

# Vancocin® Bioequivalence (BE)

Appropriate Method Development

FDA Meeting  
January 7, 2008

# Vancocin

- Vancomycin Hydrochloride Capsules, USP
- Contains chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis*
- Large molecule not absorbed across healthy gut
  - $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$  MW 1486
- Available as 125 mg and 250 mg capsules

# Product Information

- Manufacturing specifications developed empirically and incorporate a number of proprietary trade secrets
- Indicated uses for Vancocin: “. . . for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*.”

# *C. difficile* Infection (CDI)

- *Clostridium difficile* is a spore-forming, gram-positive bacillus that produces exotoxins that are pathogenic to humans
- *C. difficile* infection (CDI) ranges in severity from mild diarrhea to fulminant colitis and death
- *C. difficile* exotoxins A and B cause colonic dysfunction and cell death

# *C. difficile* Infection (CDI)

- An emerging public health epidemic
  - These rates have tripled since 2000
- Nosocomial and community acquired
  - Increase in cases without previous known antibiotic exposure
- Reemerging hypervirulent strain associated with:
  - More severe disease
  - The epidemic strain produces 16 times more toxin A and 23 times more toxin B compared with other common strains
  - Rapid disease progression
  - Increased serious morbidity and mortality
- Vancocin is the only FDA approved drug to treat CDI
- New treatment guidelines by Infectious Diseases Society of America and Society for Healthcare Epidemiology of America
  - Vancocin as first line therapy in treating severe disease

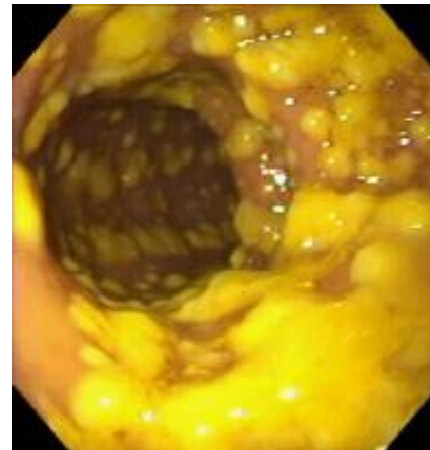
# *C. difficile* Infection (CDI)

