Specialty Pharmacy Solutions - **Client Alert** - Best Damn Article On FDA Bioequivalence Article Yet Written ©

We write a lot in these Alerts and *we go for the 'edge'… and often a bit of humor…. as often as possible*.

The article below is how I'd like to write.
Take a very complex topic – in this case how the FDA goes about determining bioequivalence (*for the new bio-generics*) and make it very understandable.

If you have a few minutes read the article below -- do so….. it sheds new light on the inner workings of the FDA, what they are 'empowered to do', and the complexities of evaluating large molecule (*specialty*) drugs…. *in a way that even I can understand*.

What is surprising is that, in spite of recently issuing all kinds of guidance related to bioequivalents and interchangeability for new 'bio-equivalents' there are still huge gaps in the process.

If I were a patient reading this article I'd stick with my 'proven brand' like glue.
In short, the FDA process is still like making cheese…. in this case Swiss….. *Es gibt löcher in dem Käse (* see translation below).*

So, it seems that the FDA has trouble determining bioequivalence with certitude…… let alone A/B rating and interchangeability.

And, it appears that it may require Congressional legislation to create the authority for the FDA to obtain those powers (*like that's going to happen any time in this Congress!*) So, it is no wonder that the 'sons of Copaxone' (whose patent expired on May 24th) have yet to break out of their shells and wiggle their ways like hatchling turtles from the dunes to the shore to begin their tenuous voyage on the dangerous seas of big Pharma.

* *Es gibt löcher in dem Käse – this cheese is full of holes.*

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FDA's Looming Decision On A Generic To Teva's Copaxone Reveals Drug Approval Woes

A year ago, the Food and Drug Administration quietly posted a public notice that it wanted to hire an independent lab to test a generic drug that it had already approved. FDA wanted to make sure the drug was safe and effective.

The issue concerned a copy formulation of a complex, intravenous medicine used to replenish kidney-dialysis patients' stores of iron. FDA had approved this "generic" version of the drug in March 2011 because it believed that laboratory data showed that the replica version of the drug was the exact same as the original branded medicine it was copied from. In announcing the request for independent testing of the generic version, FDA was indirectly saying it might have been wrong.

FDA was going back to get more evidence – including data looking at how the drug was behaving in patients – to make sure that its original decision was sound. Additional evidence was needed because this type of drug represents a new chapter in FDA drug approvals. By law, generic drugs are supposed to

contain identical copies of the active ingredient of the original branded medicine that they are copied from. With almost all generic drugs, making identical copies has been relatively easy because the original medicine was a small molecule, which has a simple molecular structure. In contrast, complex drugs involve large molecules and are difficult to copy. In fact, their physical and chemical properties may not be fully understood. Even so, FDA has begun to approve generic copies of complex drugs.

Since approving the generic IV iron medicine in March 2011, FDA has approved several other generic complex drugs, including a generic version of a drug that fights several types of cancer, called Doxil. None have been smooth affairs. At the time it approved that cancer drug Doxil, for example, FDA said it had developed a "novel bioequivalence method" to judge the copy drug same as its branded alternative. Like the case with IV Iron, FDA sought a "post-market" study in 2013 and another one in 2014 to make sure its original approval of Doxil was scientifically sound.

Now, on the anticipated eve of one of the most significant generic drug approval decisions in recent years—involving another complex drug—the lesson from the generic IV iron episode bears reminding. FDA is widely known to be considering the approval of a generic version of Teva Pharmaceutical's (NYSE:TEVA) blockbuster drug for multiple sclerosis, Copaxone. The patents covering Copaxone for its 20mg/ml strength expired on May 24th. After patent expiration, FDA could approve generic copies of the drug at any time. But some of the same challenges that caused the agency to struggle with and sometimes stumble over its similar previous decisions still linger, and will color FDA's decision concerning Copaxone.

When it comes to evaluating copies of these complex drugs, the fact is FDA doesn't have very good tools and policies. These drugs slip between FDA's other generic drug constructs. They are less complex than biological drugs, which have their own separate law governing how the agency should review and approve copy versions. (Unlike with the generic drug law, the approval of copy versions of biologicals generally must be supported by evidence from human studies.) But non-biological complex drugs are far trickier than generic versions of the normal, small molecule pill drugs that FDA is accustomed to evaluating. It's that framework for these small molecule drugs that FDA has been trying to apply to these complex drugs.

These challenges illustrate a need to reconsider how FDA approves copy versions of complex drugs. Perhaps different approval standards should be used. Current law already contains an appropriate alternative to the generic drug law in the pathway used for the review and approval of copies of biological drugs, which gives FDA more latitude when it comes to the data it can use as a the basis for these approvals. Some of these principles could be applied to a new category that addresses the complex drugs. Or Congress could re-write certain aspects of the generic drug law, tailoring generic drug principles to the unique challenges of copying complex drugs.

