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EXPERT perspectives

Narrowing the Gaps: Understanding Biosimilars

A CE/CME Activity

Overview

Leonard Calabrese, DO, and Edward Li, PharmD, MPH, BCOP, discuss how to interpret the efficacy and safety data for biosimilar products, and the implications of biosimilars for clinical practice.

Content Areas:

- Pharmacoeconomic impact
- Burden of evidence
- Interpreting clinical evidence
- Practice implications

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https://annenberg.net/Understanding-Biosimilars-CME

CE/CME Information

Target Audience
This activity was developed for rheumatologists, oncologists, dermatologists, gastroenterologists, nephrologists, pharmacists, and other health care professionals who have an interest in biosimilars.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Recognize manufacturing differences between biosimilars and their reference biological product as well as generic small molecule drugs
- Understand how the FDA uses a "totality of evidence" strategy to evaluate biosimilar compounds
- Weigh the efficacy and safety data for biosimilar products in relation to the data for their reference biological products
- Consider how the availability of biosimilars will impact clinical practice

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Speakers Bureau	AbbVie, Crescendo, Geron, Janssen

Edward Li, PharmD, MPH

Consultant	Eli Lilly, Pfizer
Speakers Bureau	Apobiologix, Pfizer

The faculty for this activity have disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners
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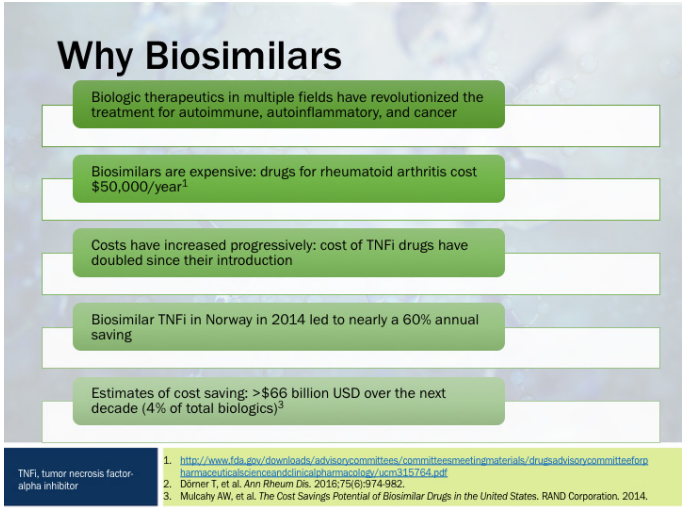
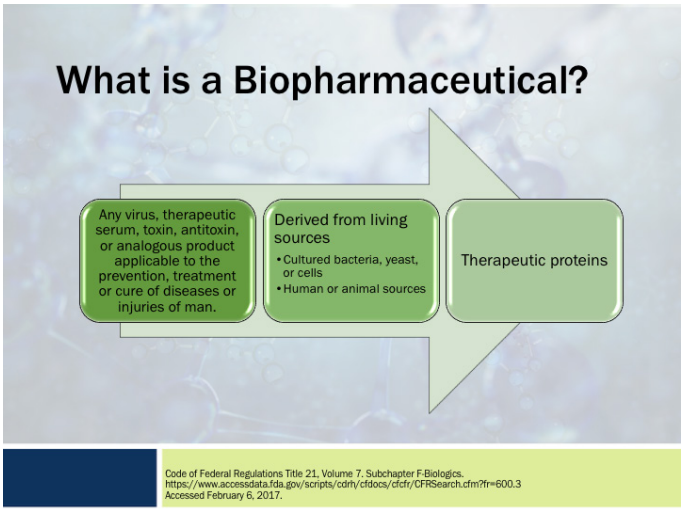
Differences Between Biosimilar and Reference Products

Dr. Calabrese: Welcome to the CME Certified program entitled Narrowing the Gap: Understanding Biosimilars. I'm Dr. Len Calabrese, a professor of medicine at the Cleveland Clinic Lerner College of Medicine here in Cleveland, Ohio. Joining me in a little bit will be Dr. Edward Li, associate professor, Department of Pharmacy Practice, University of New England College of Pharmacy in Portland, Maine. These are our disclosures, and these are our learning objectives. It really involves recognizing the process of building biologics or recognizing the manufacturing difference between biosimilars and the originator, describing the FDA pathway to the approval, which we call the "totality of evidence," then considering what impact this will have on our practice.

I'm going to lead the way here in talking about the difference between biosimilars and reference products. I suppose that the first question that we ponder when we discuss biosimilars is why do we have them? If they are truly similar to the originators, what are the advantages that may accrue to our patients or our society? There's no doubt that biologics have raised the bar in the treatment of many diseases, of which a large part of them are immunologic diseases. They have offered new standards of efficacy to many of our patients. At the same time these are extraordinarily expensive drugs. The cost of these drugs has really only increased dramatically since their approval.

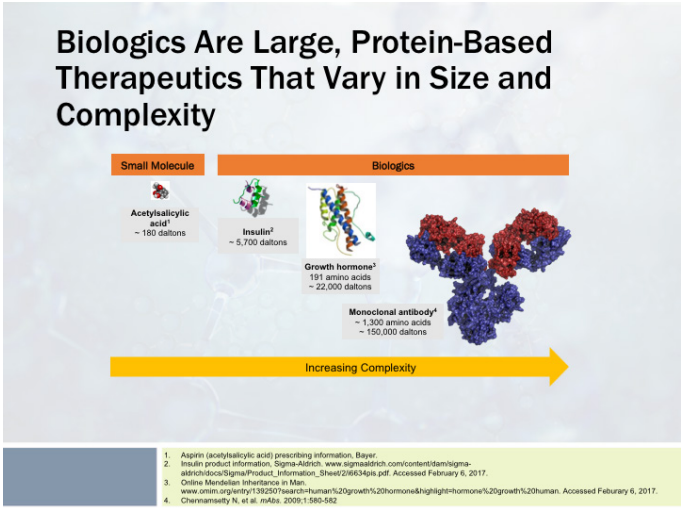


The introduction of biosimilars, particularly in Europe, has led to dramatic reductions, and in some countries that have socialized health care systems with one payor, as much as 60%. There are estimates that biosimilars may lead to savings of over $60 billion as we move ahead. The first question that we will sneak into, in terms of the process, is to answer the question of what is a biopharmaceutical? Biopharmaceuticals are really any product from a living organism that is applied to health care settings that may modify some aspect of a disease in terms of prevention, treatment, etc. I think that the more apt question might be what is a biologic drug, which is a subset of biopharmaceuticals, and these are genetically-engineered proteins that are derived from human genes, often expressed in eukaryotic or prokaryotic cell lines.

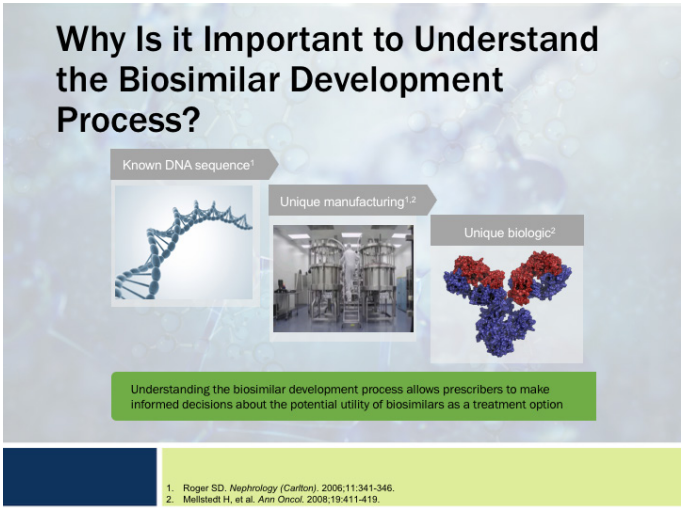


The ultimate product for therapeutic proteins, which are then put into practice. Biologics are large, protein-based therapeutics of variant size and complexity. I like this figure because it contrasts the small molecules over here that you can see in aspirin moiety compared to the large polyprotein immunoglobulin at the right side of the slide.

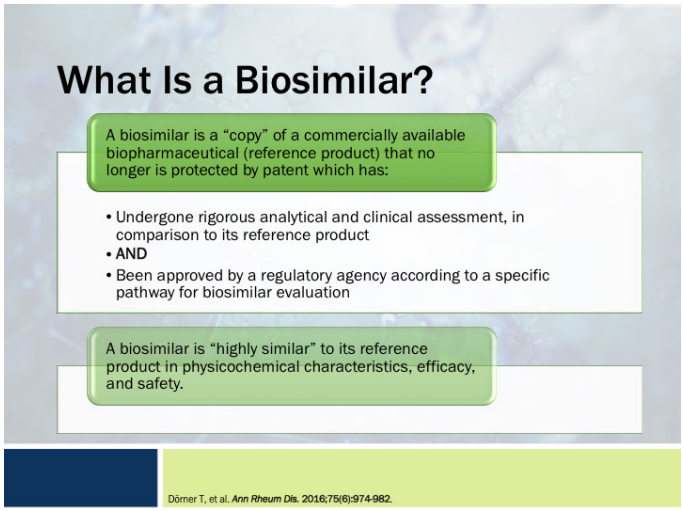
Complexity is dramatically increased over the span of evolution of these types of compounds. I think it speaks legions for why biosimilars are not carbon copies of the originators such as generics are to the small molecules.



