EXPERT perspectives

NAVIGATING BIOSIMILARS: TRANSLATING EVIDENCE INTO CLINICAL PRACTICE

A CME ACTIVITY

FACULTY

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NAVIGATING BIOSIMILARS: TRANSLATING EVIDENCE INTO CLINICAL PRACTICE

CE/CME Information

Target Audience

This activity is intended for dermatologists, gastroenterologists, oncologists, rheumatologists, pharmacists, and other clinicians who currently use or are considering the use of biosimilars.

Learning Objectives

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

- Describe the complexity of biologics and the implication for the development of biosimilars
- Interpret the FDA's "totality-of-evidence" strategy used to evaluate biosimilars
- Weigh the clinical implications of biosimilars
- Develop strategies to educate patients on biosimilars and their potential impact on overall health care

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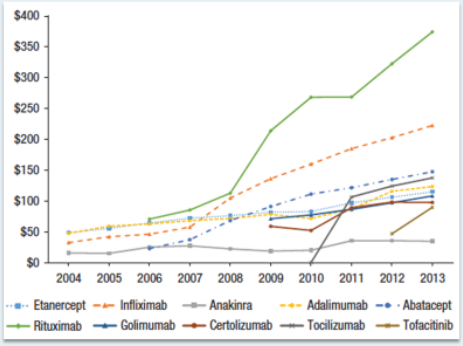
1 BIOLOGICS LANDSCAPE

Steven R. Feldman, MD, PhD: To begin, let's start by talking about the expenditures, from a patient perspective, on biologic treatment. Here we have data on average out-of-pocket expenditure for biologics by year and by medication. You can see over the last 10 years there's been a steady increase in patients' out-of-pocket expenses. Now for revolutionary treatments, these expenses may not seem enormous. On the other hand, they can affect patients' willingness to go on and stay on these treatments.

Average Out-of-Pocket Expenditure per Prescription for Biologic DMARDs by Year and Drug



Optum Clinformatics Data Mart database of 40,373 patients with rheumatoid arthritis from January 2004 to December 2013

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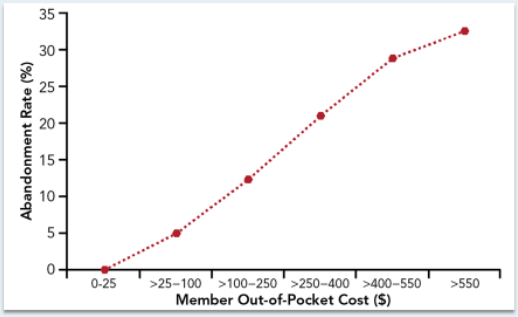
Atzinger CB, et al. *Am Health Drug Benefits.* 2017;10(1):27-36. Reproduced with permission of Engage Healthcare Communications, LLC.

Here we have the rate of prescription abandonment by out-of-pocket costs. Now this is one of the critical aspects of adherence to treatment. You would think that patients with severe immune disease—given a very effective therapy—would take their medicine, but as their out-of-pocket costs increase, there's greater and greater likelihood that they're not going to fill the prescriptions.

Rate of Prescription Abandonment by Out-of-Pocket Cost



Medicare Advantage and Prescription Drug plan for biologic disease-modifying antirheumatic drug therapy for 864 patients with rheumatoid arthritis from July 2007 to December 2012.

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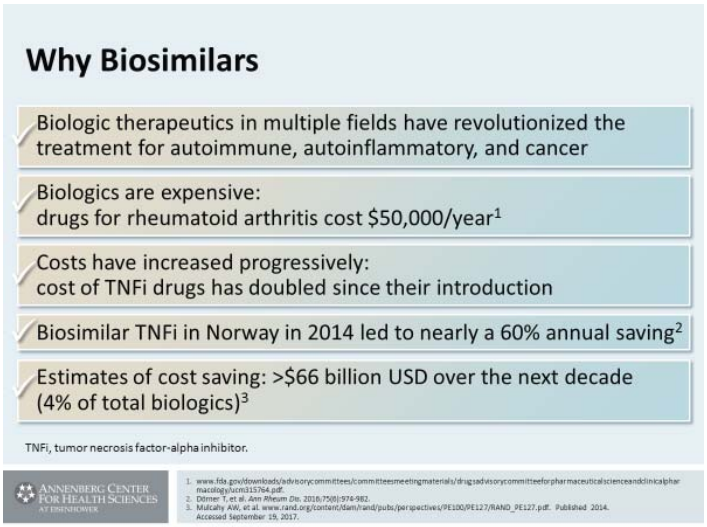
Hopson S, et al. *J Manag Care Spec Pharm.* 2016;22(2):122-130.