FDA also needs to change its practices when it comes to these complex drugs, to more clearly establish reliable principles for how generic copies of these medicines can be safely brought to market once brand-name patents have expired. It needs to develop these scientific principles in a more transparent and inclusive process that leverages the expertise that FDA doesn't readily posses to discern these laws of drug science. More on these policy challenges, and their potential resolutions later.

The complex drugs fall in a regulatory gap. FDA has tried to retrofit the "Hatch Waxman" generic drug law and policies that govern approval of small molecule drugs to these complex drugs, with sometimes

troubling results. Regardless of the decision FDA makes with Copaxone, it remains clear that Congress and FDA alike need to re-examine the regulatory process when it comes to these intricate drugs.

The problem is that FDA has refused to define these complex drugs as distinct from normal, small molecule medicines. That has forced the agency to rely on less information in approving these complex copies than it probably would like. The agency's desire to try and squeeze these complex drugs through its existing generic law approval pathway may have as much to do with political expediency as with good science. FDA is probably well aware that getting Congress to define a distinct category for these medicines, and give FDA proper tools, could be a heavy political lift. So FDA is doing what it often does: trying to massage its existing authorities and regulatory practices to fit novel challenges. But at what cost?

These non-biological complex formulations are different than small molecule drugs. As a result, they don't fit the standard paradigm on which copy (generic) versions of branded drugs are typically reviewed and approved by FDA.

To approve a generic drug, the generic drug law and subsequent regulations discourage FDA from asking for data other than bioequivalence data. As a result, these generic drug approvals typically rely on "pharmacokinetics" data that shows that the copy drug gets into the blood in the same predictable fashion as its brand-name alternative. But for complex intravenous drugs, the behavior of the medicine often depends on aspects of the mixture that are hard to copy and even harder for FDA to fully characterize (i.e., understand the physical and chemical properties). Like the IV iron formulations, Copaxone is a complex drug – perhaps more complex than any drug of this type, where FDA has been asked to review copies. When it comes to these drugs, looking at bioequivalence data alone can be insufficient to tell how the drug will behave once it's administered to the patient.

So sometimes the agency cheats a little. At times it has looked at human testing data after the fact, to make sure it didn't err (as was the case with the generic IV iron medicines). Other times, FDA tries to expand the scope of what it can include in a generic application. This was the case when it came to the approval of generic versions of the blood-clot prevention drug, Lovenox. In that example, FDA looked at human data to make sure the two drugs didn't cause different reactions from the body's immune system. (FDA was accused of exceeding its authority under the generic drug law and was sued for this, but ultimately prevailed in court because the courts give great deference to FDA. Interestingly, Europe regulates generic Lovenox as a biological product, which means that evidence from human studies is required)

Copaxone is an especially hard case, because the drug's benefits are thought to turn on the complexity of the mixture, which isn't well understood.

The drug exits as a complex mix of long and short chains of carbohydrates. It is believed that the precise proportion of these long and short chains in the solution is tied to the drug's therapeutic attributes. But making sure that a copy batch of the drug can reproduce the same quantity of long and short chain carbohydrates, in the same proportion, isn't straightforward. And the generic drug law effectively bars FDA from looking at evidence from human studies to see if the copy is working as well as the brand-name alternative. For the most part, all FDA can do is examine data comparing the two solutions, and how they get into the blood (bioequivalence data). But FDA can't look at how the generic version affects outcomes in patients.

So in the case of Copaxone, for example, FDA is widely believed to be considering gene expression data that shows how the drug turns on and off the function of certain genes. The genes FDA is looking at are thought to be involved in regulating how the drug modulates the immune system in multiple sclerosis. If FDA is relying on this sort of gene expression, it would be largely because FDA needs to find some potential surrogate marker in lieu of full comparative clinical endpoint studies, which FDA can't ask for under the generic drug approval process. But here again, FDA would be creating brand new scientific criteria by establishing that the gene expression data can stand in for clinical outcomes data. These aren't just review criteria that FDA is establishing in the context of its struggle with this particular application, and its desire to find a way to prove "sameness" based on laboratory testing data (so that it can approve the generic Capaxone). By relying on the gene expression data, FDA is establishing what should be immutable laws of drug science. Using the twists and turns of a meandering and secretive generic drug review is not the right place to be establishing these sorts of generalizable scientific principles.

To these ends, the challenge isn't just the generic drug law, which doesn't allow FDA to look at much more than bioequivalence data. The setback is what FDA has done in response to these limitations, to try and retrofit its existing policies on complex drugs where the generic drug principles are sometimes poorly suited. And FDA has entered this new chapter in generic drug approvals largely under the radar. Congress and the public generally are not aware of the new direction FDA is taking.

