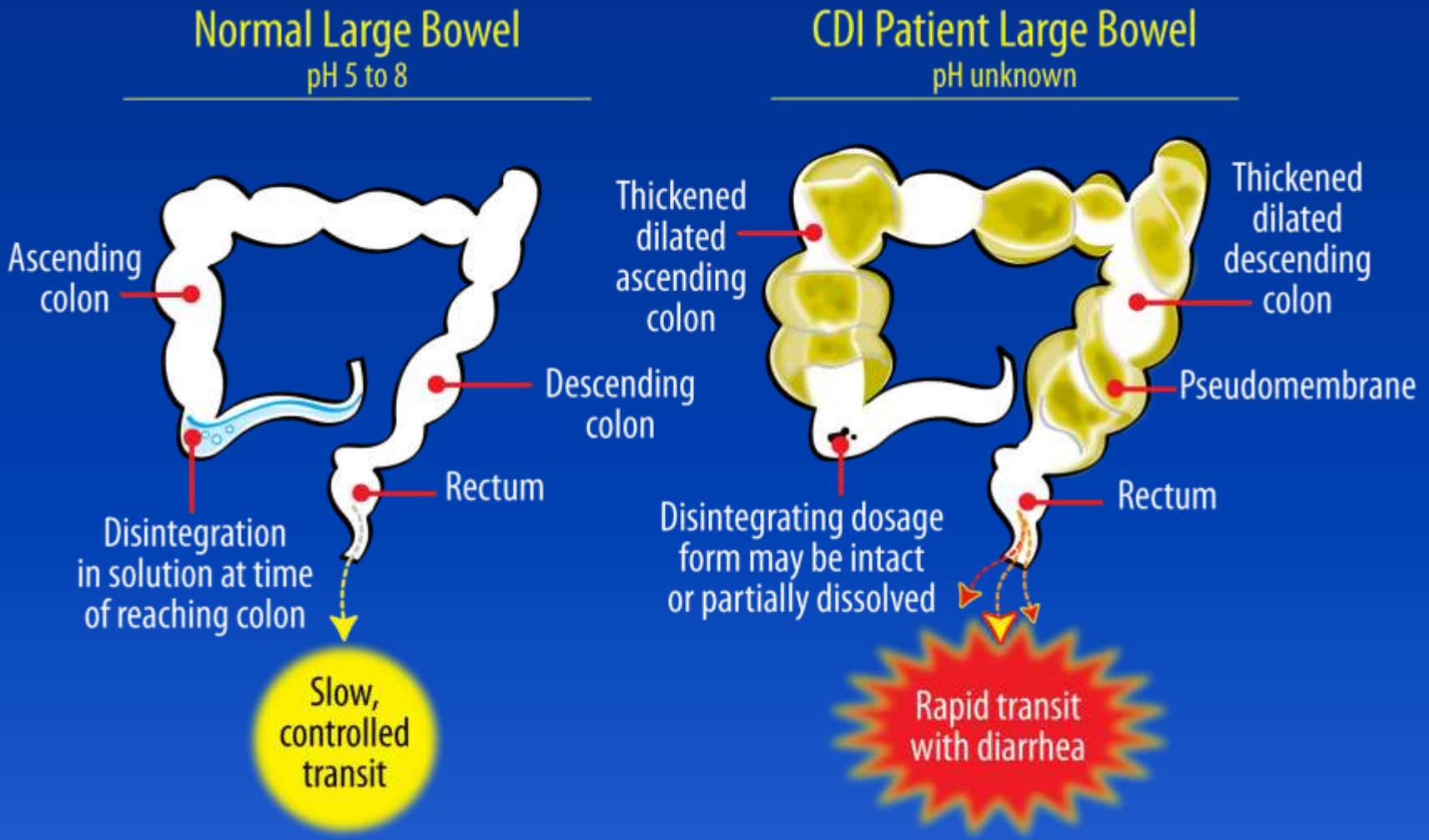
GI Tract of Healthy v CDI Patients



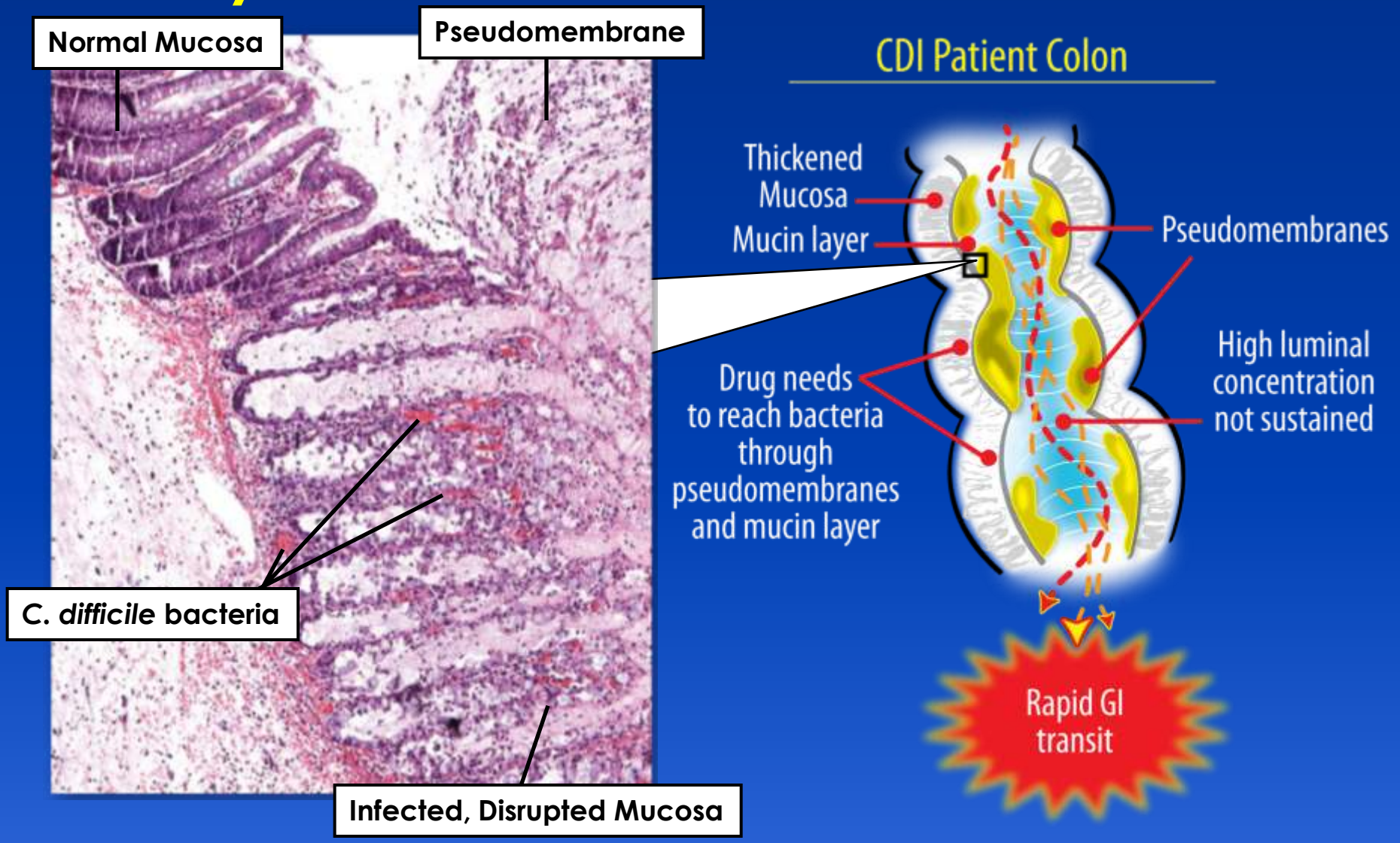


Davis 1986, (27) 886

Lower GI Tract of CDI Patients



Site of Action in Diseased Mucosa is Poorly Accessible



Courtesy of Jeannette Guarner, MD, CDC

Clinical Conclusions

- Proposed dissolution test does not simulate the GI tract of CDI patients
  - Test may not be discriminatory or predictive of the rate and extent of drug delivery to the site of action
- Severely ill patients may be put at risk
  - Diminished efficacy could be fatal

