Trends-in-Medicine

August 2009
by Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Moves a Step Closer to Approving the First Generic Oral Vancomycin

The FDA has proposed – and an advisory committee has agreed – that human clinical trials should not be required for some generic oral vancomycin products. The FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) met on August 4, 2009, to discuss the use of *in vitro* dissolution methods to establish bioequivalence for generic vancomycin oral capsule drug products. It was a very technical topic, and discussion was limited to generic versions of just this antibiotic, but the meeting had important implications for ViroPharma and for generic manufacturers hoping to get FDA approval for a generic version of ViroPharma's Vancocin.

Currently, there are no FDA-approved generic vancomycin capsules, giving ViroPharma a virtual monopoly. The high price of Vancocin has led many hospital pharmacies to compound an oral solution out of intravenous (IV) vancomycin, which is generic, but this product smells and tastes terrible. With the growing epidemic of serious and life-threatening *Clostridium difficile* (*C. diff*) infections, doctors and public health officials are anxious for new oral vancomycin products, but vancomycin is not systemically absorbed, so generics cannot be approved based on pharmacokinetic (PK) studies; clinical trials have been required.

In December 2008, the FDA issued draft revised bioequivalence guidelines for generic vancomycin capsules that would eliminate the requirement for clinical trials in certain instances and make it easier for a generic to get approved, but these guidelines have not yet been finalized. The FDA's Office of Generic Drugs (OGD) is recommending that:

1. Bioequivalence be demonstrated through *in vitro* testing only, provided the oral vancomycin contains the same **active** and **inactive** ingredients (Q1) – and in the same doses (Q2) – as the reference drug, in this case Vancocin.
2. An *in vivo* (clinical endpoint) study in either healthy volunteers or sick patients to prove bioequivalence for generic vancomycin capsule formulations that do not have the same inactive ingredients (excipients) as Vancocin.

The FDA sought the advisory committee's opinion of this new approach. The 16 voting members on the panel were unanimous that this was the appropriate pathway for a generic Vancocin.

The generic drug industry thinks these new requirements are still too tough, and their representatives argued strongly against the need for *in vivo* studies in these cases, insisting that *in vitro* dissolution studies would be sufficient. Lawrence Yu, PhD, deputy director for science at OGD, commented, "Our job is to ensure

quality, safety, and efficacy. When we propose this product (guidelines), we want to make sure it is equivalent to the innovator (Vancocin), safe, and effective…It may be difficult but it is necessary to ensure equivalence."

The advisory committee did not vote on whether a trial would be needed when the excipient varies, but their comments indicated they were divided on this issue, which makes it seem likely that the FDA's final guidance will require a clinical endpoint study when the vancomycin excipient is different. After the panel meeting, Gary Buehler, RPh, director of OGD, said, "Some of the panel felt we could go forward with products using *in vitro* dissolution. Some of the other panel members felt we could go somewhere between there and a clinical trial – using a fecal count, etc. So, we have to really evaluate all the comments to find out where we will end up with the decision."

The advisory committee's consideration of these issues – and the final FDA guidance that will be issued – is important to ViroPharma because it opens the door to a flood of abbreviated new drug applications (ANDAs) for oral vancomycin. And there appears to be a number of potential competitors (perhaps five) in the wings already. Helen Winkle, director of the FDA's Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER), said, "We have a number of applications (ANDAs) in house, and we are looking at whether we can approve these." Eight generic drug companies participated in the panel: Akorn, Impax Laboratories, Mylan Pharmaceuticals, Paddock Laboratories, Sandoz, Strides Arcolab, Teva Pharmaceuticals, and Watson Pharmaceuticals.

At this point, it is clear that any generic oral vancomycin will have to be Q1Q2 equivalent to Vancocin and will have to have done dissolution studies at three specific pH values – 1.2, 4.5, and 6.8. While it is unclear whether any of the vancomycin ANDAs pending at the FDA meet the Q1Q2 standard, it is likely that some or all may have done the required pH testing.

ViroPharma CEO Vincent Milano's own mother died of *C. diff* while taking the antibiotic metronidazole, the day his company acquired Vancocin from Lilly. Milano said he was glad the FDA convened the panel, but he was disappointed in the panel's comments and actions, "We were very appreciative of the FDA holding this advisory committee in the first place…We have been asking for a forum on this for more than 3.5 years…We are very disappointed the vote turned out the way it did…I think this puts patients seriously at risk…We still have some concerns about patient safety and patient risk (with generic oral vancomycin)…but we appreciate that the (panel) saw things differently. We hope the Agency will take the full record into account when they make their final decisions…Though dissolution is a valid model from the committee's point of view, the factors included in dissolution have to take into account not just pH but also volume and motility time (GI transit time)."

Vancocin is the main revenue generator for ViroPharma, but Milano said the company's growth engine is now Cinryze (human C1 esterase inhibitor), a therapy for hereditary angioedema that ViroPharma obtained with its acquisition of Lev Pharmaceuticals in 2008, and the company is pinning its future on an investigational treatment for the prevention of recurrent *C. diff* infections – non-toxigenic CD (NTCD), which recently entered Phase I testing. Milano said, "NTCD could be like a vaccine. The theory is that it will prevent the toxic strains (of *C. diff*) from wreaking havoc…About 20% of patients who get *C. diff* have a recurrence."