Instead of acknowledging that it needs a broader scope of data to ensure "sameness" (the statutory standard for a generic drug approval) between the original and the copy drug, FDA has typically divined new science in these circumstances – coming up with novel principles of drug science to determine how two drugs can be declared the same by comparing laboratory data that FDA often establishes on its own novel principles. Such is the case with the gene expression data that FDA is examining in the case of Copaxone. FDA will typically announce these new principles after the fact, often at the time of approval of the generic drug.

Problem is FDA doesn't do this sort of science well. Establishing new principles on which sameness can be determined between complex formulations of drugs is something that requires expertise in these fields. FDA is in the business of evaluating data against known standards, not establishing those standards de novo. The enterprise of establishing standards upon which two highly complex drugs can be judged the same requires a great deal of expertise in discrete areas of science. This sort of expertise doesn't exist in one place, and certainly isn't the province of FDA. That's not a knock on FDA, or its scientists. This sort of work just isn't the business that Congress has tasked the agency with doing. FDA is not staffed or resourced to take on the task of developing novel principles of biology and discovering the standards for measuring how drugs affect biological systems.

As a result, FDA has often established principles that are at times embarrassingly incomplete, and sometimes spectacularly wrong. The re-adjudication of the generic IV iron approvals is one example. The problems FDA had in 2008 assuring safety and effectiveness of generic, copy versions of intravenous heparin is another example. FDA had to recently walk back guidance it put out on how to copy a popular eye drop that was another complex formulation. In each case FDA had established some principles upon which the agency thought it could reliably determine that two complex drugs were the same. In each case, FDA was wrong.

When it comes to certain complex drug formulations, Congress may need to update the law to give FDA broader discretion to use a larger complement of information to make sure that a copy version of a drug

is the same as its branded counterpart (while still enabling the copy to be approved as a generic, fully substitutable medicine). If FDA had such latitude, it could actually speed generic entry of these complex drugs. Right now, each approval has been a long and tortuous process that often extends well past the expiry of legitimate patents. Congress, for example, crafted specific legislation when it came to copies of biological drugs. It recognized that the generic drug law did not adequately address how to develop and approve copy versions of these highly complex drugs. Right now, the non-biological complex intravenous drugs fall within a gap between the existing small molecule (pill form) medicines and the highly complex biological medicines. Neither approval pathway seems to address copy versions of non-biological complex medicines well.

But there's another problem. This one is of FDA's own making. In cases where FDA believes that the existing generic drug framework already gives it ample discretion, FDA needs to adopt a more transparent and inclusive process for developing the scientific principles upon which it makes these judgments. This sort of process ends up establishing final principles of drug science. Rather than these principles being divined through regulatory fiat, they need to be established in an open scientific process that readily draws on all of the available expertise in adjudicating these principles. FDA workshops and advisory panels could provide a forum for these discussions, should FDA choose to use them.

Moreover, FDA needs to generalize these principles in guidance, preferably well in advance of patent expirations that create the opportunity for generic entry. These standards, once established, often end up affecting many different kinds of generic drug approvals. By establishing them in an open process, FDA would make this important knowledge generally available, and would lower the barrier to market entry by generic firms of different levels of technical sophistication. It should be emphasized that FDA's current lack of transparency makes it hard for many generic-drug companies to get on the playing field. The big companies, that have more access to FDA's thinking, end up being advantaged over smaller generic players that don't have this proximity. Transparency could promote generic competition.

In the case of the IV iron drugs, even after approving generic copies of these medicines, FDA went back in 2013 and commissioned research to develop a methodology for how it could determine sameness between a brand name and generic formulation of IV iron. It begs the question, what criteria were FDA using all along when it approved generic copies of these drugs? The scientist who received that award issued a press release referring to her work as "uncharted territory".

The consideration of a generic version of Copaxone is being closely watched as, among other things, another indication of how permissive FDA has become in approving these generic complex formulations. In the past, the answer seemed to be as permissive as FDA needed to be in contorting rules of law and science to advance these approvals. It shouldn't be that way. Congress should be tapped to give FDA the latitude to look at the science necessary to make comfortable and reliable determinations. The broader scientific community should be leveraged, through open dialogue, to give FDA the principles on which it can base those judgments.

Dr. Gottlieb has consulted in the past with pharmaceutical companies that market complex drugs. He has not done consulting work for Teva Pharmaceuticals. Dr. Gottlieb was an FDA Deputy Commissioner from 2005-2007 and prior to that served as a Senior Advisor for Medical Technology to the FDA Commissioner.