Biopharmaceutical Limitations of the Proposed Guidance

Patrick K. Noonan PhD
Affiliate Professor of Biopharmaceutics
Virginia Commonwealth University
Principal, PK Noonan and Associates, LLC

Overview

- BCS biowaiver not applicable to vancomycin capsules
- Method does not predict in vivo performance
- Method must address Q3 differences in products

BCS Based Biowaiver

- Validated for systemic drugs
- Based on healthy GI parameters
- Excluded locally acting GI drugs

Biowaiver Requirements

- High in vivo solubility
- Rapid dissolution
- In vitro dissolution testing must cover the range of in vivo variables
- Same in vivo dissolution profile under all luminal conditions

Vancocin Does Not Meet Biowaiver Requirements

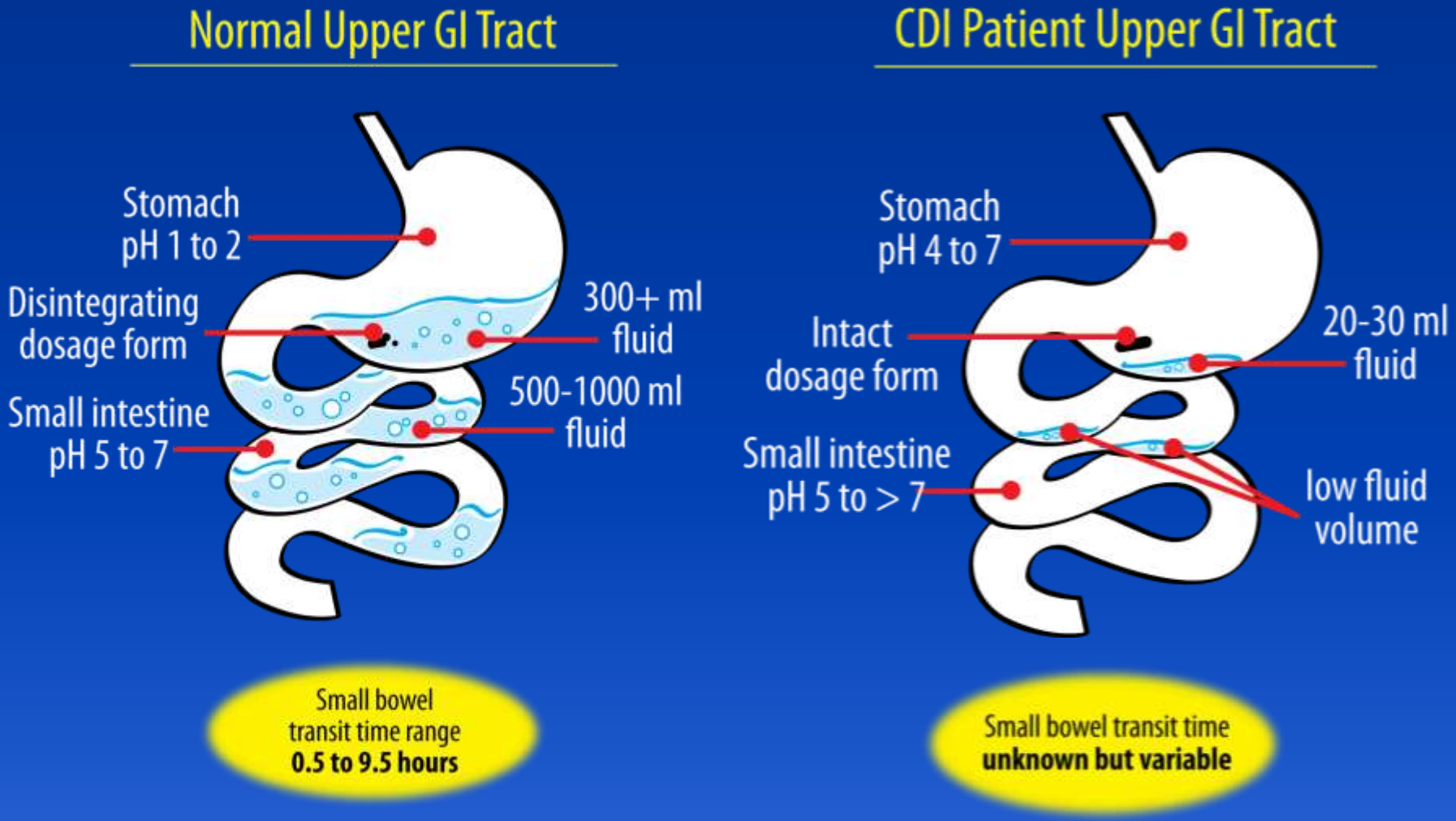
- Not rapidly dissolving
- In vivo solubility unknown
- In vitro dissolution not biorelevant