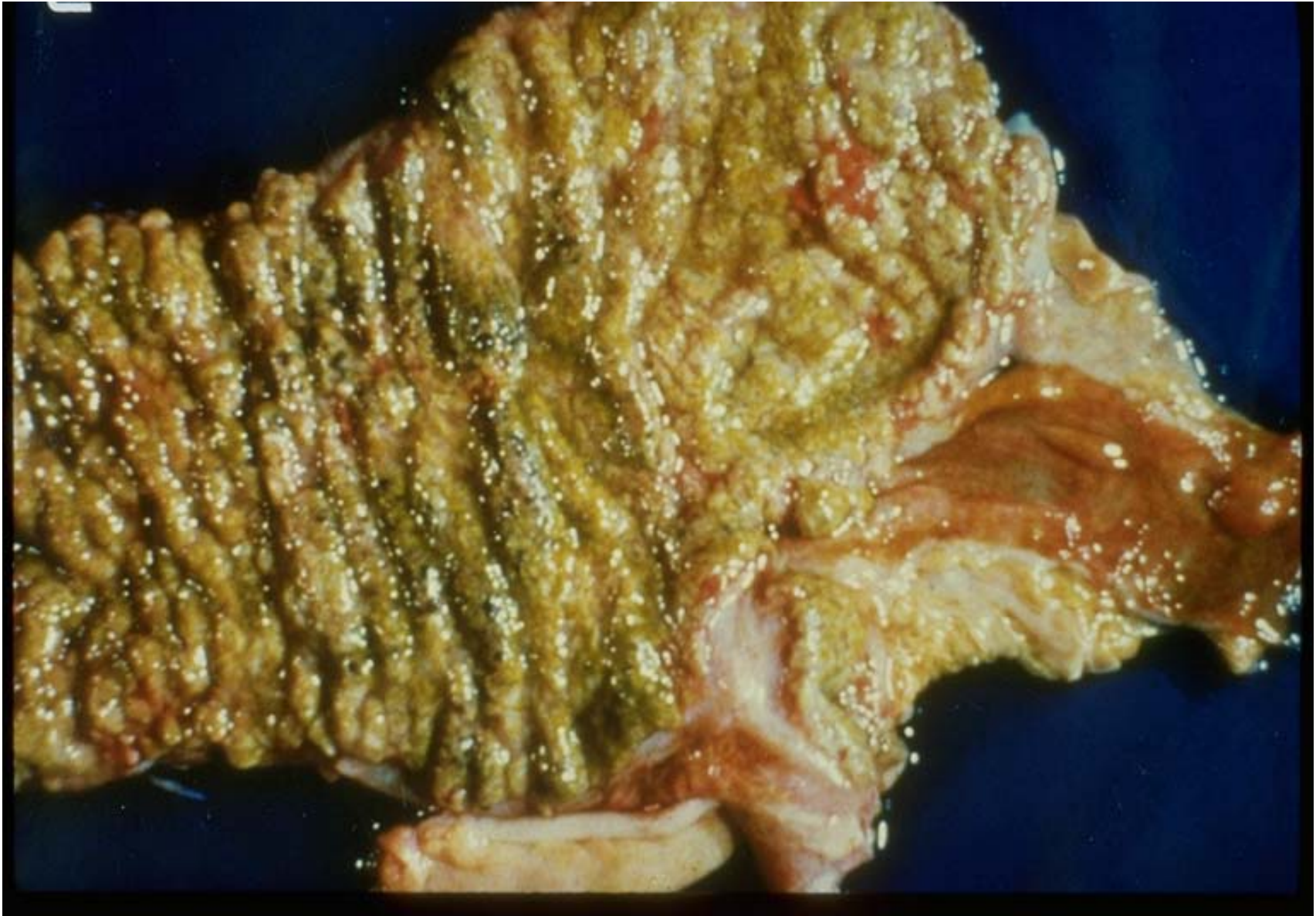
- GI tract of CDI patients is not 'normal' or well understood
- Wide range of motility
- Fluid volume, pH, composition not well understood or characterized
- Cellular changes in wall of the gut
- Significantly different from the healthy gut