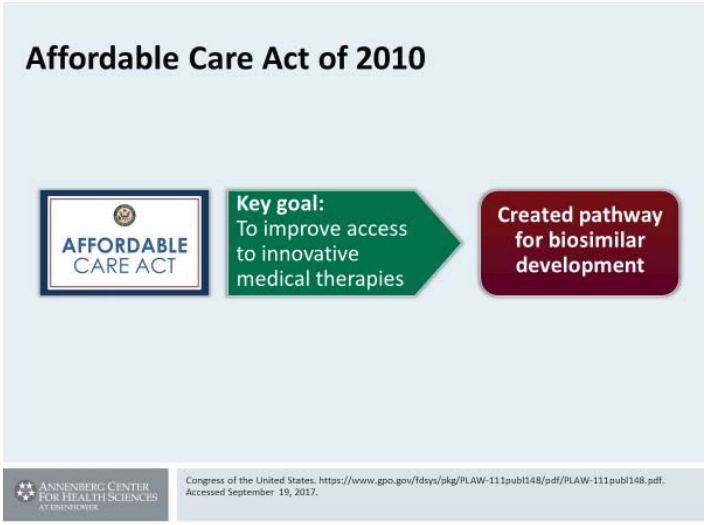
Even when they fill the prescriptions, they don't always take the medication. I like to ask my patients who are on self-injected biologic treatment, "Are you keeping the extra injectors that you've accumulated refrigerated like you're supposed to?" Patients think that I'm asking about refrigeration. And if they've accumulated some—whether they refrigerate it or not—they'll probably tell me that they are refrigerated. But this is a way I can tell whether patients are taking their medicine or not. If they're taking it properly they would tell me, "I don't know what you're talking about. I don't have any extras lying around." We have to keep adherence in mind of both primary nonadherence, from not filling the medication in the first place, which can be due to the cost of drugs, and secondary nonadherence, where they get the medicine, but they don't take it well.

Why are people interested in biosimilars? Well, first of all, biologics have revolutionized the treatment of inflammatory diseases. I specialize in the treatment of psoriasis, and biosimilars have revolutionized my ability to care for my patients with severe psoriasis. At the same time, biologics are

very expensive. Drugs for rheumatoid arthritis may cost $50,000 a year, and those costs have progressively increased. The cost of tumor necrosis factor inhibiting drugs has doubled since their introduction. Now, biosimilar introduction in Norway led to a nearly 60% annual savings. The estimated cost savings in the United States is something like $66 billion predicted over the next decade, which is a big number even though it may represent only a small proportion of the total expenses on biologics.



The Affordable Care Act of 2010 was designed to improve access to innovative medical therapies. It created a pathway so that biosimilars could be developed, with the goal being to bring down the cost and increase access to these revolutionary drugs for our patients.