In vivo dissolution profile under all luminal conditions not established

Proposed Extrapolation of Biowaiver

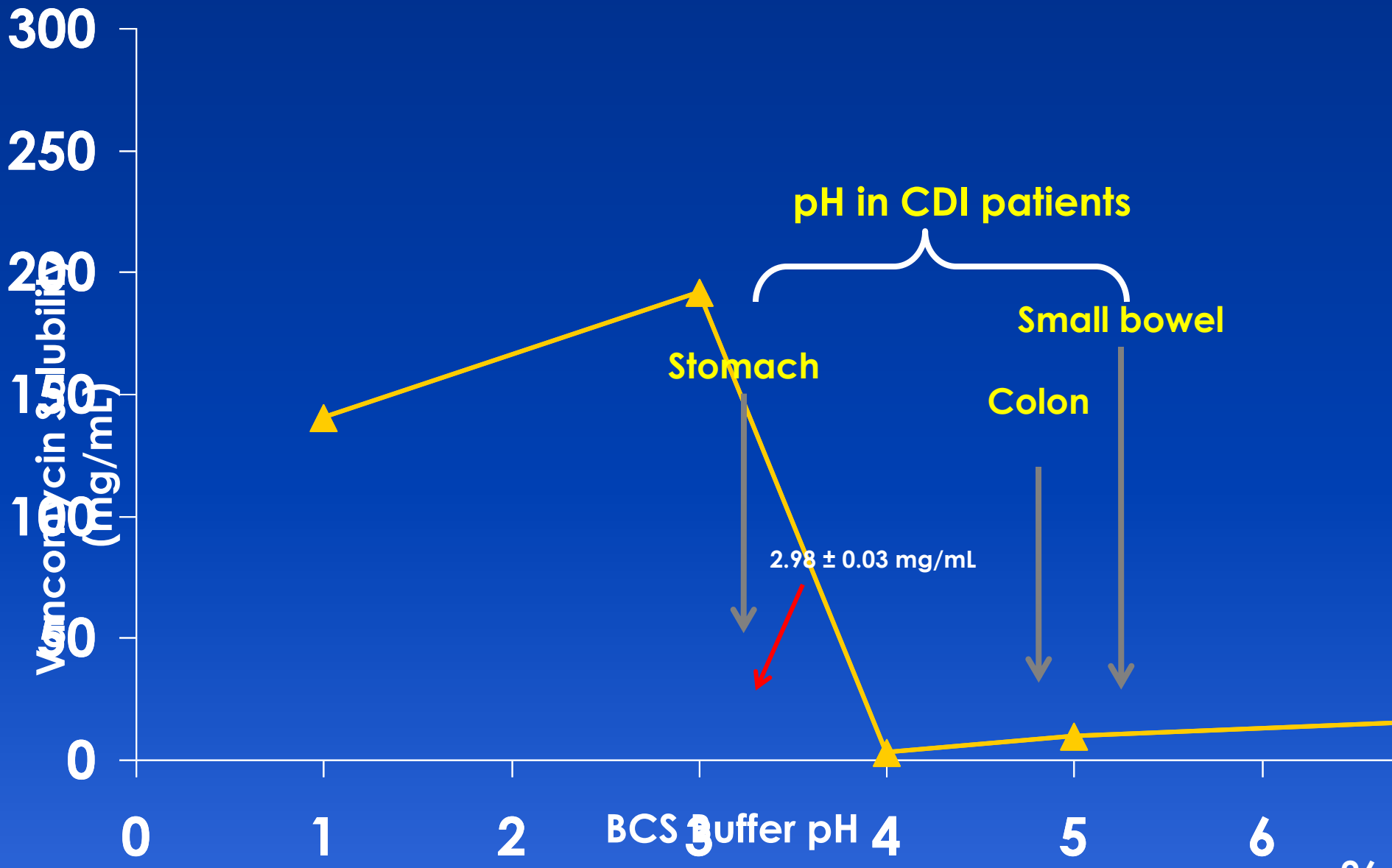
- To locally acting drug
- Severe GI disease
- Healthy gut model not applicable to diseased GI tract
- Available data do not support extrapolation