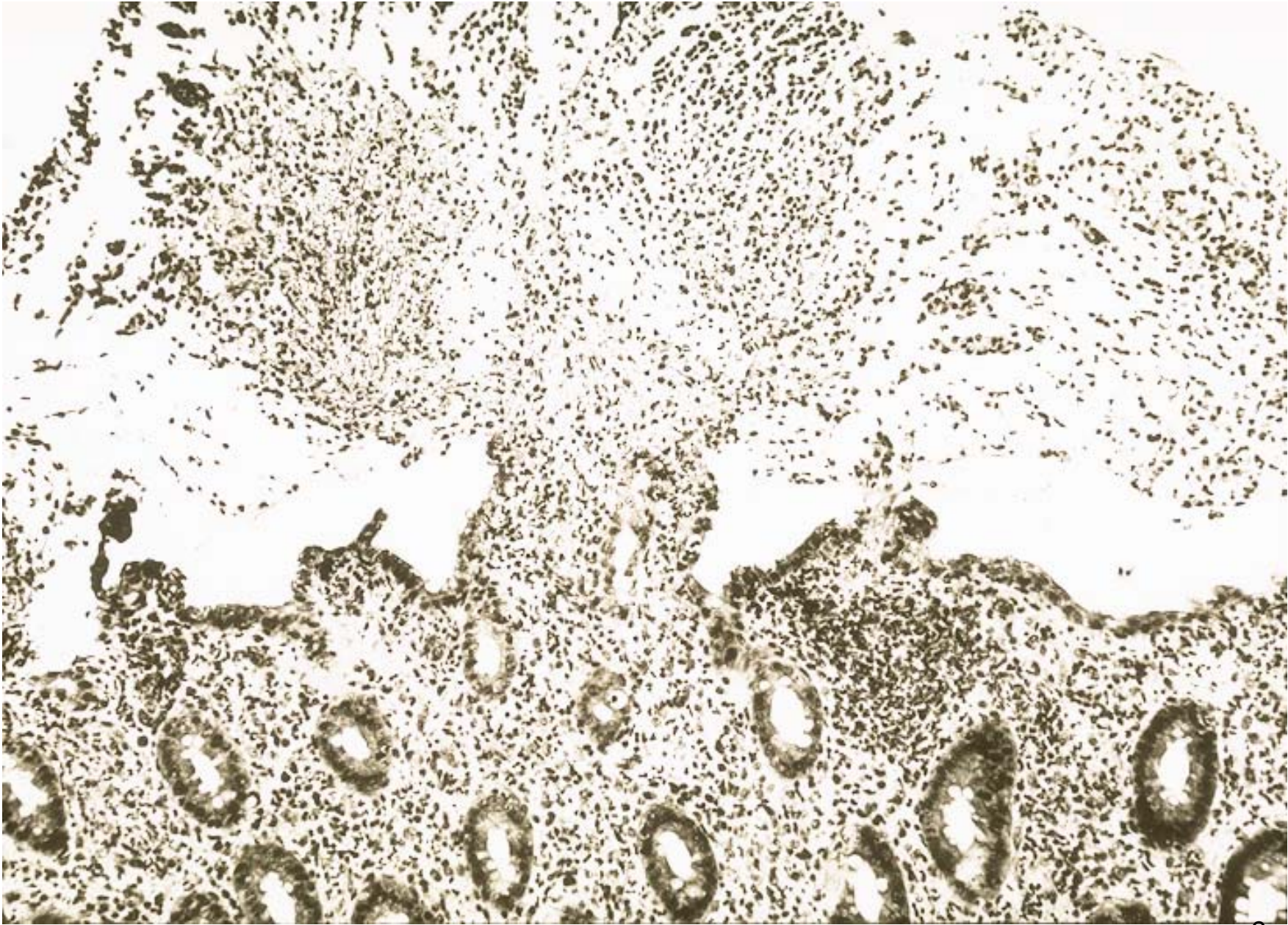
“Normal” colon

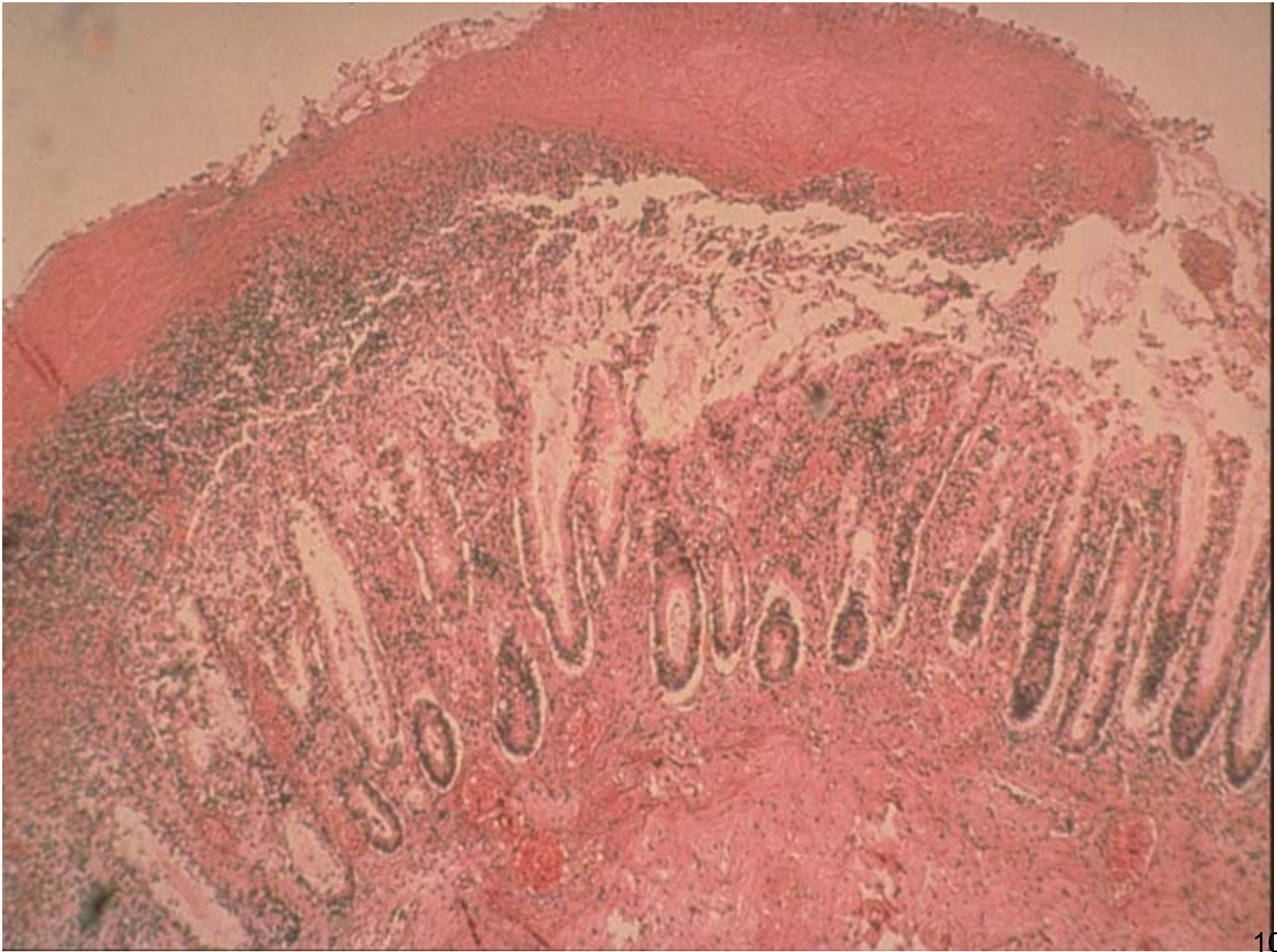


Colon infected with *Clostridium difficile*









# Bioequivalence for Vancocin

- Historically, FDA required bioequivalence studies with clinical endpoints due to lack of any established alternative method
- No public statement by OGD that it was considering changing its BE recommendation for this drug
  - In March 2006, third party announces OGD no longer recommends clinical endpoint BE for Vancocin
  - New recommendation is *in vitro* dissolution testing
  - Only cited basis is reference to BCS-based biowaiver developed and used with BCS Class I drugs

# Biopharmaceutics Classification System (BCS)

- A drug development tool for identifying the contribution of three major factors, dissolution, solubility, and intestinal permeability, that govern the rate and extent of oral drug absorption from immediate release solid oral products (Amidon, 1998)
- Explicitly does not consider nonabsorbed drugs such as “GI” drugs
- Vancocin is not a BCS drug

# BCS Guidance

- Issued in 2000
- Product of decade-long process
  - Participation of academia, industry, professional societies
  - Working groups, Advisory Committees, Conferences
  - Draft and final guidances
- Included possibility of biowaiver for BCS-1 drugs

# BCS-Based Biowaiver

- Intended for rapidly dissolving, highly soluble, highly permeable drugs
- For use where dissolution  $>$  gastric emptying (dissolution not rate limiting to drug absorption)
- Only a limited number of drug approvals have relied on BCS biowaiver

# BCS-Based Biowaiver

- The BCS-based biowaiver has been available since 2000
- Expressed goal of many involved with developing and implementing the model is to expand the use of the waiver beyond BCS-1 drugs
- To date, FDA has not determined that the waiver can be applied to other BCS classes

# BCS-Based Biowaiver

- When applied to the intended products, FDA states that the risk of bioinequivalence associated with use of the waiver is minimal
- FDA's factors when evaluating risk of bioinequivalence
  - Likelihood of occurrence
  - Severity of consequences
- FDA asserts two principles significantly reduce risk of bioinequivalence associated with use of biowaivers:
  - Restrict waiver to use with BCS-1 drugs where dissolution is not the rate limiting step in absorption (dissolution > gastric emptying)
  - Test method is an appropriate simulation of *in vivo* conditions