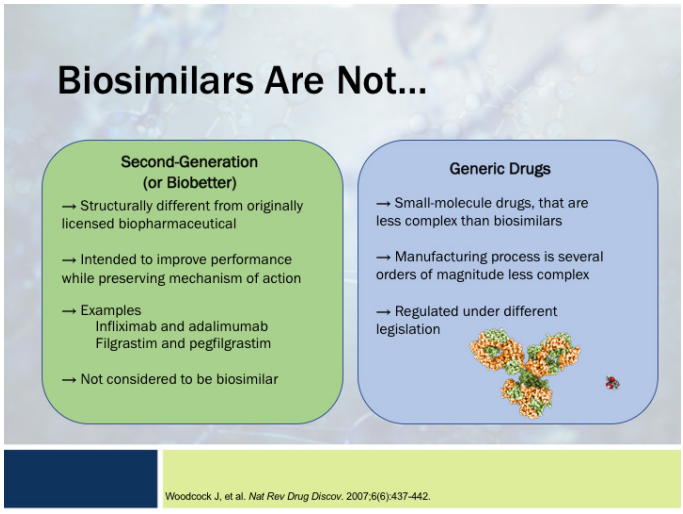
Another question is why it's important to understand biosimilar development process because really, this is at the core of what a biosimilar is. As we will point out in the next few minutes the DNA sequence is of public record of this proteins that uses biologic therapeutics. However, aside from that, much of the rest of the process is propriety and we'll get into that in a more granular fashion. At the end of the day, the biologic, the originator compound, the ones that have been approved by traditional pathways are unique macromolecules. So we have to go into this development process a bit more.



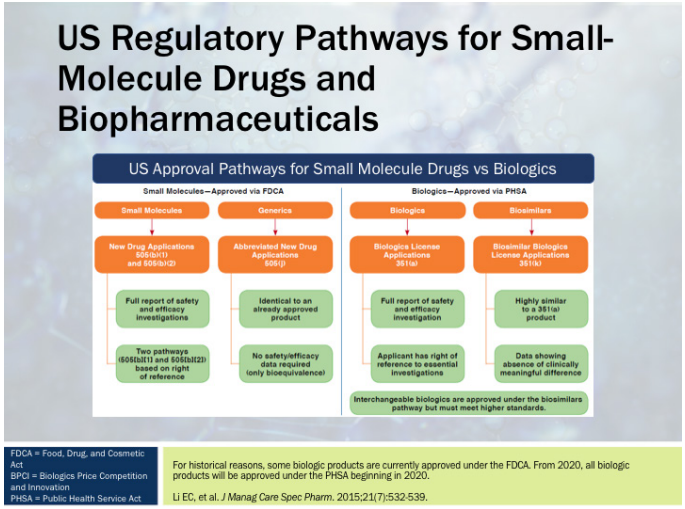
Biosimilars are a sort of copy of a commercially available biopharmaceutical, which we often call either the originator or the reference product. These are developed after these drugs come off of patent. At 30,000 feet I will tell you that these biosimilars, which are approved have undergone rigorous [00:05:30] analytical and clinical assessment and have met all the requirements of the regulatory agencies for the biosimilar pathway. We like to use the term "highly similar," because that is in the pathway, and I'll give you a more granular view of what that is in the next few slides.



In terms of cautionary notes, biosimilars are really not what some people refer to as "biobetters." A biobetter would be an originator drug that has undergone modification to enhance it, that actually is structurally different from the original license firm biopharmaceutical. In that token, it is really a different drug from the first chimeric TNF, infliximab, developing human antibodies such as adalimumab would be part of this evolution. Generic drugs, as I told you, are literally carbon copies of small molecules and they're regulated under different legislation.



This is a complex slide that I really don't want to go into any depth, but what it points out is that there are multiple pathways to biologic drug approval. Small molecules, generics, biologics, and biosimilars, each of these have their own regulatory components and their own detailed pathways for approval. We'll enumerate them as we move along in the following slides.



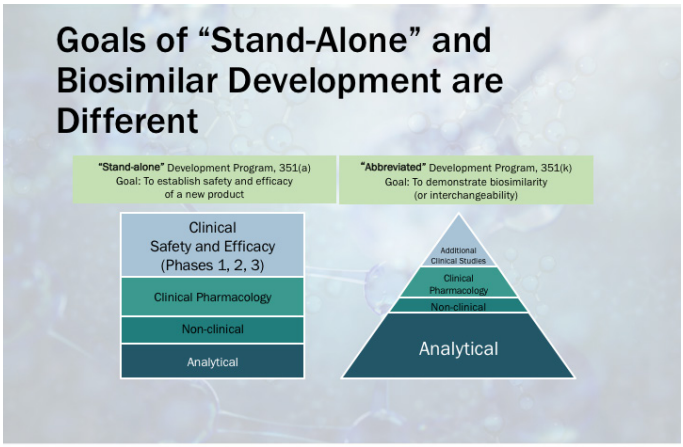
FDCA = Food, Drug, and Cosmetic Act
BPCI = Biologics Price Competition and Innovation
PHSA = Public Health Service Act

For historical reasons, some biologic products are currently approved under the FDCA. From 2020, all biologic products will be approved under the PHSA beginning in 2020.

Li EC, et al. *J Manag Care Spec Pharm*. 2015;21(7):532-539.

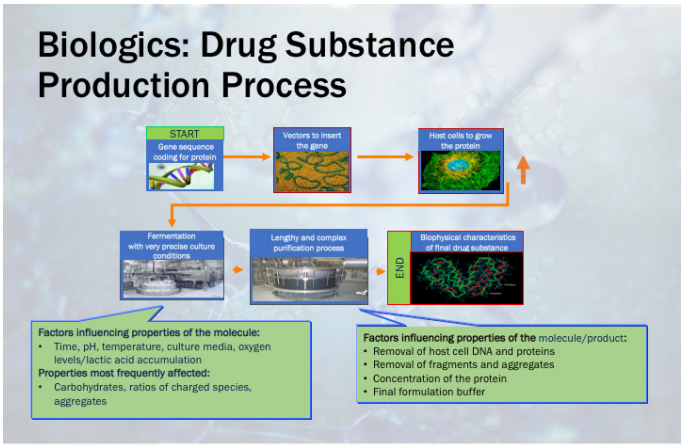
The goals of standalone biosimilar development are actually quite different. The originator compounds are developed based upon developing a biologic therapeutic by creating these express proteins, as previously described. There is an analytic program which characterizes them. There's, of course, toxicology, there's pharmacokinetics, and pharmacodynamics. But the bulk of these programs are robust clinical studies that must go through first phase 1, phase 2, and then phase 3, which are rather expansive. On the other hand, the biosimilar pathway is somewhat abbreviated in terms of its clinical pathway, but as you can see—and it's graphically depicted—the analytics of this are far more robust. You have to demonstrate this fingerprint similarity to the biosimilar in terms of its physiochemical biologic and immunologic properties.

Then go into non-clinical studies, which are highly abbreviated. Then the clinical programs are quite small. As I'll show you, and as we'll talk later, with the approval pathway extrapolation, only a limited number of diseases have to be looked at for full therapeutic across the full spectrum of the reference product.



Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US. http://www.fda.gov/downloads/AdvisoryCommittees/Committees MeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM486171.pdf. Accessed February 4, 2017.

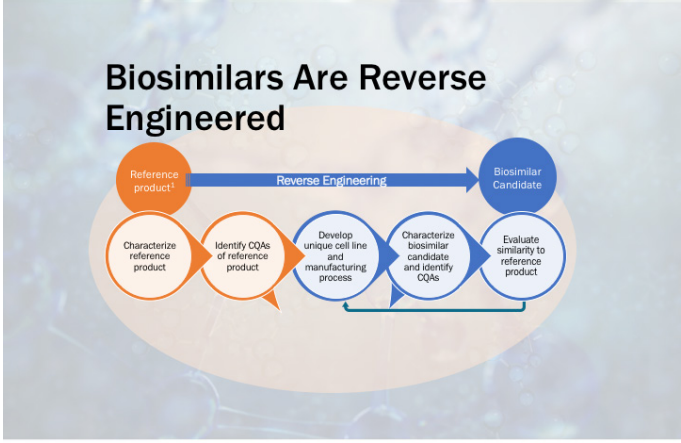
This is a nice flow diagram that depicts how biosimilars evolved. We start with the DNA sequence of the reference product because that is a part of public domain. This DNA then is inserted into a vector that will allow it to be used to transfect a host cells to grow the protein. At this point in time, the vector is proprietary, the host cell-line is proprietary, and as we move down to look at the fermentation and the actual process of cultivation of these cells that will be the actual machines for biosimilar.



Liu HF et al. mAbs. 2010;2:(5):480-499
Li F. et al. mAbs 2010;2(5):466-477

All of this is proprietary in terms of time, pH, temperature, media conditions, all which go into an influencing post-translational modification. There are numerous processes in the expression of the protein, purification of the protein, and the stabilization and packaging of the protein, which can influence the biologic properties of the biologic agent. So the term reverse engineering is often applied.

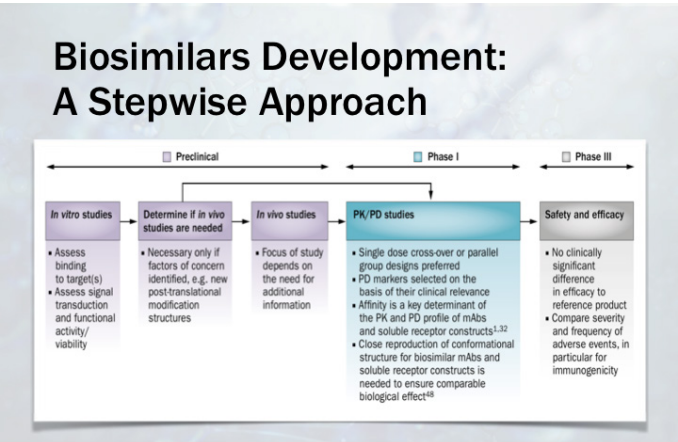
Reverse engineering means that we know what the DNA is, but we must develop a product that matches up to the reference product in virtually every way in terms of its physiochemical properties, pharmacokinetics, pharmacodynamics, immunogenic properties, and these are evaluated at each and every step of the biosimilar evaluation process. Each step has critical ramifications in the drug development.



CQAs = critical quality attributes.