Solubility Under Relevant In vivo Conditions Not Assured

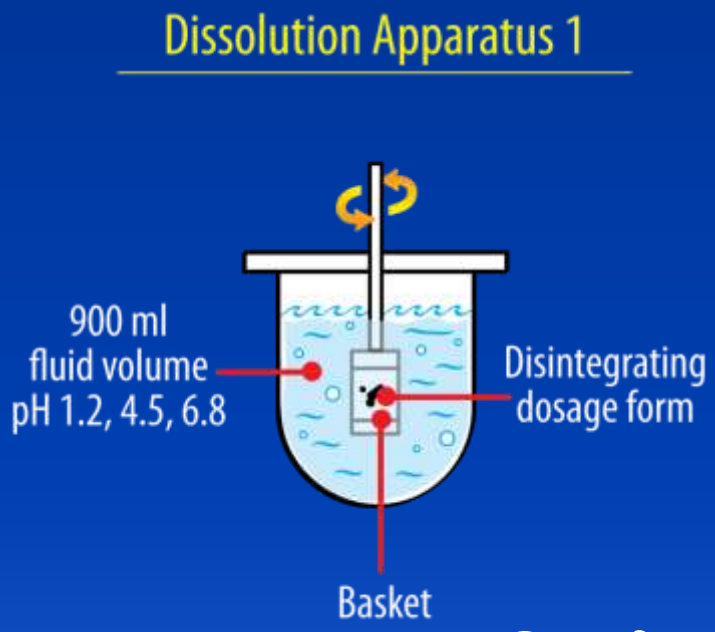


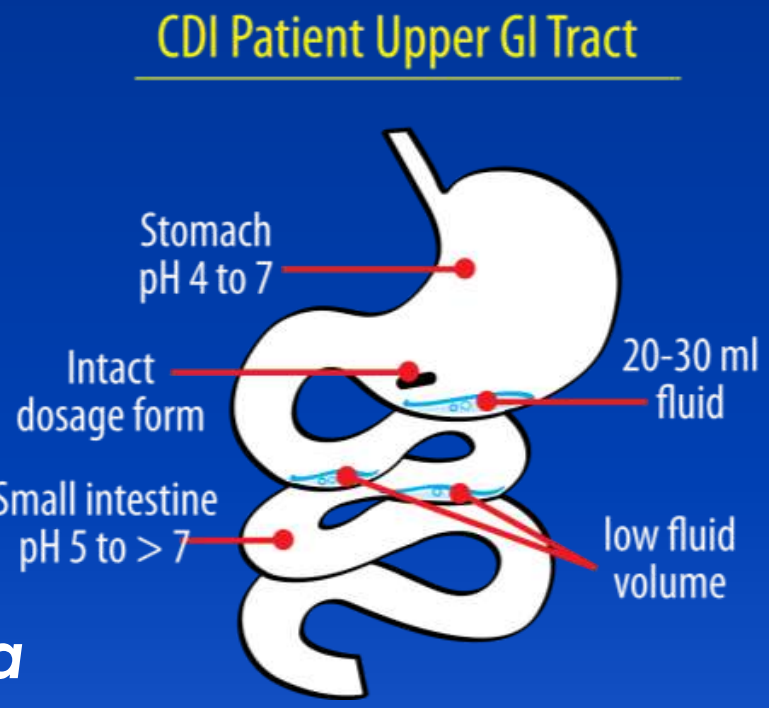
Davis SS et al. *Gut* 1986, (27) 886 892.