# BCS-Based Biowaiver

- It is not clear from public presentations or guidance that OGD incorporates the severity of consequences associated with bioinequivalence into its decision process
- In contrast, biowaiver monographs developed for the WHO essential drugs include discussion of “Patient Risks Associated With Bioinequivalence” which incorporates both chemistry and medical science into the decision making process

# Considering Patient Risk When Determining Biowaiver Eligibility

- Cimetidine
  - “has a wide therapeutic index and is not indicated for serious diseases. Therefore, even in the unlikely situation that a bioinequivalent drug product would pass . . . this would be unlikely to result in serious public health concerns.”
- Ranitidine
  - “The unproblematic use of doses six times higher than the recommended dose indicates that ranitidine has a wide therapeutic range. Its IR oral dosage forms are not used for life-threatening indications. These two considerations open the possibility for a biowaiver.”

# Considering Patient Risk When Determining Biowaiver Eligibility

- Chloroquine

- “When considering a biowaiver for a drug substance, its therapeutic index and indication also need to be taken into account. Chloroquine is indicated for serious diseases....In malaria therapy, resistant parasites are most likely to be selected if the parasite population is exposed to subtherapeutic drug concentrations.”
- Led Germany to categorize chloroquine as a drug for which biowaivers could not be granted

# How Does OGD Extrapolate BCS-Based Biowaiver to Vancocin?

- OGD states, without reference to supporting data, that Vancocin capsules are highly soluble and rapidly dissolving
- Does OGD use the fact that vancomycin is not absorbed from the healthy gut as the basis for considering it a BCS-1 compound for purposes of abandoning clinical endpoint trials and applying a biowaiver developed and validated for use with systemically available oral drugs?
- Does OGD believe that as Vancocin acts in the colon, it exhibits essentially solution-like behavior with respect to availability at the site of action?

# Scientific Principles for BCS-Based Waivers

- “If two drug products have the same *in vivo* dissolution profile under all luminal conditions, they will have the same rate and extent of availability at the site of action.”
- “For locally GI acting drugs, . . . *In vitro* dissolution testing must cover the range of the *in vivo* variables.”  
(Amidon, October 2004 to ACPS)
- *In vivo* variables are unknown for CDI gut, therefore, *in vitro* dissolution currently cannot cover the range of *in vivo* variables

# Concerns with *In Vitro* Test for Vancocin

- Untested hypothesis
- Consequences of bioinequivalence are severe
- Available clinical data are not consistent with apparent underlying assumptions for *in vitro* test
- Vancocin dissolution data do not support use of *in vitro* biowaiver
- Safety concerns exist as Vancocin can be absorbed in diseased patients

# Untested Hypothesis

- Appropriateness of the *in vitro* method
  - Unclear as to the range of potential *in vivo* conditions found in patients receiving the drug
    - Relevant hydrodynamic conditions
    - Fluid volumes
    - Biorelevant dissolution media
    - Multi stage dissolution approach
- FDA and outside experts have stressed the need to better approximate *in vivo* conditions to increase the reliability and utility of *in vitro* testing

# Consequences of Bioinequivalence Are Severe

- Apparent failure by OGD to consider consequences of bioinequivalence
  - Serious morbidity or death
  - Difficult to detect under clinical use conditions whether bioinequivalent vancomycin product contributed to treatment failure
  - OGD's expressed position that there is no need to consider seriousness of disease

# Available Clinical Data Are Not Consistent With the Hypothesis Underlying Proposed Biowaiver for Vancomycin Capsules

- FDA determined that the oral solution and Vancocin capsule were shown not to be the same
- Early clinical development of teicoplanin, a glycopeptide similar to vancomycin, for treatment of CDI found that efficacy associated with BID treatment was only observed with solution. Efficacy with teicoplanin capsules required QID administration