Before issuing its final guidance on approval requirements for a generic oral vancomycin, Dr. Buehler said the FDA will study the transcript of the panel's discussion as well as written comments that were submitted, "Our primary concern is that the generic perform in an equivalent manner to the Vancocin product. That is what we care about, that we are approving an equivalent product."

However, Dr. Buehler noted that the FDA does not have to wait for that guidance to be finalized or published to approve a generic vancomycin capsule.

There is strong demand for a less expensive alternative to Vancocin, which has nearly tripled in the past five years. Before ViroPharma acquired Vancocin from Lilly in 2004, a 10-day course of 125 mg Vancocin cost $257.20; in 2009 the cost is $677.08. For a 10-day course of 250 mg Vancocin, the cost has increased from $513.20 to $1,248.60. Milano defended the pricing of Vancocin, "Vancocin is not the most expensive drug in the hospital for life-threatening infections… From our point of view, all that was discussed today (by the advisory committee) was the cost of the product, not the cost of not having the product…Before we had this product, it was perceived as hard to get…We keep supplies adequate and keep adequate supply on hand in case of epidemics. We have invested significantly in medical education. This more virulent strain came to the forefront in the mid-2000s, and we have been there to serve with that…And we spent a lot educating not only infectious disease experts but also the community physicians. And our investment in the *C. diff* world has expanded. $800-$1,000 for 10 days is reasonable."

The key different views at the advisory committee meeting were:

- **FDA's Office of Generic Drugs** – recommends only *in vitro* testing, provided Q1Q2 is met, a conservative approach but an easier road for generic drug companies than current regulations.
- **FDA outside expert** – argued that *in vitro* testing is the best way to show bioequivalence and that the FDA's Q1Q2 recommendation is too conservative.
- **ViroPharma** – warned that *in vivo* testing should be mandatory for any generic for safety reasons.

- **Generic drug industry** – urged the elimination of *in vivo* testing altogether for vancomycin, even when excipients vary. The FDA's Dr. Yu said, "Generic companies believe the FDA's recommendation for bioequivalence is way too conservative. In fact, they believe Q1Q2 should not be required."

THE FDA PERSPECTIVE

Vancomycin is a highly soluble antibiotic (at all pH values encountered in the GI tract), is poorly absorbed in the GI tract, and acts locally within the GI tract. It is used to treat staphylococcal enterocolitis and pseudomembranous colitis caused by *C. diff*. Oral vancomycin is effective for these conditions, but parenteral vancomycin is not. Vancocin was approved in 1972 without any clinical data.

To date, no clinical safety and efficacy studies for vancomycin capsules (Vancocin) have ever been submitted to the FDA. Before 2006, the OGD recommended bioequivalence studies with ***clinical*** endpoints in patients for generic Vancocin, primarily because oral vancomycin is poorly absorbed and plasma and urine concentrations may not correlate to the concentration in the tract following oral administration. However, the FDA has a long history of waiving *in vivo* bioequivalence based on acceptable *in vitro* dissolution.

In March 2006, the OGD revised the bioequivalence recommendations for generic products (generic oral vancomycin) using Vancocin as the reference drug and recommended that bioequivalence be demonstrated by comparative *in vitro* dissolution to Vancocin. However, ViroPharma filed a petition objecting to this, claiming that Vancocin is not rapidly dissolving as generic drug companies claimed.

The FDA then conducted its own investigation of the dissolution properties of Vancocin and found that the dissolution properties actually did ***not*** meet the Agency's definition of rapidly dissolving (within 30 minutes). However, the OGD does not believe this would affect the proposed *in vitro* bioequivalence approach for generic competitors because "there is consensus among academic, industry, and regulatory scientists that the definition of rapidly dissolving should be 60 minutes, and Vancocin does dissolve within 60 minutes." In addition, the OGD argued that additional time is justified for Vancocin dissolution because vancomycin is poorly absorbed and acts primarily in the lower GI tract.

Robert Lionberger, PhD, a chemist in the FDA's Office of Generic Drugs, CDER, provided the panel with a broad overview of the bioequivalence issue. He pointed out that the FDA approves ~600 generic drug applications (ANDAs) each year, and all of these are required to show:

- cGMP.
- Pharmaceutical equivalence – the same active ingredient, the same dosage form, the same route of administration, and identical strength or concentration, though shape, excipients, and packaging may differ.
- Bioequivalence to the reference drug (brand). The FDA is proposing that this be shown by:
  - Same active and inactive ingredients (Q1) in the same amounts (Q2) as Vancocin.
  - Assay, potency, purity, and stability standards equivalent to Vancocin.
  - cGMP.
  - Equivalent dissolution to Vancocin in pH 1.2, 4.5, and 6.8.

Dr. L. Clifford McDonald, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC), outlined the growing problem with *C. diff* infections, with at least 80% healthcare-related – particularly in non-acute care settings – as well as *C. diff* deaths. The problem is also becoming more common in previously low-risk populations such as pregnant women, healthy people in the community, and people without prior antimicrobial use. The BI/NAP1/027 strain of *C. diff* used to be uncommon, but Dr. McDonald said it is now "epidemic."