1. Kozlowski S. *US FDA Perspectives on Biosimilar Biological Products*. 2014; Rockville, MD. Accessed February 6, 2017.
2. US Food and Drug Administration. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. Guidance for Industry*. Published April 2015. Accessed February 6, 2017.

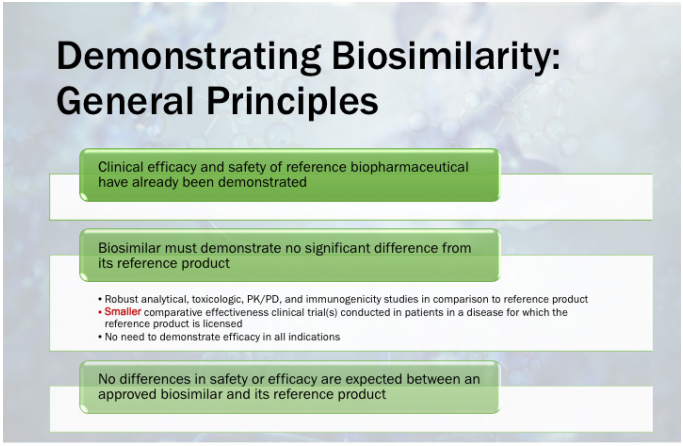
We also the term stepwise approach. If you look at preclinical phase 1 and phase 1 the largest part of this program is really pre-clinical. These in vitro studies really identify the physiochemical similarities between the biosimilar and the reference product. They determine if in vivo studies are needed. It's really not mandated that in vivo studies and preclinical models be performed if the entire package and totally of evidence is looking good. Phase 1 studies are really the most important where these drugs have to match up particularly in PK/PD, and immunogenicity. Then finally, phase 3 studies you'll pick a disease that is an approved indication and demonstrate a noninferiority and a similar safety signal.



PK = pharmacokinetics
PD = pharmacodynamics

Dörner T, et al. *Nat Rev Rheumatol*. 2015;11(12):713-724. Reprinted by permission from Macmillan Publishers Ltd

The general principles of biosimilarity, I think I've already gone over, but it revolves around the ex vivo studies and then the clinical efficacy and safety. These are not intended to be superior or inferior. They're intended to be equivalent and that is what drives the design of these clinical studies. No differences in safety or efficacy are expected or tolerated in this biosimilar approval process.

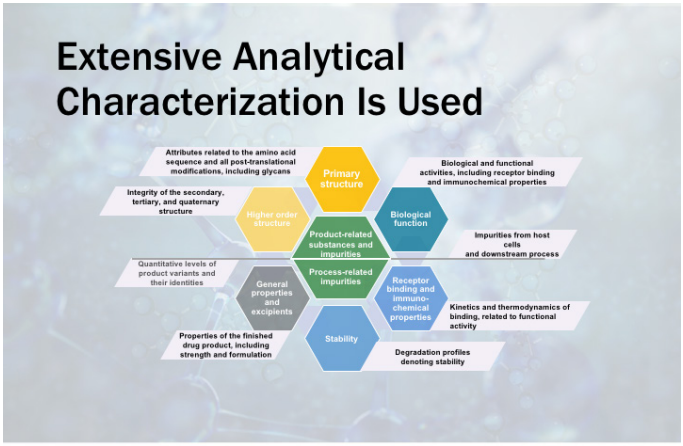


PK = pharmacokinetics
PD = pharmacodynamics

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed February 6, 2017.

Just to give you a snapshot of the extensive analytical characterization that is used, there are tools, which can outline the primary structure, there are higher order structures that can be identified by sophisticated physiochemical techniques.

Certainly, there are innumerable tests that are applied to demonstrate biologic function, and this has to do with immunologic function. These are particularly for those things that are monoclonal antibodies, do they have appropriate FC binding? Do they have appropriate affinity? Is there some symmetry to the glycosylation pattern? Will this affect their PK or PD? Obviously, impurities from host cells have to be

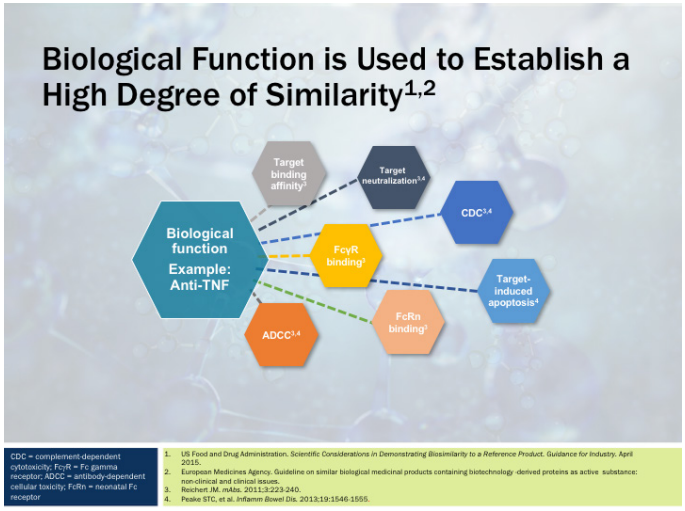


CQA = critical quality attribute

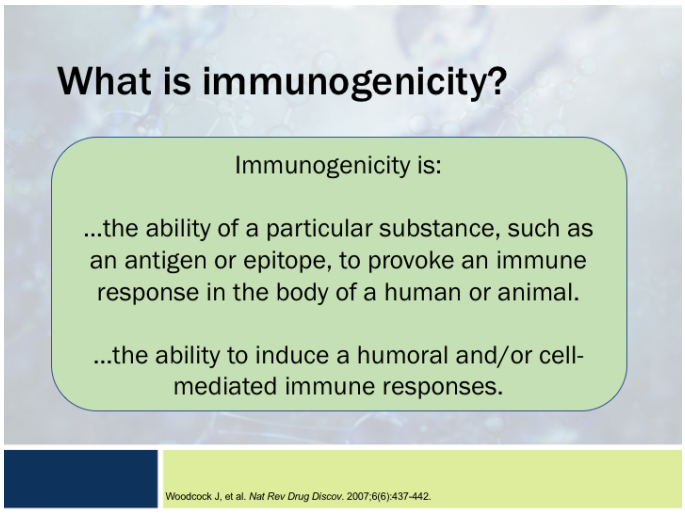
US Food and Drug Administration. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. Guidance for Industry*. April 2015.

eliminated, and then finally, the finished product has to have a similar pattern of excipients that have been added to the reference product so it's not altered in any type of vital way.

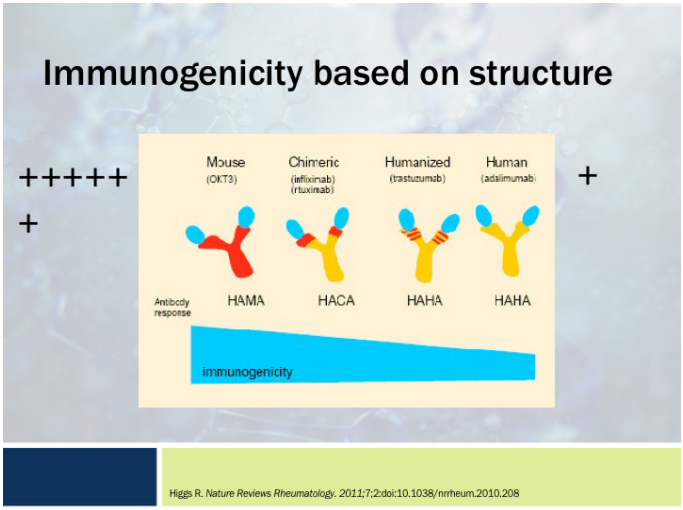
Here we see biologic function used to establish a high degree of similarity. I've already mentioned this, target binding affinity, confluent dependent cytotoxicity, will these induce target cell apoptosis? Is there FCRN binding, which would influence its metabolism and in vivo half-life FC binding and ADCC and beyond. A tall tale and a tall task ahead.



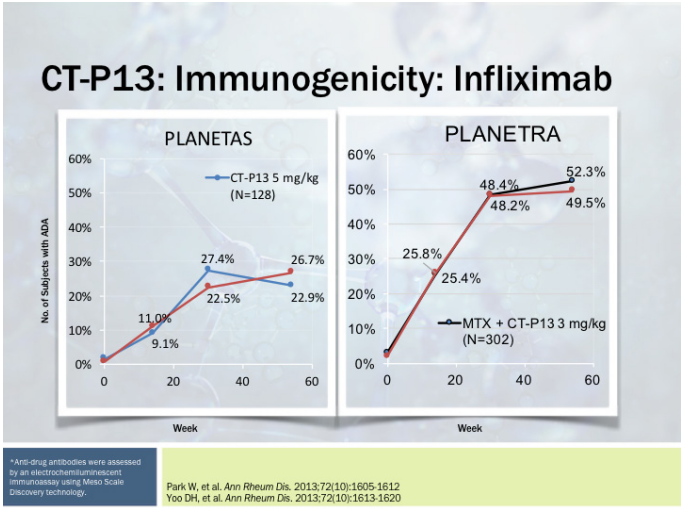
Finally, no discussion of biosimilars would be complete without at least mentioning immunogenicity. This is the ability of a particular substance such as the biosimilar and some component thereof, to elicit an immune response in the host. We call these anti-drug antibodies. These have been correlated with both toxicity and efficacy.



This little cartoon points out that on the left we have a purely xenogenic antibody, which could be of mouse origin or rat origin or something, highly immunogenic. The first biologics were chimeric, it means that largely in a human, but the FAB and variable regions may be of nonhuman origin. Certain compounds are humanized, that means that they're predominantly human but still have usually just the hypervariable regions expressed. Finally, we now have totally human, which means they meet a certain regulatory standard that there is a minimum reciprocity of xenogenic proteins.