# Vancocin Dissolution Data Are Not Consistent with *In Vitro* Test

- Data generated by ViroPharma and submitted to FDA do not support OGD's statement that the RLD for oral vancomycin capsules is rapidly dissolving under all of the recommended test conditions
  - 250 mg capsules are not rapidly dissolving at neutral and weakly basic conditions

# Safety Concerns Exist

- Safety concerns with lack of *in vivo* testing
  - Administration of vancomycin capsules to patients can result in systemic absorption of therapeutically relevant levels of drug due to compromised GI tracts
    - Systemic toxicity has been associated with use of the oral capsule product in some patients
      - Listed as a precaution in package insert
  - Proposed dissolution method does not account for safety concerns related to the absorption of vancomycin or excipient materials

# Bioequivalence for Antibiotics

- Ensuring bioequivalence for generic antibiotics is critical for patient care
  - Unique concerns with antibiotics
  - Different from other classes of drugs
- Bioequivalence method development for these agents requires the application of rigorous science and a transparent process that solicits the expertise of government and nongovernment stakeholders

# Bioequivalence for Vancocin

- The proposed *in vitro* dissolution test to establish BE for Vancocin is not appropriate
  - *In vivo* GI conditions in patients receiving the drug are unknown
  - Requires a new model that accounts for the biopharmaceutics of the drug in patients
    - Permeability is an important part of the BCS model
      - Ignoring permeability is not a valid approach to application of the BCS-based biowaiver
    - *Vancocin is simply not a BCS drug and should not be treated as one*

# Open Method Development

- Development of novel BE methods requires process and transparency
  - Importance of predictable open and transparent process
  - Need for advice and review from external stakeholders and scientific experts

# Pathway Forward

- There are 2 viable options to demonstrate BE for vancomycin capsules that ensure patient safety
  - (1) Maintain clinical endpoint BE for vancomycin capsules
  - (2) Appropriate method development of alternative to clinical testing

# Appropriate Method Development of Alternative to Clinical Testing

- Extrapolation of BCS-based waivers to non-BCS drugs is a significant step
  - These agents represent different classes of drugs
- Approach should be data-driven, not an untested hypothesis that relies on the application of ‘scientific principles’ developed for other classes of drugs
  - Especially important for drugs used to treat acute, life-threatening diseases or conditions
- In order to adequately protect patient safety and public health, careful consideration needs to be given to selection of relevant *in vitro* conditions
- Development of any *in vivo* marker of BE for this agent requires correlation with activity and availability at the site of action or clinical outcome
- In the absence of sufficient new data, OGD should not abandon clinical endpoint BE for vancomycin capsules

# Maintain Clinical Endpoint BE for Vancomycin Capsules

- Clinical trials are the appropriate endpoint for this disease/drug given the current state of dissolution science
- Clinical endpoint BE trials for vancomycin capsules can be designed
- The fact that generic companies may not be capable or willing to carry out these studies is not an appropriate basis for abandoning *in vivo* BE for this drug in the absence of an appropriately developed alternative method

# Public Confidence & Generic Drugs

- “Transparency is one of the Agency’s key goals. It is critical that our audience understand what we do, how we do what we do, and why we do something.” FDA Data Quality Guidelines, F.IV
- “Methods for equivalence based on sound science build the confidence of health care providers, patients, and the public that generic products are equivalent to innovator products.” Crit. Path Opportunities for Generic Drugs, 5/07
- “To win people’s confidence is to be extremely up front with them” – Dr. Woodcock, 9/07

# OGD Has Not Been Up Front About New Vancocin BE Method

- Adopted without public notice or opportunity for comment
- To date, no official notice of new method (some 2 yrs after revelation by 3d party)
- To date, no notice of any data or rationale believed to support new method
  - despite 3/06 FOIA request for admin record of its adoption
- No apparent intent ever to disclose (i.e., but for the Canadian stock analyst, the public today still would not know about new *in vitro* method)

# Confidence Has Suffered

- Among experts, e.g., “[T]here is considerable room for concern that generic vancomycin may not offer therapeutic equivalence.” Dr. William Bishai, Johns Hopkins, 8/06
- Among consumers, e.g., “I am concerned that removing the requirement for clinical trials before approving a generic version of Vancocin could cost the lives of many elderly and sick people.” Juan Antonio Flores, Consumer, 5/06