He estimated that *C. diff* adds $2,380-$3,240 per index hospitalization and $3,797-$7,179 to inpatient costs over 180 days of follow-up. In addition, *C. diff* adds 2.8 days to hospital length of stay and is associated with a 19.3% readmission rate and 5.7% mortality at 180 days. Furthermore, patients who get *C. diff* are more likely to be discharged to long-term care.

Comparison of Metronidazole vs. Vancocin

Measurement	Metronidazole	Vancocin
Route	Oral or IV	Oral
Dose	250-500 mg TID or QID	125-500 mg QID
Duration	10-14 days	10-14 days
Cost	$48	$847
Disadvantage	Systemic side effects	Vancomycin-resistant enterococci (VRE)
Resistance	<1%	<1%

Proposed Treatment Guidelines for *C. Diff*

Disease level	Definition	Treatment
Mild	No systemic symptoms, only mild diarrhea	Metronidazole 250 mg orally QID or 500 mg orally TID for 10 days
Moderate	Fever, profuse diarrhea, abdominal pain, leukocytosis	Vancomycin 125-250 mg orally QID for 10 days
Severe	Paralytic ileus, toxic megacolon, dehydration or sepsis	Surgical consult plus intraluminal vancomycin
Inability to take oral medications	---	Intraluminal vancomycin with or without intravenous metronidazole

The antibiotic metronidazole is not FDA-approved to treat *C. diff*, but Dr. McDonald said it is used to treat more than half the *C. diff* cases in the U.S. However, studies presented in the last 2-3 years have shown that vancomycin is superior to metronidazole, particularly in moderate-to-severe disease.

Dr. Thomas Moore of the University of Kansas School of Medicine said the Infectious Disease Society of America will be issuing new guidelines for the treatment of *C. diff*, following this approach.

Several new antibiotics for *C. diff* are in development, including ActivBiotics Pharmaceuticals' rifalazil, Romark Labs' nitaxoxanide, and Optimer Pharmaceuticals' fidaxomicin (OPT-80). In addition, Acambis is working on a vaccine, and Medarex has monoclonal antibodies under investigation.

Dr. Gordon Amidon, a pharmacy professor from the University of Michigan, discussed the importance of dissolution in bioequivalence. He explained that bioequivalence "connects the product in the bottle with the claims on the label… Bioequivalence is essentially a quality standard for both branded and generic drugs."

Dr. Amidon said European regulators are taking the lead from the U.S. in developing standards for biowaivers. In addition, he said the World Health Organization (WHO) has published specifications for essential medications, "They divide dissolution into very rapid (15 minutes), rapid (30 minutes), and not rapid (>30 minutes)…Both the EMEA and WHO are recommending biowaivers for BCS (Biopharmaceutics Classification System) Class I and III, which means high and low dissolution…BCS dissolution specifications are conservative. They are based on metoprolol – a product, which is our borderline high permeability drug…but dissolves in <30 minutes and is bioequivalent to the innovator, suggesting the BCS dissolution standard is conservative…My personal scientific opinion is that the current guidance on vancomycin is capturing the key dissolution processes…If two products have different excipients but meet dissolution criteria, I think that would capture what is going on *in vivo*. If the two products meet dissolution criteria, requiring equivalent excipients is going too far."

Panel member Harriet Nembhard, a statistician from Pennsylvania State University, was concerned the process changes could affect bioequivalence. She asked, "If you change the experimental process parameters for the manufacturing in an experimental fashion, how much do those changes affect the response in general? You spoke of pH being a key factor, but it seems to me the scientific question is by how much the manufacturing changes affect the response, in this case dissolution." Dr. Amidon answered, "They are relevant. The manufacturing process can have a huge effect. The same excipients and a different manufacturing process can have a huge effect. But manufacturing differences, if significant, would be observed in the dissolution methodology. You would use dissolution methodology as an indicator of whether a manufacturing change is having a significant effect."

Barbara Davit, PhD, acting director of the FDA's Division of Bioequivalence 2, OGD, CDER, reviewed the key performance factors for locally-acting GI drugs:

- Dosage forms (*in vitro* release rate).
- Excipient factors.
- Manufacturing factors. "These obviously will differ between generic and brand. Q3 (same components, concentrations, and microstructure) was intended to characterize performance of semi-solid (topical) drug products, where drug release is much more complicated than with vancomycin (capsules)."

Dr. Davit said no PK study is recommended for vancomycin capsules because plasma concentrations are not detectable in most patients, and systemic exposure has safety issues. She dismissed concerns about fluid volume or GI transit time as factors that would be different between brand and generic oral vancomycin.

THE VIROPHARMA PERSPECTIVE

Not surprisingly, ViroPharma opposes the FDA's new approach to bioequivalence because it will lead to generic competitors entering the market. ViroPharma argued that there is insufficient evidence to waive *in vivo* bioequivalence in favor of *in vitro* dissolution testing for oral vancomycin, charging that the FDA is acting "prematurely." ViroPharma believes that there is significant uncertainty associated with assuming that an *in vitro* dissolution test can accurately discriminate between the *in vivo* performance of generic and innovator vancomycin capsule drug products.