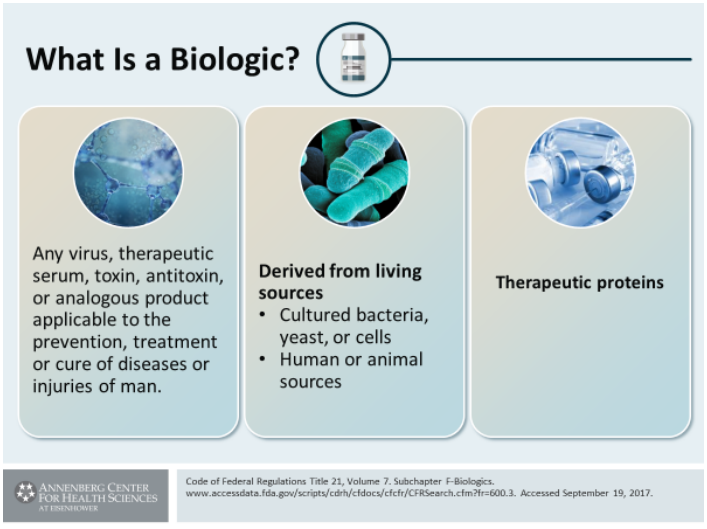


Now that we've learned about the landscape of biologics, let me just summarize. Biologics have revolutionized the treatment of severe inflammatory diseases. I find them to be very safe and very effective and unfortunately very costly. Biosimilars are being developed that may reduce those costs somewhat.

2 BIOLOGICS AND BIOSIMILARS

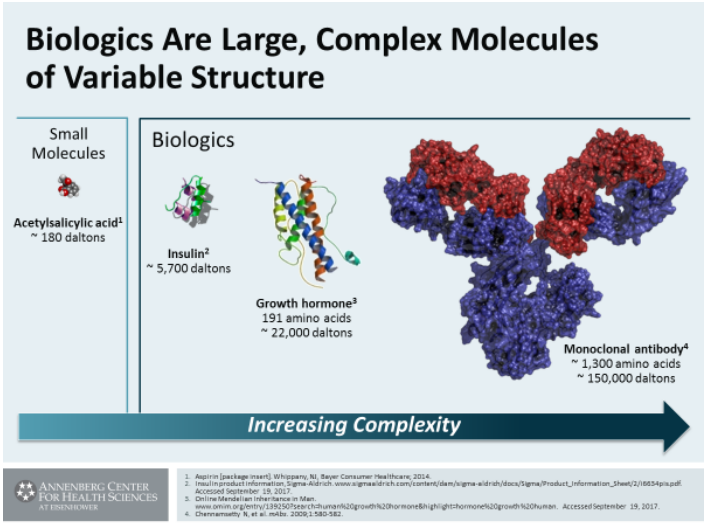
Steven R. Feldman, MD, PhD: This is the gray line in which we will discuss key characteristics of biologics and the 2 pathways for developing a biologic in the United States. We'll also learn that biosimilars are not generic versions of the reference biologic. There are major differences in how generic small-molecule drugs and biosimilars are developed.

What is a biologic? Biologics are viruses, therapeutic serums, toxins and antitoxins, and similar products that are used for the prevention, treatment, and cure of diseases in humans. They're derived from living sources. Typically, they could be either derived from a human or an animal, or made in cultured cells, bacteria, yeast, or other cells. Ultimately, from these, come our therapeutic proteins.



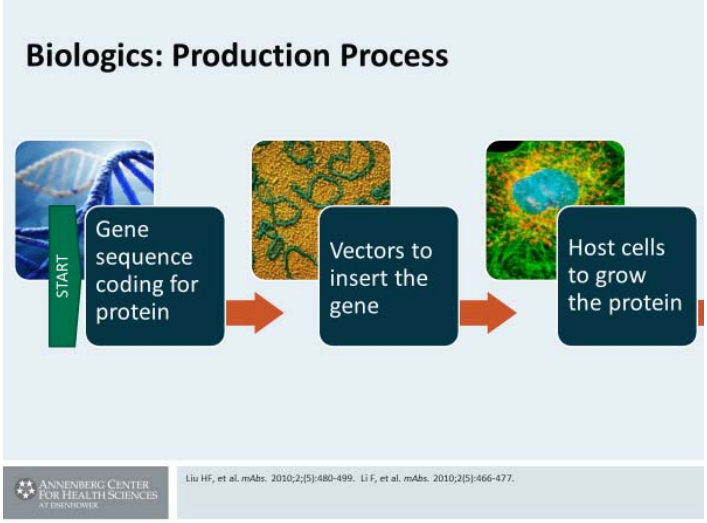
Biologics are large molecules and they're very complex. Their structures are much larger and more complex than the small-molecule drugs that we've traditionally given to patients.