Vancomycin Solubility-pH Profile



Complete Dissolution at Site of Action Not Assured





Confounding Fa

- ***Lower volume***
- ***Lower solubility***
- ***Slower dissolution***
- ***Variable transit time***

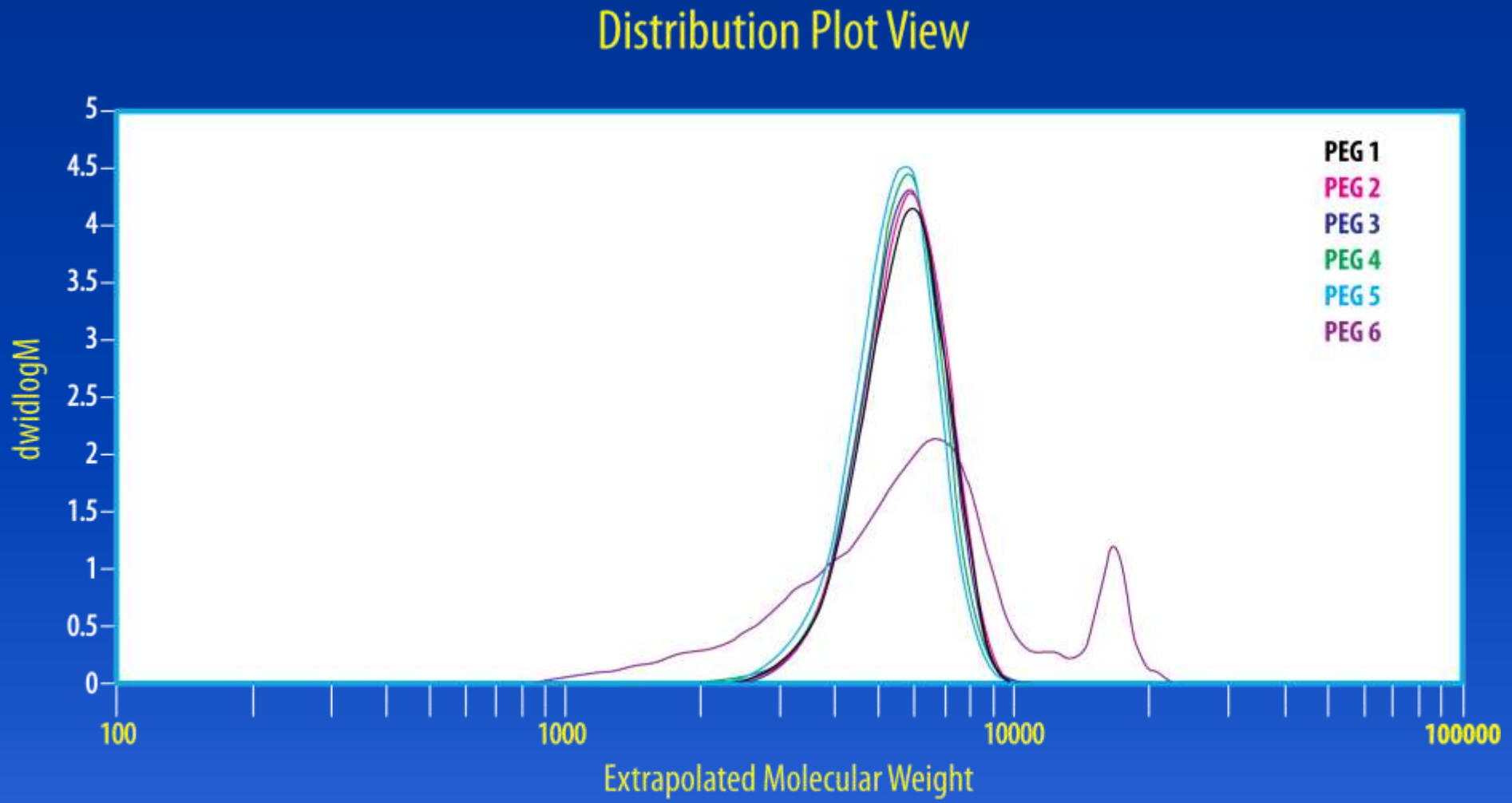
Criteria for Product Sameness

- Q1 = Same ingredients
- Q2 = Same quantities
- Q3 = Same components, concentrations, and microstructure

Select Elements of Vancomycin Q3

- Individual ingredient quality attributes
  - Testing beyond pharmacopial
  - Particle size
  - PEG molecular weight distribution
  - Morphic control
- Manufacturing process variables
  - Temperature, humidity, pressure
  - API milling speed
- PEG melt characteristics
  - Hot melt viscosity

Q1Q2 Sameness Cannot be Assumed to be Adequate: Not all PEG 6000 are the Same



Q3 Functional Linkage Not Established

Formulation type:
PEG Melt v. Other

Formulation:
Composition, grade of PEG, drug to excipients ratio, etc.