In briefing documents prepared for the meeting, ViroPharma disagreed with the FDA on several points, claiming:

- Vancocin is not a BCS drug.
- Vancocin is not rapidly dissolving.
- Systemic absorption in patients does occur, though at very low levels in healthy volunteers.
- Vancocin is not prescribed to patients with healthy GI tracts.

ViroPharma also argued that the FDA's proposed bioequivalence method:

- Does not address the conditions of the *in vivo* environment of the diseased GI tract in which oral vancomycin will be used.
  - The product's dissolution and solubility have never been studied using relevant physiological conditions associated with the patient population taking the drug, including decreased fluid volumes, elevated pHs, and altered fluid composition.

- pH is likely higher in the GI tract of patients than the highest pH level examined in the FDA's proposed method, and elevated pH is known to slow the dissolution and reduce the solubility of vancomycin capsules.
- GI transit times associated with the population treated with oral vancomycin are highly variable, and estimates of GI transit times from healthy subjects do not provide estimates of this parameter in the treated population.

➢ Is essentially the BCS-based biowaiver, which "was not intended for use in predicting the *in vivo* performance of locally-acting GI drugs."

➢ Assumes the drug's site of action is the lower GI tract, when the small bowel is also a site of action, making the target more proximal in the GI tract than is modeled in the proposed FDA method.

➢ Relies on a premise that the drug will be in solution long (e.g., hours) before it reaches the site of action in the lower GI track. The potential combination of decreased solubility, slower dissolution, and faster GI transit associated with the patient population being treated may, in some instances, result in incomplete dissolution of drug prior to reaching the site of action in the distal small bowel or colon.

➢ Does not consider reports of systemic toxicity in some patients associated with oral administration of the drug.

ViroPharma urged the panel to consider that:

- Healthy GI physiological parameters may not be an appropriate *in vitro* model for assessing bioequivalence with locally-acting GI drugs used to treat serious GI disease. *Should the FDA consider the potential impact of differences in particle size distribution of the active ingredient between products on the in vivo performance of the drug as part of its bioequivalence method development for this agent?*
- Oral vancomycin is systemically absorbed in some patients and has been linked with systemic toxicity. *Does a biowaiver ensure safety or should in vivo testing be considered for this drug? Should systemic absorption be considered as part of establishing the safety of generic vancomycin capsules?*
- Understanding how inactive ingredients contribute to a product's systemic uptake and performance is important, and the science in this regard remain under-developed. *Does the Committee have advice on the need to develop an evidence-based rationale for assessing the potential effect of excipient variations from the accepted Qualitative and Quantitative (Q1/Q2) limits established for systemically-absorbed drugs?*
- Extension of a biowaiver to a new class of drug should be evidence-based and data-driven. *Should the extension of a biowaiver to vancomycin capsules be reconsidered before the Agency has developed greater expertise and understanding of biowaivers with other locally-acting GI drugs to validate the approach…where the in vivo environment is severely diseased?*

In an oral presentation, Colin Broom, vice president/chief scientific officer for ViroPharma, made an impassioned argument that:

1. The proposed *in vitro* test for generics does ***not*** consider the relevant *in vivo* environment.
2. Q1Q2 is inadequate given formulation and critical manufacturing process controls.
3. The precedent the new guidelines would set – and patient risk – must be considered.

Dr. Ciaron Kelly of Harvard Medical School, speaking on behalf of ViroPharma, reviewed the *in vivo* GI consideration in *C. diff*. He said the typical patient is 67-years-old, acutely ill, with multiple comorbidities, and on multiple medications, "The entire GI tract is abnormal in *C. difficile* patients…The proposed dissolution test does not simulate the GI tract of *C. diff* patients. The 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."

Patrick Noonan, PhD, affiliate professor of biopharmaceutics at Virginia Commonwealth University, pointed out the biopharmaceutical limitations of the FDA's proposed guidance. He said:

- The BCS biowaiver is not applicable to vancomycin capsules.
- The method does not predict *in vivo* performance.
- The method must address Q3 differences in products. This is a rather new concept. It includes particle size, morphic control, PG molecular weight distribution, manufacturing process variables such as humidity, pressure, API (active pharmaceutical ingredient) milling speed, polyethylene glycol (PEG) melt characteristics. However, the statistician on the panel took issue with this, "I find that an interesting idea, but I'm not sure the case was fully made."

Dr. Noonan insisted that Vancocin does not meet biowaiver requirements because it is not rapidly dissolving, the *in vivo* solubility is unknown, and the *in vitro* dissolution is not biorelevant. He said the *in vivo* dissolution profile under all luminal conditions has not been established. He also charged that Q1Q2 sameness cannot be assumed to be adequate, and he noted that dissolution testing is inadequate to establish product equivalence despite Q1Q2 sameness.

What potential differences between generic vancomycin capsules and Vancocin capsules are not accounted for in the FDA recommendation? Dr. Noonan said the differences are:

- 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.