# Confidence Has Suffered

- On Capitol Hill, e.g.: “[W]e have agreed to engage with FDA through the oversight function of the HELP Committee to ensure that the scientific standards and procedures used in establishing bioequivalence for this life-threatening antibiotic are appropriate.” Senator Orrin Hatch, May 7, 2007 Cong Rec. S5650

# Potential OGD Responses

- Secrecy is OK because OGD has experts
- No particular public process is required when adopting BE methods
- Trade secret confidentiality prevents disclosure of new methods/data/rationale if they come from a generic applicant
- ViroPharma's petition = sufficient process

# The Risk of Secrecy

- OGD Might Get it Wrong
- Outside review enables better decisions, helps prevent mistakes reaching patients (e.g., DPK)
- “FDA recognizes that public access to high quality information is critical to achieving [FDA’s mission to promote and protect the public health] and public input, in turn, improves the quality of the information we disseminate.” FDA Data Quality Guidelines, F.II
- Public process most important with drugs like Vancocin where bioinequivalence of generic copies could cause serious morbidity/death

# Credibility of OGD Expertise

- MDS Pharma Audits: leaving 140 generic drugs on market despite “serious questions” about the validity of their BE data; refusing Congressional request to publicly identify the 140 drugs
- Wellbutrin XL: return of depressive symptoms seen with generic versions, independent lab tests indicate generics not equivalent
- EMLA Cream: OGD approved generic versions based on PK shortly before OGD Dir of BE stated publicly PK “not suitable” to show BE for topical generic products

# Public Process IS Required

- FDA said as much when writing the bioequivalence regulations 30 years ago:  
“The Commissioner believes it is inconsistent with due process to issue a proposed bioequivalence requirement on the basis of ‘secret data and information’ that interested persons can neither see nor comment upon.” 42 FR 1634, 1/77

# Public Process IS Required

- Disclosure of record of OGD's adoption of new method was required by April, 2006. 5 USC 552(a)(3)
- Failure to index, make available/publish prevents use of new method to review or approve ANDAs. 5 USC 552(a)(2)
- Failure to explain new method invalidates it. 5 USC 706(2)(A); caselaw
- Continuing nondisclosure (22 months so far) further undermines confidence in new method

# Public Process IS Required

- Notice-and-comment rulemaking required when FDA significantly changes regulatory interpretation. See, e.g., Alaska Hunters, 177 F.3d 1030, 1034
  - Not a significant change to apply established science, e.g., blood PK for systemically acting products
  - Clearly a significant change to abandon established BE method of clinical endpoint studies in favor of an untested, unvalidated *in vitro* assay extracted from a model developed for a different class of drugs
- “[Good Guidance Practices] must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.” 21 CFR 10.115(e); see 21 USC 371(h)

# Trade Secrets Not An Issue Here

- OGD disseminated *in vitro* method to multiple private parties in early 2006 = no longer a trade secret, if it ever was
- Dr. Yu stated 5/06 that OGD (not a private entity) had generated “lots of data” supporting new *in vitro* method = was never a trade secret in the first place

# Selective Disclosure of New BE Methods Violates the Law

- OGD only disseminated new *in vitro* BE test to selected parties; no general public announcement made to date
- Administrative Procedure Act, 5 USC 706(2)(A), violated when similarly situated parties treated differently, i.e., selective disclosure of new BE recommendations
- FDA Regulations Also Prohibit, 21 CFR 19.6(5)

# Petition Not A Substitute for Appropriate Process

- OGD triggered this petition by changing BE methods for Vancocin in the absence of public process
- OGD-triggered petitions not a substitute for open BE method development
  - Absent notice of proposed method change, petitions unlikely to be filed in time to prevent bioinequivalent drugs reaching patients
  - Without data or rationale for method change, difficult to comment meaningfully
  - OGD more objective re outside input at proposal stage than after adoption, when petitions are more likely to be filed
- Ex parte communications between OGD and generic firms regarding subject matter of petition hurt confidence