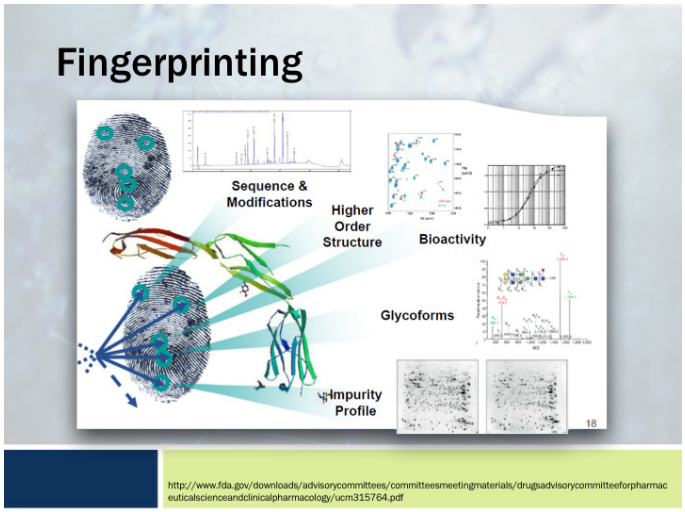


Here is some data of a biosimilar, infliximab, looking at CT-P13, looking at immunogenicity, and here you see the originator or the reference product and the biosimilar, and these lines are virtually identical.



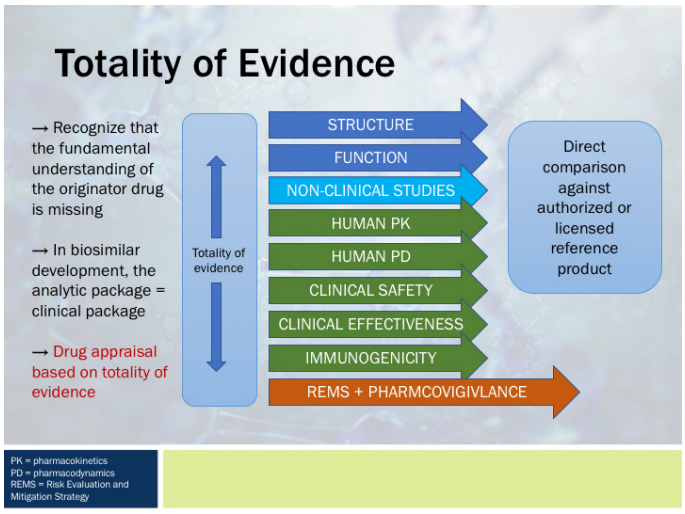
The totality of evidence is often referred to as fingerprint similarity. Here you can see mass spec analysis, all these higher order analysis of complex biologic data, bioactivity, patterns of glycosylation

which are not proprietary, and then patterns of impurities. All these are looked at.



This goes to make up what we now call the totality of evidence ranging from structure, function, nonclinical studies, all the PK/PD, and then finally clinical effectiveness and immunogenicity. That will determine whether there's any similar product of risk reduction or pharmacovigilance that will be needed. This is the groundwork of a biosimilar drug development.

I'm now going to turn this over to my colleague, Dr. Edward Li, associate professor at the University of New England, College of Pharmacy to address how biosimilars will impact clinical practice. Dr. Li.

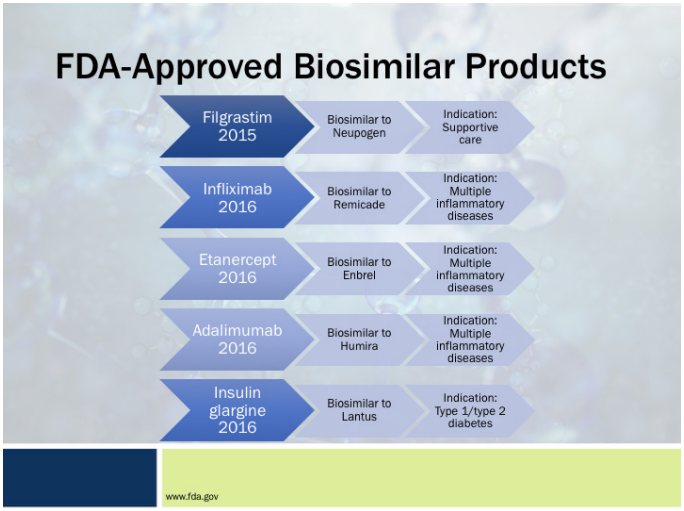


How Biosimilars Will Impact Clinical Practice

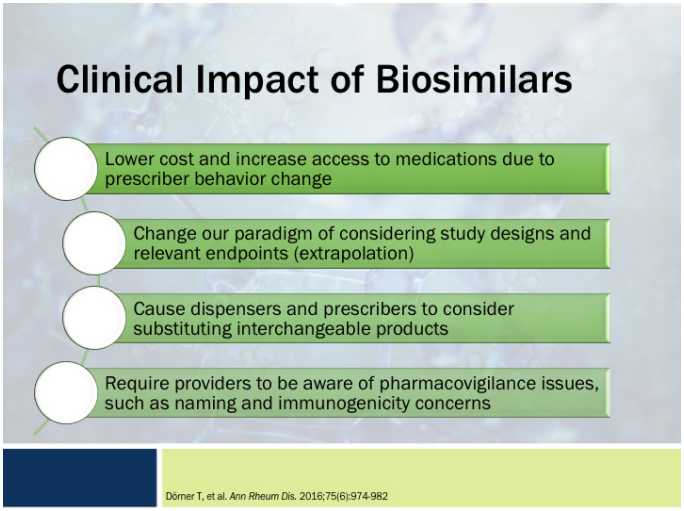
Dr. Edward Li: Thank you for that introduction. I'm an oncology pharmacist by training so most of the spin I'll be giving on this portion of the presentation will actually revolve on oncology as a specific example about how biosimilars will impact what we do in clinical practice. Before we get into some of the actual impact as far as how this new regulatory class of drugs will impact us in the clinics and in our practice, let's talk about what currently are the approved products out there that this biosimilar law allowed us to get approved.

We have a number of drugs, new biosimilars approved for indications ranging from this port of care of cancer, that's a filgrastim biosimilar to inflammatory diseases such as infliximab, etanercept, and adalimumab are biosimilars. Also, insulin glargine, although it's theoretically and from a strict regulatory standpoint, not a biosimilar. The data that was submitted with the biosimilar package, but it's really based off a technicality that Insulin glargine is approved currently as a new drug Through the new drug application process, it was classified as more of a follow-on biologic, but for all intents and purposes it was approved through submitting data that showed it was a biosimilar to its reference product. Of course, we know that its to be used for diabetes.

In terms of what are biosimilars going to do for us in our clinical practice and how we go about treating our patients, I think the first and foremost, the most important impact that it's going to have is to help to lower cost of this expensive therapeutics. These are really impactful therapeutic agents and we know them to be very expensive. Through lowering costs perhaps we're going to see a behavior change in how we use these products, which will hopefully lead to an increase in access to these medications.



We all know that the principle is that as cost approaches zero, utilization of that particular product will increase. This also changes our paradigm in terms of looking at the study designs and the relative endpoints in terms of how we review our products for formula consideration. It also changes our paradigm and our thinking about now dispensing and substituting these biological products out in the real world. Before we were operating in a world of substituting generic products, but this class of medications now will have us start to think about substituting biological products in addition to small molecules.



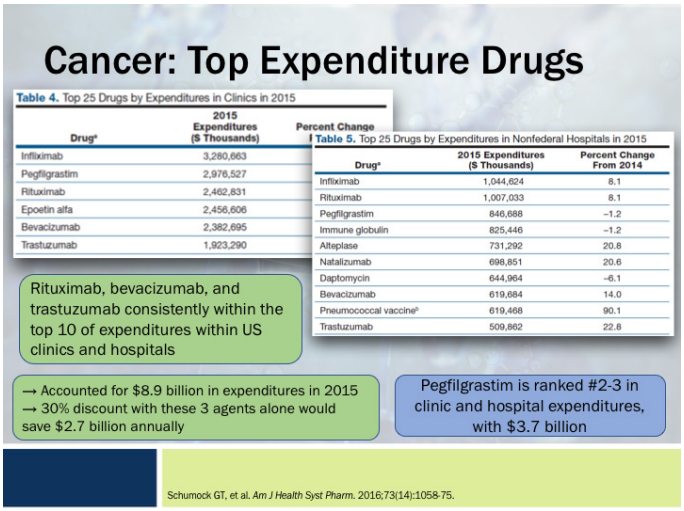
Lastly, I think our role as providers is to be aware of pharmacovigilance issues again because of the issues regarding immunogenicity as previously described, and how pharmacovigilance really spins them to different regulatory standards such as naming of biologics and biosimilars.

Let's start off with cost considerations and what we think about how biosimilars will affect the overall cost of these products in the United States and how that's going to change what we do. If we look at the top expenditures in the United States, this is our report that we publish every year in the American Journal of Health-System Pharmacy. Our updated report will be published in just a few months, a month or two.

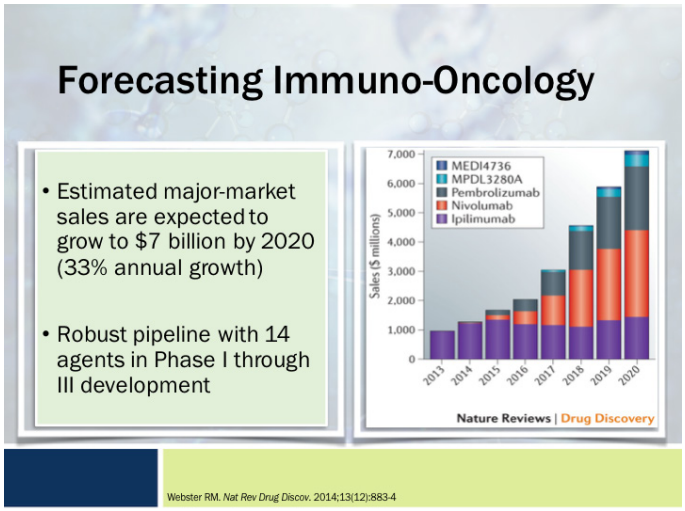
This particular data is from 2015. So if we look at the top expenditures in clinics—these are physician offices, primarily—we see that the highest utilization and expenditures would be essentially the biological products. Things like infliximab, pegfligrastim, rituximab, epo, bev, and trastuzimab, bevacizumab and trastuzimab. You can see how a lot of these products are used in cancer.