Dr. Kelly then warned that there are risks to patients from the FDA's bioequivalence proposal. He said the FDA's proposal:

- Does not take into account patient risk, and WHO recommends a risk assessment when extending a biowaiver beyond BCS I.
- Has no ability to discriminate treatment failures in clinical practice.
- Offers no opportunity to confirm the methods.
- Has the potential to increase the already high morbidity and mortality of the disease (*C. diff*). "The protection of the patient requires *in vivo* testing as part of bioequivalence…In my opinion, this is the wrong population and the wrong disease to set a precedent…I have no objection to the use of generic drugs. I use them each day…My objection isn't to generic vancomycin but to the (proposed bioequivalence approach)…I do not believe the *in vitro* dissolution method is sufficient." He said his hospital compounds oral vancomycin to create a generic oral vancomycin for patients.

Panel member Dr. Kent Sepkowitz, director of hospital infection control at Memorial Sloan-Kettering Cancer Center, took exception to the ViroPharma objections, "Almost all of us use, for price reasons, an unstudied, unapproved formulation – by compounding vancomycin solution in the hospital pharmacy – and it works just fine…If we didn't have a long experience with home brew, the doomsday scenario you are building would be quite alarming…but for this drug, the horse is long out of the barn in terms of finding therapies that are clinically equivalent. So, I think all this Sturm und Drang that we will punish patients if we allow this method of testing to be the gold standard I think is very misplaced and somewhat cynical of the company, knowing what we know about your hospital, my hospital, and almost every hospital using FDA-unapproved but clinically effective therapy (compounded vancomycin solution), I have trouble with the 'sky is falling' comments."

THE GENERIC DRUG INDUSTRY PERSPECTIVE

Generic drug manufacturers made a plea for elimination of both human trials and equivalence in excipients, and they appeared to get half a loaf. The half they got was the most important – no human clinical trials for equivalent products. This was good news because such a trial would have to be too large for a generic company to even consider. However, if the excipient is not the same, it appears likely that a trial will be required, which did not make generic manufacturers happy.

Russell Rackley, PhD, vice president, pharmacokinetics/drug metabolism, for Mylan Pharmaceuticals, spoke on behalf of the generic drug industry. It was not a stellar performance. He spoke quickly, slid through his slides, and didn't make a very powerful or, obviously, convincing presentation.

Dr. Rackley called the current draft FDA guidance recommendations for demonstrating bioequivalence "excessive." He said the recommendation for strict Q1 and Q2 relative to the reference drug ***and*** the recommendation for an *in vivo* study with clinical endpoints in patients with *C. diff* is "not grounded in a fundamental understanding of oral vancomycin therapy. These should not be technically required."

He emphasized that:

1. Oral vancomycin solution was withdrawn from the market in ~2004, leaving only Vancocin capsules available for oral administration, but "current economic conditions" have driven many institutions to utilizing IV preparations compounded for oral administration due to the "exorbitant" cost of Vancocin capsules ("20-fold higher than IV").
2. ViroPharma's Vancocin has never been subjected to any *in vivo* controlled studies.
3. *In vitro* dissolution testing provides "a high level of assurance that a proposed generic product would complete solubilization prior to reaching the site of action within the GI tract."
4. The generic industry is in general agreement with the FDA on requirements for bioequivalence, particularly as it relates to bioequivalence determination by *in vitro* evaluation of dissolution testing.

Other interesting points Dr. Rackley made included:

- "We believe the brand was formulated in a capsule to facilitate taste masking."
- "We believe the ANDA method of a rotating basket, as proposed by the FDA is a robust challenge."
- "Dissolution is rapid enough for Vancocin capsules to be considered equivalent to administration of an oral solution."
- "There has been no apparent concern regarding addition of excipients to vancomycin IV solution for oral administration nor concern over interaction, diminishing any real concern of a requirement of Q1Q2 or a clinical endpoint study."
- "By its very use, Vancocin may be considered as a standard solid oral formulation, interchangeable with oral vancomycin solution and, hence, effectively functioning similar to a solution."

- "The formulation we don't think is that complex."
- "One must conclude that solubilization of an oral vancomycin formulation is the key requirement to achieving therapy. This can be readily demonstrated *in vitro*… Many solid oral dosage forms are approved on the basis of *in vitro* dissolution testing."
- "Oral administration of oral vancomycin was originally approved based on administration of solution."
- "The capsule formulation (Vancocin) has not undergone clinical safety and efficacy testing, though it is considered to have an equivalent therapeutic effect relative to oral solution."
- Citing a ViroPharma document, he said, "(The FDA's) representations regarding the requirement of clinical studies to demonstrate bioequivalence to Vancocin were a key factor to ViroPharma's decision to acquire Vancocin from Lilly in late 2004."

Douglas Slain, PharmD, an infectious disease specialist from West Virginia University Hospitals, spoke on behalf of the generic industry as well. He said the use of compounded oral vancomycin therapy appears to be increasing, but treatment is empiric and based on clinical appearance and response. He complained about the high cost of Vancocin, calling the cost "prohibitive," saying, "(Cost) is the major reason that oral Vancocin capsules are ***not*** used. Why does an oral drug, discovered in the 1950s cost $800-$1,000 for a 10-day course?"