Process parameters:
Melting, Mixing, Temperature, Environmental Controls

Vancomycin and Excipients

Source, quality, purity,

Solubility, intrinsic dissolution rate, particle size, amorphous form, pKa

Relationship of Q1-Q2-Q3 to Dissolution Behavior Not Defined

Lack of information does not support Biowaiver

What potential difference between generic vancomycin capsules and Vancocin® HCl capsules is not accounted for in the FDA recommendation?

- Rate and extent of delivery of drug at the site of action
  - Failure to assure high in vivo solubility and rapid dissolution
- Q3 differences between products

Dissolution testing inadequate to establish product equivalence despite Q1Q2 sameness

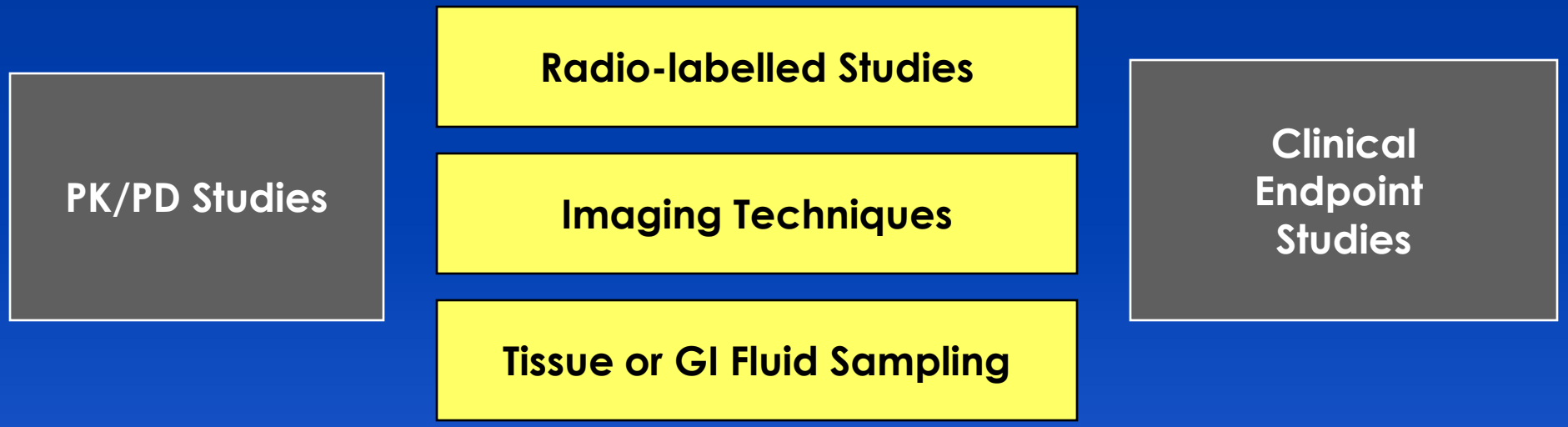
Risk Analysis and Conclusions

Ciarán Kelly MD
Professor of Medicine Harvard Medical School
Beth Israel Deaconess Medical Center
Boston