# Petitions Asking to End Secrecy Become New Reason for Secrecy

- No OGD intent to announce new method publicly
- Stock analyst announces new OGD policy
- Despite 3d party revelation, OGD refuses to disclose new method to ViroPharma, claiming it is confidential
- ViroPharma forced to file petition in effort to make public new method and any supporting data, scientific rationale
- OGD says petition precludes disclosure
- Secrecy is perpetuated, one way or another

# Recent Colazal Petition Response

## Why Vancocin is Different

- Bioinequivalence risk higher with Vancocin (serious morbidity/death) than with Colazal (unresolved ulcerative colitis)
- OGD relied on PK for Colazal, but PK is unavailable for Vancocin
- Unlike Colazal, data submitted to FDA contradict key OGD assumption (rapid dissolution) for using *in vitro* method with Vancocin
- Unlike Colazal, clinical data do not support *in vitro* dissolution BE for Vancocin
  - FDA determined that the oral solution and Vancocin capsule were shown not to be the same
  - Teicoplanin (structurally similar to Vancocin) clinical trial found lack of equivalent efficacy between capsule and solution in CDI patients

# Colazal: Some Public Process

- Unlike Vancocin, there was some public process re alternatives to clinical endpoint BE studies for Colazal's active moiety – discussion at 10/04 ACPS, data developed on other mesalamine formulations and discussed at various meetings
- Nonetheless, OGD states non-public BE method development remains an option for locally acting drugs like Colazal:
  - “FDA need not have published...product-specific bioequivalence guidance prior to evaluating or approving ANDAs.”
  - “Whether FDA will include publication of a draft guidance as part the process for identifying bioequivalence methodologies...will depend upon a number of factors....”

# Colazal is Inconsistent with Open Process

- Assertion that absence of public process remains an option contradicts May 2007 Guidance promise of opportunity to comment before final adoption of new BE methods:
  - “Product-specific BE recommendations will be developed and posted on the Internet... to facilitate public comment.”
  - “Comments... will be considered in developing final BE recommendations.”
- While bioinequivalence risk is lower with Colazal, OGD did not enumerate patient risk as a criteria in its assessment

# Uncited Assertions in Colazal Response Inconsistent With Law

- Colazal response cites no caselaw, and does not seek to support its assertion that non-public BE method development is a legitimate option
- Procedural approach asserted in Colazal response is arbitrary and capricious under the law. 5 USC 706(2)(A)

# Missing Legal Authority for *In Vitro* Method or BCS Guidance

- Once FDA engages in proper process for BE method development for Vancocin, it will also need to identify appropriate legal authority for whatever BE method is eventually adopted
- The only authority currently cited for the new Vancocin *in vitro* BE test is an unexplained cite to the BCS Guidance; the only authority cited for the BCS Guidance is unexplained cite to the “good cause” biowaiver regulation, 21 CFR 320.22(e)
- Consequently, both the new BE test for Vancocin and the BCS Guidance are invalid for failure to explain the legal authority on which they are based, Motor Vehicles v. State Farm, 463 US 29, 48

# BCS Guidance Insufficient Legal Basis for New Vancocin BE Method

- Good Cause reg narrowly tailored to permit *in vivo* BE waiver only when necessary for “continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted.” 42 FR 1642, 1/77
- Reg would only apply if there were risk to the continued marketing of Vancocin (there is not) and even then would merely permit biowaiver to keep Vancocin on the market, not to allow generics to avoid clinical proof of BE
- Thus, Good Cause reg is not a legal basis for waiver of *in vivo* BE for generic copies of Vancocin
- Using Good Cause reg for generics would also render superfluous the other narrowly tailored biowaiver regs, thus violating the law, US v. Alisal Water, 431 F.3d 653

# In Closing

For an agent where a bioequivalence mistake could cause death, the Agency should:

- engage in open process to ensure the highest quality BE science
- return to clinical endpoint studies until a robust alternative method is developed

ViroPharma is prepared to assist the Agency in a path forward that will result in scientifically-sound alternatives to clinical trials