Dr. Slain said that patients have difficulty filling Vancocin outpatient prescriptions, and third party insurance often requires a first treatment with metronidazole before approving use of Vancocin, which he claimed can delay appropriate therapy, "It is difficult to get third party payers to pay for homemade oral solution or oral use of IV vancomycin, as they are not marketed oral prescription formulations."

Dr. Slain also noted that:

- There is no evidence-based guidelines recommending Vancocin capsules over other forms of oral vancomycin, supporting experts condoning the continued use of "homemade" oral solutions or oral use of IV vancomycin.
- Vancocin did not have a trial with clinical endpoints, and a clinical endpoint study would require a very large sample size to identify a possible difference between a generic formulation and Vancocin, making it prohibitive for any generic company to consider such a trial, and creating a "continued monopoly on marketed oral vancomycin by ViroPharma."

Dr. Dale Coy, a gastroenterologist from Advocate Healthcare System in Chicago, urged the FDA to make less expensive, generic vancomycin capsules available. He called *C. diff* "the new hospital plague" and said there are currently only two effective antibiotics: metronidazole and vancomycin, though the efficacy of metronidazole is being questioned, particularly with the increase in the new, hypervirulent NAP1 strain of *C. diff*.

Why is metronidazole still first-line therapy when vancomycin is more effective? Dr. Coy said it is cost. "Vancocin is much higher cost…People simply can't afford oral Vancocin, which makes it problematic for insurance approval, and it is particularly problematic in treating recurrences which occur in 20% of patients…And there are concerns I have over the oral solution in terms of reconstitution of the IV powder leading to dosing errors and patient safety risks, and, more importantly, compliance. (Reconstituted) oral vancomycin tastes horrible."

Dr. Coy predicted, "Vancocin will likely become first-line therapy. I have concerns with ViroPharma being the only producer of vancomycin capsules. What happens if there is a problem with their plant or contamination?"

Panel member G. K. Raju, PhD, of the Massachusetts Institute of Technology (MIT) commented, "We also have to consider the risk (to patients) of not having a generic on the market."

PUBLIC WITNESSES

Among the public speakers were:

Former congressman Tony Coelho, who spoke on behalf of the Epilepsy Foundation. He described the problems for patients – especially epilepsy patients like himself – with brand-to-generic switches, "Switching among bioequivalent drugs is difficult for a small number of patients. Unfortunately, we don't know when and if a patient will have a problem with a switch…This past May I unfortunately had such a problem…I want to emphasize this is not a brand vs. generic issue. It is rather a switching issue. I feel strongly that my doctor or myself should be notified when such a switch occurs."

Dr. J. Patrick Caulfield, an orthopedic surgeon from Maryland, who said he himself became violently ill from *C. diff* after a prosthetic biopsy in 2007. After two days of metronidazole that had little effect, he switched to Vancocin, "I don't remember (the Vancocin) being terribly expensive. I would have paid anything for it. I take issue with…remarks that 3.5 vs. 4.4 days of diarrhea is not a big deal. The hell it isn't." Dr. Caulfield said he uses vancomycin in his hospital to cover patients prophylatically who are having joints replaced and who are allergic to penicillin or cephalosporin. Dr. Caulfield said the cost of a total joint replacement increases from $16,000 to $164,000 in patients who develop multiple infections.

Charles DiLiberti, a Teva Pharmaceuticals/Barr employee, who described his own personal experience with *C. diff*, "I was a swimmer and got an ear infection and chronic diarrhea for a month, then became violently ill…Vancocin was the lifesaver for me. That said, if I were presented with the same

condition today and the option of a generic, I would have no concern with taking the generic, either Q1 or Q2 and without *in vivo* testing…as long as it met dissolution criteria."

Dr. Frank Young, a former FDA Commissioner, who urged the FDA to convene a comprehensive bioequivalence hearing like one he chaired ~25 years ago. Dr. Young told the panel, "I believe we are at a critical juncture in our scientific understanding and regulation of bioequivalence…The increased availability of generic drugs…heightens our need to be sure that our bioequivalent standards are appro-priate and to make any refinement that may be warranted." He raised concerns about three "higher-level issues lurking in the background:"

1. The significance of mandatory and automatic substitution. "The FDA cannot ignore the fact that many consumers will not have meaningful choices between a brand and generic product, or among different generic products, because formularies and pharmacy supply contracts sub-stantially control which particular drugs are reasonably available to consumers."
2. The safety and effectiveness of medicines used to treat high-risk illness or conditions and those drugs with narrow therapeutic indexes. "We are not sufficiently equipped to monitor the safety and effectiveness of all generic drugs…Our current adverse event reporting system is largely limited to innovator products…In my opinion, FDA should maintain a reporting system that enables FDA, physicians, and consumers to identify the name of every manufacturer and search adverse events related to that manufacturer, identify the source of API in each generic formulation, and review the history, if any, of regulatory actions regarding a particular generic formu-lation…Furthermore, I recommend that a new system be developed to register each generic product in such a manner that physicians could, in certain circumstances, be able to restrict substitution of innovator drugs to particular generic formulations."
3. Increased uncertainty before approval should be balanced by increased post-marketing evaluation as appropriate. "I posit we must consider post-marketing evaluation as appropriate, not just for innovator products but also for generic drugs."