If you look at the top 25 drugs in hospitals they're pretty much the same in terms of infliximab, iituximab, pegfligrastim, being up there as well as bevacizumab, trastuzimab being on that list as well. You can see that's, again, the big 3 cancer drugs, rituximab, bevacizumab, and trastuzimab are consistently within the top 10 of expenditures within the United States in the clinics and hospitals channels.

If we were just to do a little bit of arithmetic and think about if there was just simply a 30% discount on these 3 agents alone that would save us about $2.7 billion annually on this. That's a lot of money to be using for other, potentially, other products. The other side of this is pegfligrastim is ranked typically around number 2 or 3 in clinic and hospital expenditures, with about $3.7 billion spent in 2015. There's a lot of room for improvement in terms of lowering the cost and being able to lower the overall cost of care in the United States.



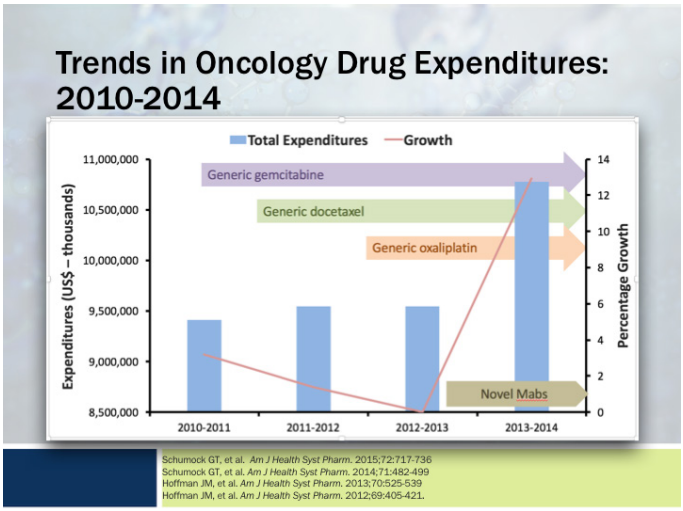
The other thing that we have to think about is specifically in oncology the focus is now on what we call immuno-oncology agents. These are checkpoint inhibitors that essentially prime the immune system to recognize cancerous cells in the body. We already have 3 checkpoint inhibitors approved, that's ipilimumab, nivolumab, and pembrolizumab, and these drugs, these biologics, are seeing enormous growth in their utilization and expenditures in the United States. It's actually estimated that this whole class of medications by 2020 will reach about $7 billion in the United States. You can see that graph on the right hand side just escalate up. Actually, I can tell you that in 2016 it's actually outpacing this particular forecast right now. So it's probably going to be far more than $7 billion by 2020. Also, this is a focus of the pipeline as well. There's many, many drugs in the pipeline in various phases of their development.



What is our health care system going to do to pay for these novel therapeutics that have a favorable toxicity profile and a favorable efficacy profile as well? How are we going to pay for that? To get the answer to that, in terms of one strategy to do that, we have to look at history in terms of how we paid for new products before the era of biosimilars. What we did was we looked at all of our expenditure reports going back to 2010. You can see that the blue bars are the actual total expenditures of just oncology products in the United States, and the red line is the percentage growth from the previous year during that time period. You can see that from 2010 to 2013 there's really not much growth in oncology drug spending in the United States. But in 2013 that's when our spending really started to escalate. For 2014, '15, and '16 it just continues to rise.

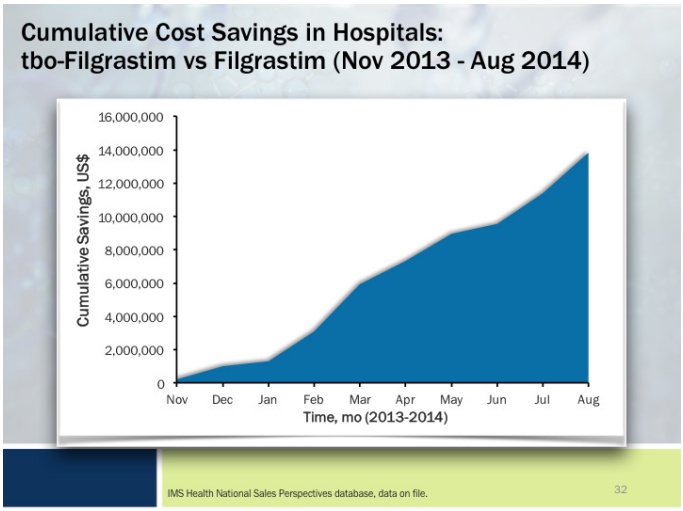
What really happened during that time that allowed this moderation of growth this was generic gemcitabine was starting to become more prevalent. Docetaxel, generic docetaxel, was approved, and generic oxaliplatin was approved during that time. Those were the 3 most expensive cancer drugs at the time, which suddenly became generic. By allowing providers to have this increased competition, and be introduced in the marketplace, this helped to moderate the growth of oncology drug expenditures during this time period.

Whereas in 2013 to 2014, and every year since then, there really hasn't been a blockbuster drug that's actually gone generic that helped to moderate the growth. So that's what we're seeing here today in terms of why these expenditures are continuing to increase.



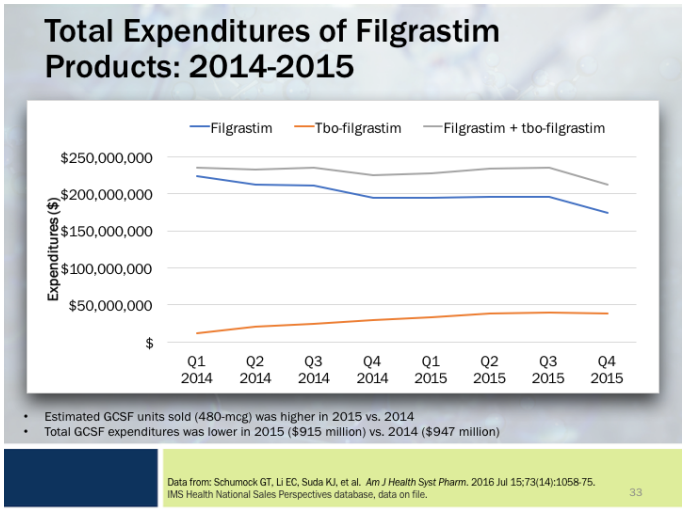
Here's another example with some cost savings once you introduce some competition with another filgrastim product. This is tbo-filgrastim—while it's not approved as a biosimilar in the United States—the equivalent product is actually biosimilar in Europe. So the whole concept of competition applies in this situation where if you looked at a 1-year period of time you could see that there's a cumulative cost savings in terms of this.

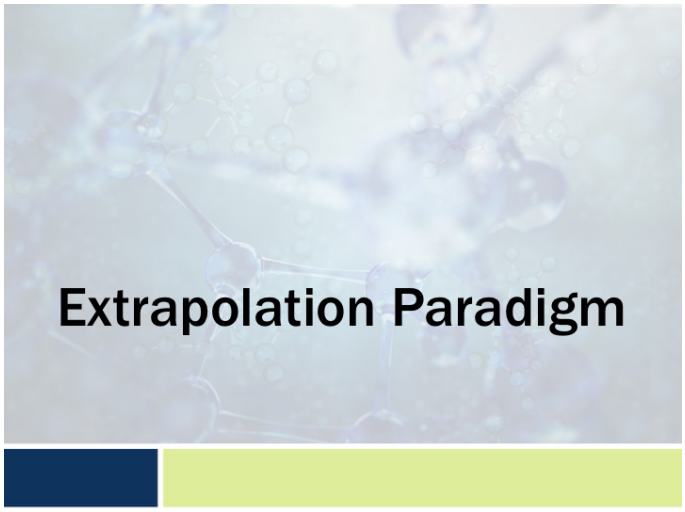
In this particular analysis, if you just replace tbo-filgrastim utilization with the cost of filgrastim, the difference between reality and that scenario would have been about $14 million in terms of this particular timeframe. You can see that there's significant cost savings to be achieved just through competition itself.



Again, when you look at the real-world patterns of filgrastim products, that's filgrastim and tbo-filgrastim, you can see kind of this moderation. It's starting to moderate in terms of the total decrease in myeloid growth factor spending as market share of the

competitor product started to increase. I can tell you that when you take this data out to 2016 it looks a lot better than the spending actually has decreased even more because of the introduction of the biosimilar filgrastim products as well. So that's essentially the summary of the cost considerations and how, hopefully, this increased competition will help to moderate the cost in practice.

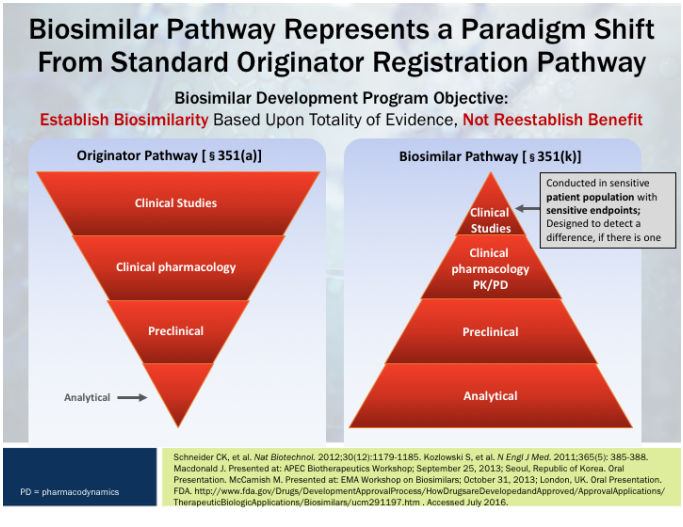




The second aspect of how this is going to influence what we do on a day-to-day basis is the whole concept of evidence-based medicine and understanding this extrapolation paradigm. To do that we have to look first at kind of how the biosimilar pathway compares with the branded or standard originator registration pathway. Remember that the originator when a new molecule is approved, the purpose of the regulatory approval pathway is to demonstrate benefits, demonstrate efficacy and safety of that particular product.