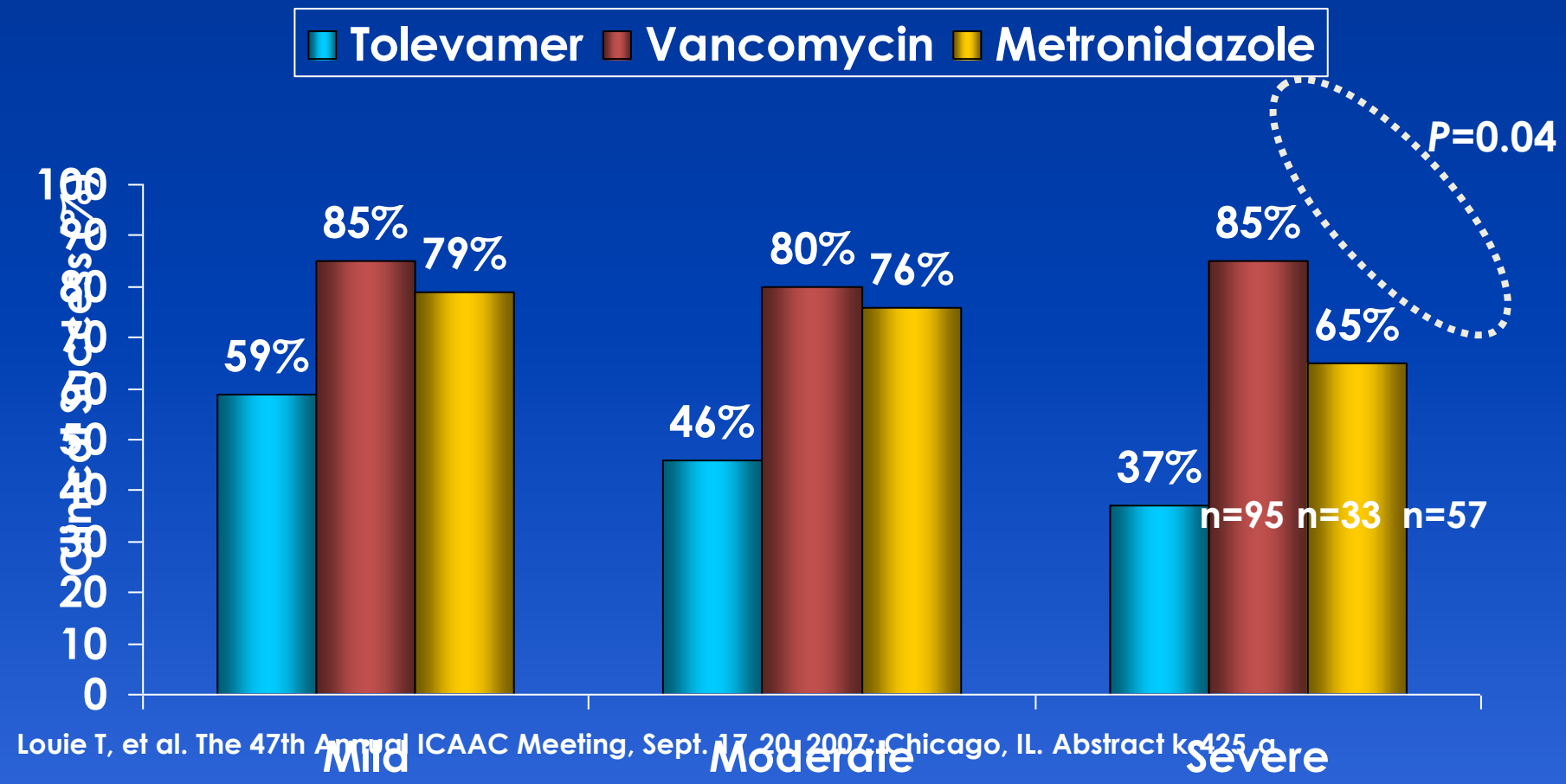
Risks of Proposed BE Method

- No consideration of patient risk
  - WHO recommends risk assessment when extending biowaiver beyond BCS 1
- No ability to discriminate treatment failures in clinical practice
- No opportunity to confirm method
- Potential increase in morbidity and mortality

Other Options to Validate In vitro BE for Vancocin Capsules



Tolevamer Study Data: Vancomycin Is More Effective Than Metronidazole in Treating Severe CDI



Louie T, et al. The 47th Annual ICAAC Meeting, Sept. 17-20, 2007; Chicago, IL. Abstract k-425.a

Conclusions

- Proposed method not relevant to diseased GI tract
- Proposed method does not account for Q3 differences
- Risk to fragile population not considered
- Extrapolation of biowaiver not supported by data

In vitro dissolution testing must be supported by additional in vivo data to establish bioequivalence for this drug