PANEL DISCUSSION OF FDA QUESTIONS

The FDA asked the panel to discuss two things. First, does the panel agree that *in vitro* dissolution testing is sufficient for generic vancomycin capsules that have the same active and inactive ingredients as Vancocin? Second, does the panel agree that *in vivo* clinical trials should be required when the inactive ingredients are not the same?

Among the issues raised by the panel during the discussion were:

- PEG and what happens with osmotic pressure effects.
- Whether the FDA approach is too conservative.
- The role of the manufacturing process and whether dissolution testing would pick up manufacturing or excipient differences.
- The public health importance of increased access to oral vancomycin.
- Balancing risk when introducing a generic, including possible adverse events, the likelihood of missing detection of those side effects, and increased vancomycin resistance.
- Patient group empowerment.

Some panel members, including the panel chair Elizabeth Topp, PhD, head of the department of industrial and physical pharmacy at Purdue University, commented that they, per-sonally, would prefer a liquid vancomycin. Other panel comments during the discussion period were mixed.

For *in vivo* testing:

- *Salomon Stavchansky, PhD, a professor of pharmacy from the University of Texas at Austin:* "In this case, the risk to the regulator is small. What is the risk to industry? That we make a bad apple and everyone suffers. But with a drug like vancomycin – and if we keep the same excipients – the innovator has the risk minimized. I believe that changing excipients may increase the risk, so the most conservative approach we can take is to use the same excipients as the innovator…And the risk to the patient will also be minimized. I think, personally…that it may be luck that we are using PEG in the (Vancocin) formulation…My only concern is more in terms of using the API that has the same synthetic method to be sure we don't have impurities there we didn't look for…We are entering into an age of patient group empowerment, and these are dangerous things because there can be a lot of public pressure to do the wrong thing. And that is a risk for regulators. They may be forced into situations where they have to develop *in vivo* testing to prove the medication they are getting is…actually what they expect a medication to do from a clinical standpoint…(One solution might be) if we had a mechanism like an animal study to show patient groups and Congress that this product works similarly…I worry that we forget we live in a new era where patient group empowerment is real."
- *Jessie Aug, a pharmacy professor from Ohio State University:* "I think it is important to keep the excipient constant."
- *Dr. Raju, MIT:* "Materials, design of the process, and the processing details…all three have effects, but the biggest effects I've seen in my work is the material, then process design, and third is technical process. All three can be tracked…However, the highest risk is also in the materi-als because…materials are often coming from outside your process…And since you don't do dissolution tests on every batch…to me this is a relatively easy question."

- *Dr. Topp, panel chair:* "The question is: Does it matter what you do to the excipient to the effect in the end?...The answer is: Yes, it can make a huge difference…If I were a *C. diff* patient, the product I would want to be available is a taste-masked oral solution. Based on what I've heard about efficacy issues, that is the product I would want to have. It seems the process of going from a solution to the initial capsule (Vancocin) happened in an interesting way and would not be okay with the Agency today."
- *Marilyn Morris, PhD, a professor of pharmaceutical science at the University of Buffalo:* "I agree…the *in vitro* dissolution test for compounds with the same excipients, same drug, is scientifically sound based on the data we have and I agree with that. On the other excipients, theoretically there may be differences. There is a possibility of a risk, but it may not be large. The major changes I would anticipate are changes in transit time and adhesion to tissue possibly…Theoretically, there could be some differences, but the risk is very small. I would agree there should be additional *in vivo* testing or data to support any sort of generic preparation product with a different excipient…And it seems to me that (fecal concentrations of vancomycin) may give the best representation of what is at the site of action."

Against a requirement for *in vivo* testing:

- *Patricia Tway, an industry representative:* "I doubt changes in excipients would cause (a problem)…Once in solution, it is in solution…I do believe that…I do believe the dissolution test would pick that up. If someone used an off-the-wall excipient, I would assume that could get picked up in the CMC (chemistry, manufacturing, and control) testing…I think if you change excipients, the dissolution test is very discriminating."
- *Dr. Moore:* "When you change excipients you are potentially introducing significant variability…(but) the main function of (the) Hatch-Waxman (Act) was to avoid unnecessary, lengthy studies…My question is whether it could be done as satisfactorily *in vitro* as *in vivo*, and I think it can…As a clinician, I really am in favor of moving forward on the generic for this drug, given the data we have already…Given the increasing incidence and severity of *C. diff* – I see a lot of *C. diff* patients – it seems more important than ever to increase access to oral vancomycin for these patients, especially the elderly who really have trouble affording this medication and for whom we often have to give an oral solution…If the FDA can – and I think they have – guaranteed the manufacturing process is held to the same standard, then I think we can count on the generic doing the same thing."
- *Kenneth Morris, PhD, a pharmacy professor from the University of Hawaii at Hilo (who participated by telephone):* "The main impact will be due to the material properties itself…Even if you could get the dissolution properties you want, the slope of the curve – how rapidly the properties change as you change the processing itself – would have to be studied under some experiment to establish that…But the risk is lower for something like vancomycin, given its (clinical experience)."
- *Merrill Goozner, the consumer representative:* "The standard for a generic is higher than for the innovator, it seems…It would take an extremely large trial to discover the risk (to a generic)…The way to get more people on the best therapy is to have a generic…We have to compare the risk of a generic, which would be small compared to the other risks…so I would say we need to evaluate those risks (of not having a generic) as well."
- *Dr. McDonald, CDC:* "I agree. I want liquid vancomycin…(With respect to Q3), I am really concerned with setting a precedent, whether you like it or not. In Q3 if you go to the bar of clinical data to show a change in excipients, you may kill innovation…Generics could innovate in the area of excipients…It may mean showing that there is no interaction with excipients…but (not) to set the bar up to clinical endpoints. A big study is expensive, and just changing excipients a little, (a trial) will never be financially viable for generics. I am concerned about precedent here…Meaningful post-market surveillance may (be the answer)…We (at CDC) know something about post-market surveillance…I think this is more outright detection of outbreaks of poor response, not post-market surveillance…This is what happened with (the contaminated) heparin events. You are dependent on the clinician noticing something is wrong…That is not the same as surveillance and getting every event. Rather, it is clusters and following up on that (which is important)."
- *Richard Stec, PhD, vice president, global regulatory affairs, Perrigo, and the panel's generic drug representative:* "Vancomycin is not manufactured through a chemical synthetic process; it is by fermentation…My thoughts on fecal fat studies – I have concerns by generic industry on what value it adds. You are merely measuring what percent you get out of what you put in…On Q3, I would encourage us to look for additional *in vitro* studies on efficacy differences of excipients before leaping to the need for a clinical endpoint (*in vivo)* study. It is not clear what that would be, and the size probably would be prohibitive...Oral liquid would appear to be the gold standard, but I would point out…that the MIC levels are 3,000-fold higher than organisms levels, so the oral product has a sufficient kill rate vs. the liquid standard."

FDA Questions for the Panel

Question 1. Do you accept the FDA recommendation to demonstrate bioequivalence through equivalent dissolution in media of pH 1.2, 4.5, and 6.8 for potential vancomycin HCl capsule generic products that:

a. Contain the same active and inactive ingredients (Q1) in the same amounts (Q2) as Vancocin HCl capsules,

b. Meet currently accepted standards for assay, potency, purity, and stability (equivalent to those in place for Vancocin), and

c. Are manufactured according to cGMP?

VOTE: Unanimously Yes.

Panel member comments after the vote included:

- *Consumer rep:* "I think the risk of not having generics come into the field is much greater than from any generic."
- *Dr. William Hasler, an internist from the division of gastroenterology at the University of Michigan Health System:* "I was also swayed by anecdotal reports of people using liquid vancomycin…so I think the likelihood of a generic vancomycin getting into the bloodstream is low."
- *Dr. K. Morris:* "There is a low risk associated with small differences in the concentration of vancomycin in the intestine…I would like to emphasize the importance of post-market surveillance."
- *Dr. McDonald, CDC:* "The low risk of inferiority (is) outweighed by the public health benefit to increased access."
- *Dr. Nembhard, statistician:* "The preponderance of the evidence is that this (*in vitro* testing) is sufficient for this case."
- *Dr. Raju:* "(I voted) yes based on the data I saw…I saw a lot of robustness in the product performance when it comes from solution…and I think dissolution studies may pick up small differences."
- *Dr. Stavchansky:* "The risk:benefit ratio is in favor of the benefit, and the risk to the patient is minimal."
- *Panel chair:* "I really felt the evidence persuasive that dissolution testing would be discriminatory (of differences). And the benefits to the patient group were quite compelling."
- *Dr. Melvin Weinstein, a pathologist from Robert Wood Johnson Medical School:* "The science I thought clearly supported that vote…I have some concern about widespread use of oral vancomycin, not only for more VRE but also for vancomycin-resistance in staphylococcus… That is the potential downside, but the benefits of oral vancomycin far outweigh the risk."

Question 2. Do you accept the FDA recommendation of a *clinical endpoint* bioequivalence study in patients to evaluate the effect of the different *inactive* ingredients for potential vancomycin HCl capsule ANDA products that:

a. Contain different inactive ingredients from Vancocin,

b. Meet currently accepted standards for assay, potency, purity, and stability (equivalent to those in place for Vancocin), and

c. Are manufactured according to cGMP?

NO VOTE: The FDA had originally asked for a vote, but several panel members had to leave to catch a plane, so the vote was eliminated. However, the general sentiment was mixed.

Panel comments included:

- *Dr. McDonald, CDC:* "I think this is a sucker's choice…I think there is something in between (*in vitro* and *in vivo*) – animal studies, stool studies…The point is that this is a higher hurdle than what Vancocin was required to jump over. Maybe what it has to be is that… when you deviate from (Q1Q2), there has to be a more customizable feature (test)…but it would be better (for the FDA) to get it out *a priori*, before a generic comes to you. We haven't really found a lot of issues with vancomycin…I'm not clear there is any excipient that interacts with vancomycin. I don't think there is a lot of binding with vancomycin."
- *Dr. Au:* "I disagree. This is a drug for a life-threatening disease, and the drug out there (Vancocin) is really good. To not have a comparable drug with comparable efficacy for me is difficult. I understand it is costly to do a clinical trial."

♦