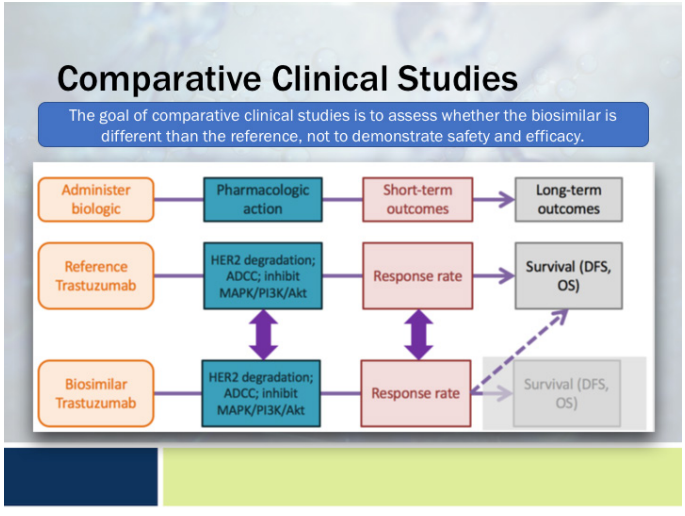
In that situation, yes, you know, analytical studies are going to be done, preclinical studies, and clinical pharmacology studies, PK/PD studies are going to be done. But really, what we focus on as clinicians and where the data is extensive in its development and its resource utilization to get it approved is under the clinical studies. As clinicians, we spend a lot of time discussing these clinical trials. We do a lot of journal clubs with our students and our colleagues, and we talk about the clinical studies a lot in order to inform how we're going to use that in our patient population. However, with regard to the pathways, the purpose of the regulatory approval is not to establish benefit in terms of efficacy and safety, but the purpose is to establish biosimilarity and how this molecule, the biosimilar, compares to the originator molecule to ensure that there are essentially no clinical differences between the 2 products. So you can see that the paradigm is much more focused on the analytical part of the data package, the structure of function, the preclinical pharmacology assays, the clinical pharmacology program, PK/PD studies are going to be important as well. The clinical studies are actually the least important or the smallest triangle as part of this pyramid because that simply is the cap of the data package—the double check that's conducted in a sensitive patient population using sensitive endpoints.

This study is designed so that if there was a difference between the 2 products we would be able to detect that difference in a sensitive endpoint in a sensitive population of patients. So again the exercise in those clinical studies is not to demonstrate safety and efficacy, it's to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product.



So what's a good example of this in the oncology world? A good example is for something let's say trastuzumab and biosimilar trastuzumab. So if you can think about how we get to the long-term outcome we want, which is disease-free survival or overall survival with trastuzumab when we administered biologically expect the pharmacologic action and we expect a certain level of PK/PD metrics and that informs our short-term outcomes, which is response rate, which will then translate into long-term outcomes that we want to see. We know what the pharmacologic action of reference trastuzumab is, and we know what the response rate is, and we know what the kind of survival data is with reference trastuzumab. That's all been well documented. So the biosimilar trastuzumab, then—before it's even administered to patients—it's developed through that reverse engineering again, concepts where the structure and function will be highly similar to the reference trastuzumab, so it's pharmacologic action will essentially be the same as reference trastuzumab. Again, it's not on here but the PK/PD studies are done to inform that those are essentially going to be the same, as well, in terms of pharmacokinetics and pharmacodynamics. So the clinical comparison to again, confirm that there are no clinically meaningful differences between biosimilar trastuzumab and reference trastuzumab is that response rate. If that's similar to each other then there's really no reason to believe that there would be any difference in the long-term outcomes that we want to see which is survival, such as disease-free survival and overall survival, right?

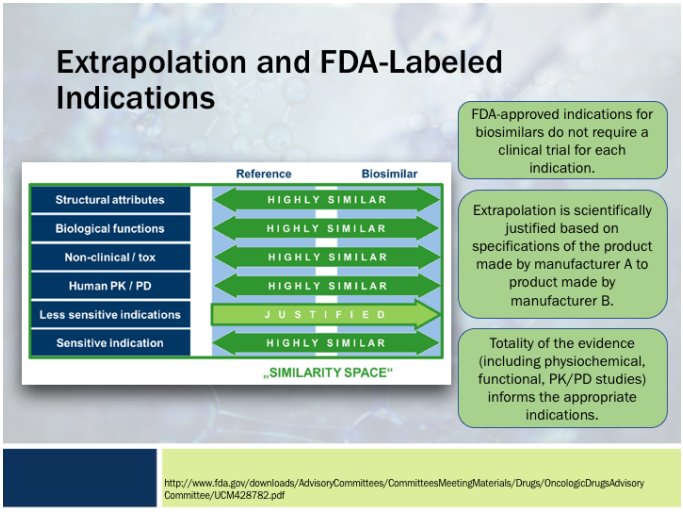
Again, if the purpose of the regulatory exercise is to demonstrate that comparability not to demonstrate safety and efficacy of the product.



That's one specific example in one specific indication, but again, if a biosimilar is going to be approved for all of the reference products, FDA-approved indications, there has to be some sort of justification to allow that indication to be in the products labeling. Going back again to the concept of this exercise, it is not to demonstrate safety and efficacy. The data package—to allow the FDA to approve the biosimilar for all of the reference products indications—is based off of a concept called extrapolation based on scientific justification.

So unlike the reference product the biosimilar doesn't need to conduct a clinical trial for each indication. And the reason for this is because if the structure of the biosimilar is the same or is highly similar to the reference, as is the biological function, as is the clinical- the non-clinical studies and toxicology studies, as is the human PK/PD studies, and again, all of this is submitted to the FDA for their review, and there is a clinical study in the sensitive indication. Again, what sensitive means is that if there was a difference that between the biosimilar and the reference product you'll be able to pick that up in that population. So if that's highly similar then there's really no reason to believe that you can't justify using the biosimilar for all the other reference products indications as well.

Again, that's based off of the scientific justification, based off the totality of the evidence that includes the physiochemical studies, the functional characteristics, the PK/PD studies, and all of the clinical data as well.

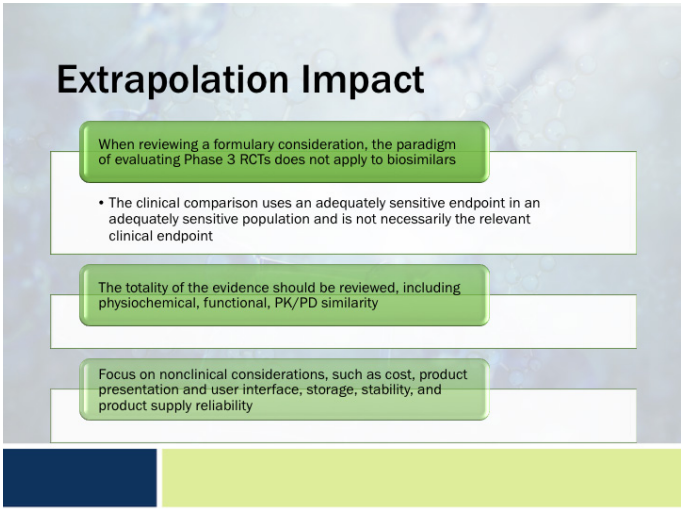


So what does this paradigm do for us and how does this will affect us as clinicians? Well, remember when we do our formulary reviews we are looking at those randomized phase 3 control trials that demonstrate safety and efficacy for a particular indication. However, when we review by somewhere else for formulary considerations we're not going to see those phase 3, the same phase 3 randomized controls trials that the reference product had. Again, because if that clinical comparison using an adequately sensitive endpoint in an adequately sensitive population.

So that endpoint may not be the clinical endpoint that we want to see to demonstrate safety and efficacy. Again, that's not designed to look at that. That's not the purpose of the biosimilar exercise. If we were married to the evaluation of these randomized phase 3 control studies, we're really going to think that biosimilars then don't have the same level of data. So it really has to change our thinking in terms of what data do we need to look at for formulary considerations. So the data package that we should be looking at is pretty much the same data package that the FDA looks at, which is the totality of the evidence.

So it's including that physiochemical features, functional studies, PK/PD, and also those clinical comparison as well. I think the FDA briefing documents that submitted and publicly available online would be very helpful to look at when we do our formulary considerations as well. They include their interpretations of the evidence and whether or not the FDA staff believes that it actually is a biosimilar, and to what extent there is similarity between the 2 products. So this can be really helpful resources to look at when we look at these products for formulary considerations.

The other aspect is we should also focus on those nonclinical considerations, as well, because again, to be approved as a biosimilar these products have to be not clinically significantly different from each other. So we're going to focus on those nonclinical considerations such as the cost of the product, which product we can get for a better cost, the product presentation, and user interface. So how this is handled, so it's something actually formulated in and presented to us in an auto injector, and a single-use syringe, or a multi-dose vial. And what's going to be the most advantageous to our practice in terms of using it in our patient population. We're going to think about storage and stability. There can be, within limits, some differences in storage and stability between the products.

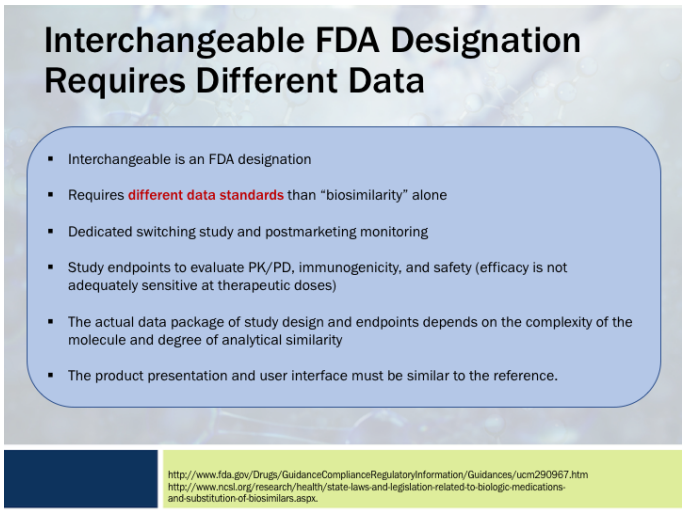


So there could be a situation where one product is more advantageous of storage or stability profile than the other, and the products supply and how reliable the supplies of getting these products are. We live in an era, at least in oncology, of oncology drug shortages. So knowing that you can get an adequate supply of the product is going to be very important as well. That concludes the extrapolation portion of that.

The other aspect we need to think about is substitution and how biologics will be substituted in real life. To understand substitution we need to go and look at this additional designation by the FDA, which is interchangeability.

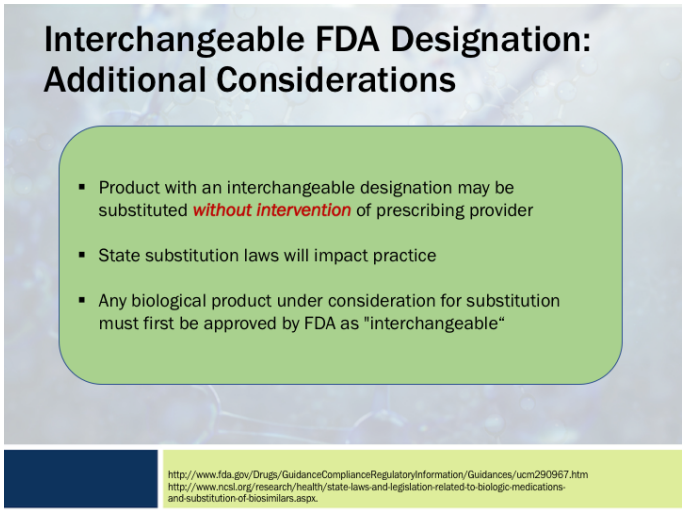
Again, interchangeability is an additional FDA regulatory designation that requires a different data

standard than biosimilarity alone. And what this means is that there need to be a dedicated switching study that's performed looking at some endpoints like PK/PD to ensure that if theoretically you switch back and forth between the biosimilar and reference product that you would actually achieve the same exact outcome as if you gave the reference product alone.



The impact of this interchangeability designation is that the FDA and the law actually makes it pretty clear that these types of products may be appropriate to be substituted without the intervention of the prescribing provider.

This impacts our state substitution laws for biosimilars and actually opens the door for state substitution laws to allow a pharmacist actually to substitute biological products.



So again, it's the state pharmacy practice laws that gives a person like myself, a pharmacist, the authority to act independently of the prescriber to dispense an equivalent, keyword being equivalent, a low cost and another keyword being lower cost, medicinal product. In certain states, we are mandated to do this not just to be given the authority, but actually mandated to dispense the lower cost product. The framework for substitution here is built upon the same framework as for the substitution of generic drugs.

There's a typically a product criteria attached to this. There's an FDA publication that rates the interchangeability and the equivalent of generic products vs their branded counterparts, and typically states you use that criteria for substitution, as the product criteria for substitution. In this situation that's going to be tied to the FDA interchangeability designation for biosimilars. DAW is an important part of it. The dispense is written in allowing no substitutions, so you know this as "brand medically necessary" or "no substitution" on the prescription, communicating with the prescriber and the patient that a substitution is made. In many laws about generic substitution, as well, record keeping or keeping records on substitutions is always important and not an issue in this digital age.

A lot of the state law framework includes hospital health system exemption and then if you have a robust formulary system and P&T committee then you're kind of exempted from this whole process.

So if you take a look at some of the enacted biosimilar substitution laws out there you could see that yes, there is that DAW provision in all of them, which we all agree is a good thing. The substitution criteria is all tied to the FDA designation of being

interchangeable. The difference really is in the record-keeping timeframe. Again, not a big deal of the digital era and the prescriber-patient communication can be a little bit different.

Again, some communication plans talk about informing through either phone calls or letters, but then some states allow for notification through a shared EMR.

Enacted Biosimilar Substitution Laws: Sample

State	DAW	Product's criteria for substitution/interchange	Prescriber/patient communication	Record Keeping
DE	Yes	FDA designated interchangeable or therapeutic equivalent	Inform patient; inform prescriber in 10 days	Same as generic law
FL	Yes	FDA determined interchangeable	Inform patient same as generic; EMR notification for institutions	2 years
VA	Yes	FDA determined interchangeable	Inform patient of cost; inform prescriber within 5 days	2 years
MA	Yes	FDA determined interchangeable	Inform patient and prescriber (no timeline)	1 year

DAW = dispense as written

http://delcode.delaware.gov/title24/c025/sc06/index.shtml
http://www.flsenate.gov/Session/Bill/2013/0365/BillText/er/PDF
https://leg1.state.va.us/cgi-bin/legp504.exe?131+ful+CHAP0412
http://www.foleyhoag.com/publications/alerts-and-updates/2014/june/massachusetts-enacts-new-biosimilars-substitution-law

So the common element for a substitution of interchangeable biosimilars again, is that they're all going to be tied to this FDA designation of being interchangeable. So a pharmacist would not be allowed to substitute a biosimilar for the reference if it wasn't designated as interchangeable by the FDA. The prescriber would be able to still write "brand medically necessary" or "dispense as written" to prevent that substitution. You can do that with branded products currently—for branded products for generics you can do that—so you should be able to do that for biosimilars as well.

The prescriber has to be notified in essentially all the substitution laws. Some of the laws they communicate with, but again you'll be surprised if you get notifications saying that somebody was substituted for the interchangeable biosimilar based off of this provision. Then again, patients must be notified in many of the states substitutions of law, and that's a good thing to just to inform patients of what they're actually getting. There are different variations between the states. Again, each state acts independently and decides on legislation that's appropriate for their population. So again, it's not going to be standard across the board.

Common Elements of Interchangeability Rules for Biologics

- ✓Biological product under consideration for substitution **must first be approved as "interchangeable"** by the FDA
- ✓**Prescriber** (physician, specialist, PA, etc) would be able to **prevent substitution** by stating *"dispense as written"* or *"brand medically necessary"*
- ✓**Prescriber must be notified** of any substitution. In 2015 bills, language adjusted to say *"communicate with"*
- ✓**Patient must be notified** that a substitute or switch was made. In some cases, state law requires patient consent prior to switch

State-to-state variations possible

National Conference of State Legislatures

All of the substitution goes into another aspect that's important to clinicians

Pharmacovigilance

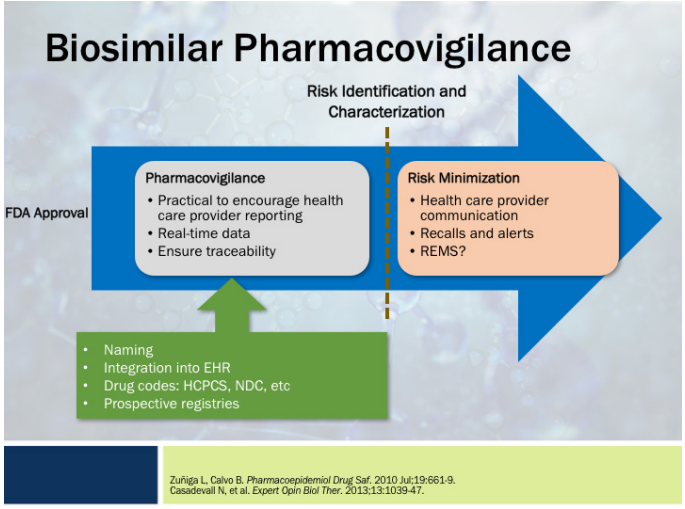
The last aspect that's important to clinicians, which is pharmacovigilance. And fairly broadly defined, pharmacovigilance is risk identification—post-market risk identification. This particular slide says biosimilar pharmacovigilance, but really you can just eliminate the word biosimilar from this and just call this pharmacovigilance in general, in that post-FDA approval…Because again, with all biologics—not just biosimilars, with all biologics—there is a risk that we didn't identify a rare but serious adverse event, before—in those registration studies, those preapproval types of studies—because the numbers are not robust enough to detect these rare adverse events.

So in terms of pharmacovigilance and being able to track these products over time, to identify whether or not additional risks exist is an important thing, and we've seen this happen and package inserts being updated based on safety events over the years. A good

example of that would be opportunistic infections with the TNF inhibitors and having those be updated over the years. A lot of that is based off of information that is collected that the FDA gets from health care providers and voluntary reports to the FDA about the risks that are identified in the broader patient population. Once a risk is identified and characterized that's the right hand side of the chart here, which the FDA will start to think about a risk minimization plan.

But we're not talking about the risk minimization plans right now, we're simply just talking about risk identification and whether or not there actually is a difference in risk between the biosimilar product and the reference product. To facilitate this kind of tracking and traceability and the data reporting, there's a bunch of ways that we could facilitate that. Number one is just integration of orders and robust medical records in the electronic health record and it's going to be important to be able to track the specific product that's actually being given to patients, integrating drug codes, like HCPCS codes and the claims, and being able to sort through those, through claims data studies, to identify risks.

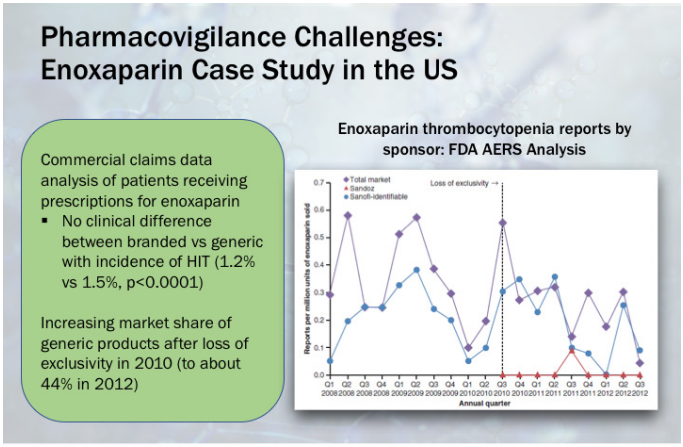
But also, the naming of these products is going to be important to help facilitate proper attribution of adverse events because really the important part of this is when adverse events are reported that the correct product is attributed to the adverse event. So it's not really going to be good enough just to say filgrastim caused the specific adverse event, but it's important to talk about which specific filgrastim product actually caused that particular adverse event, because now we are in an era of multi-source biologics.



Zuñiga L, Calvo B. *Pharmacoepidemiol Drug Saf*. 2010 Jul;19:661-9.
Casadevall N, et al. *Expert Opin Biol Ther*. 2013;13:1039-47.

So to really highlight why this is important in terms of correct attribution this is a case study that we performed on enoxaparin products looking at branded enoxaparin vs generic enoxaparin products. So we looked at claims data to look at the incidents of HITS with branded vs generic enoxaparin and saw essentially no clinical difference between the 2 products and the incidents of HIT. We saw market share for the generic enoxaparin increase after the loss of exclusivity in 2010, but the chart on the right hand side actually essentially says that a lot of the voluntary, spontaneous adverse event reporting was actually labeling the branded products over the generic products in causing HITS.

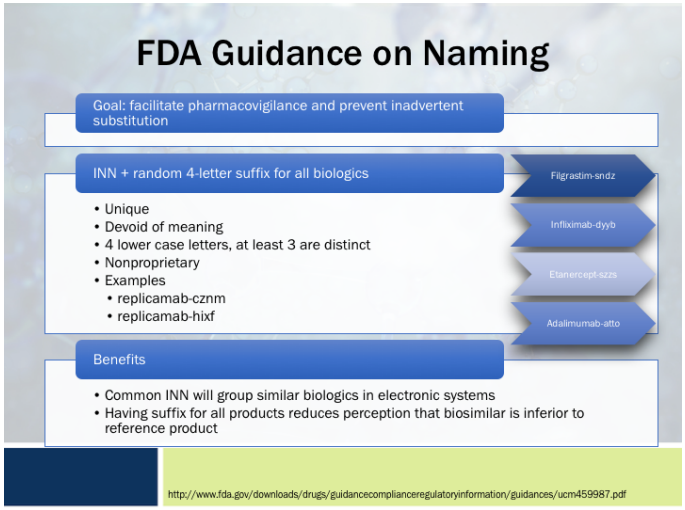
So a lot of that is questionable as far as do people know exactly which product they were getting. It was pretty unclear in terms of having a robust way of documenting exactly whether the brand or generic.



That's why the FDA came out with some more specific guidance on how they want these biosimilars to be named again to facilitate that pharmacovigilance that if you are going to report an adverse event this distinguisher in the name will help you facilitate that pharmacovigilance and report correctly which exact product actually caused the problem. So this guy just basically says that the FDA is going to institute a random 4-letter suffix to all biologics, so it's not just biosimilars—but the reference biologic—will have this 4-letter suffix as well.

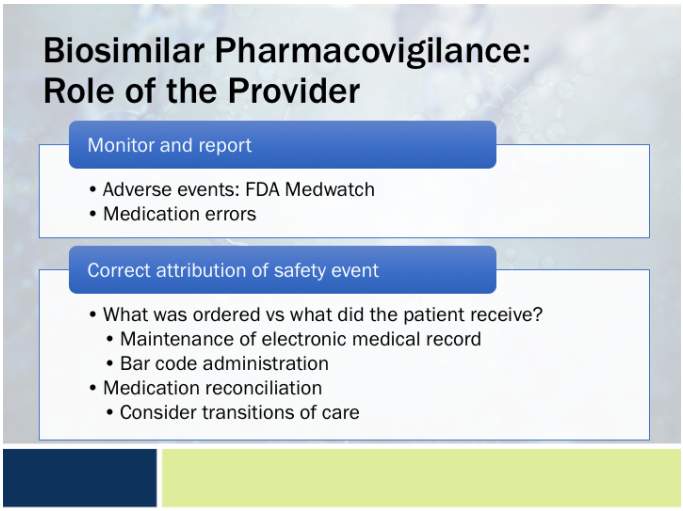
You can see the example here for a hypothetical biologic—replicamab. So you'll have hypothetically these 2 suffixes there and this allows the common nonpropriety name to be grouped together like in an

electronic medical record. Really the reason why the FDA made the suffix mandatory for all biologics now is to kind of reduce that perception that the biosimilar is inferior to the reference price, so if only the biosimilars had this perception that the biosimilar is inferior, when in reality it was just another mechanism to help track what product is causing what adverse events.



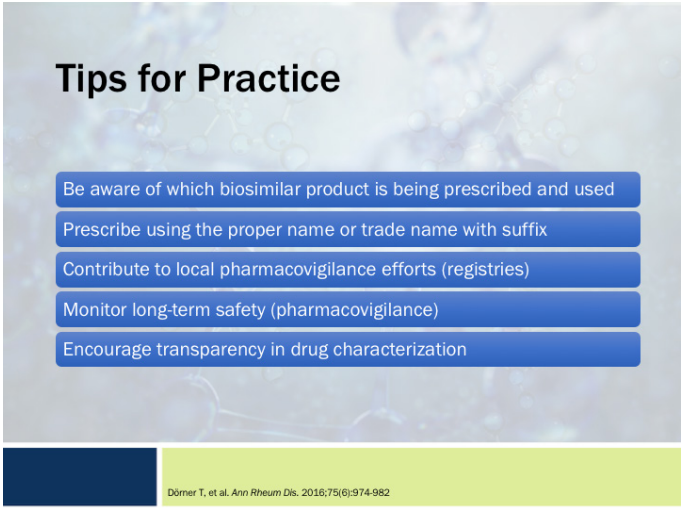
The role of the provider in pharmacovigilance then is mostly to monitor and report. Some of you out there may be involved in research and specifically outcomes research as well and will participate in perhaps this claims data studies. But for the most part, as the clinician, we're going to be doing mostly adverse event reporting, the voluntary reporting to FDA's mid-watch program. We want to avoid medication errors in that if it was intended for the patient to receive one product, but in actuality the patient received a different product, while there may be no clinically, you know, clinical consequence of that that's still is technically a medication error and something that should not happen. Those are things that we want to keep our eye on and report.

Again, it's a correct attribution of the safety event of what was ordered vs what did the patient actually received and then what the event actually was. We can facilitate that to robust electronic health records and medical records through bar code administration, through robust medication reconciliation, and thinking about when patients transition from different settings of care that it's well-documented, what particular biological product that they're actually getting. So that again, everybody is on the same page of what the person's getting.

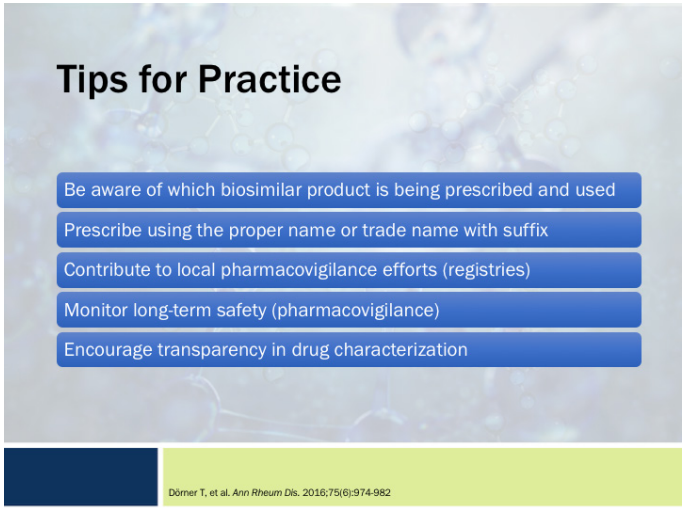


So that's it and I just want to end with a couple of tips for practice in terms of what we should be aware of in terms of biosimilars because again, the introduction of a new regulatory class of medication is going to just change around a little bit of what we do and add on onto our workflow a little bit of differences.

So the first is just being aware of what biosimilar product is actually being prescribed and used and really think about prescribing the product with either the proper name or the trade name with the suffix. You're going to have to think about how are you going to write the prescription if you're sending this to a specialty pharmacy, how you going to write this prescription. Do you care if it's been substituted or not and just being a little bit more aware of how that prescription is written to facilitate the actual product you want the patient to receive. Contribute to local pharmacovigilance efforts so that could be either to voluntary adverse event reporting, or just participating in prospective registries if there is one.



Monitor long-term safety of that so some of you again, might be involved in the research aspect in looking at either claims data, or doing reviews at your own institution and also to just encourage the transparency in the characterization of these products in terms of being aware of with the physiochemical characteristics of these products are. So that we're much more well-informed if there any differences between the products.



So with that, I'd like to conclude the presentation. At this point, I want to thank everybody for attending, and have a great day.

Participate in interactive questions, download activity slides, and obtain your CE/CME credit online.
https://annenberg.net/Understanding-Biosimilars-CME