You can compare here, aspirin vs insulin. Insulin, considerably more than 10 times as large. Growth hormone is another factor of 4 larger than that and the monoclonal antibody drugs are absolutely enormous, maybe 1,000 times larger than an aspirin molecule, and they are complex structures. Typically, we think of them as protein molecules, but they're glycoproteins. There's going to be sugar molecules attached to the chain that create additional potential for variability, and the folding of these complex molecules may represent another area where there can be complexity.

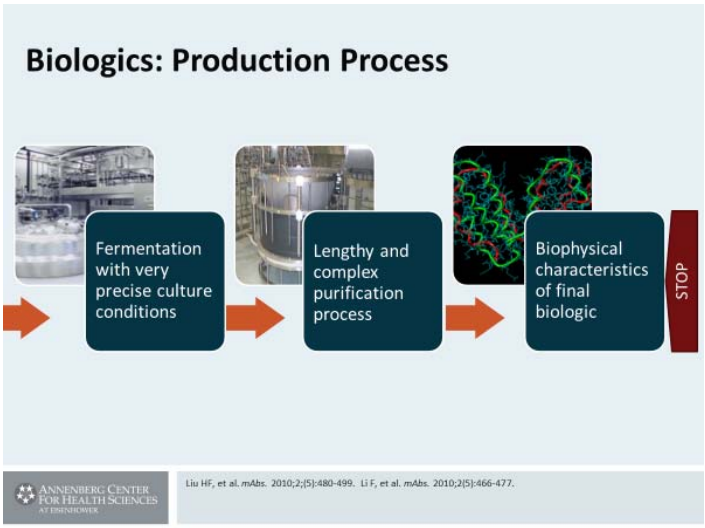


Now, some variation is acceptable within and between medication. Generally, if a drug provides 80% to 125% of the blood level at 90% confidence interval, that's considered acceptable similarity. Biologics provide a more complex question because it's not just the amount of the drug in the blood level that has to be within an acceptable range, but the variability in the complex molecule has to be similar as well.

The biologic production process is complicated and has a lot of room for potential variation. To start off, we're going to try to make a protein, but we start with the gene for that protein. That can be made identical. You know what the genetic coding sequence is, so if you were going to make a biologic or a biosimilar, you would use that same genetic coding sequence. You would insert that gene into some cell that would grow and make the protein.

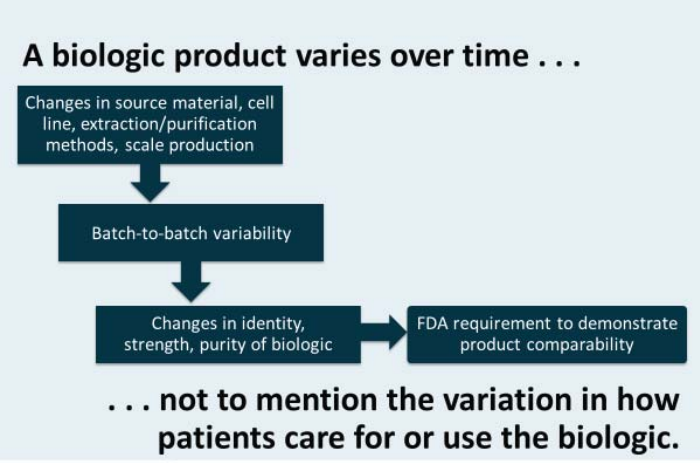


Now, there's a lot of potential variation in those host cells and then those cells are cultured under very precise conditions, but tiny little changes in those conditions could affect the carbohydrate that gets put onto the protein, the tertiary structure, the folding of that protein molecule, the charge on that molecule, and whether that protein aggregates or not. This is followed by a purification process designed to remove the host cell DNA and other proteins, the aggregates. The protein is eventually concentrated and put into some final formulation, but again, there's a lot of potential for variability there.

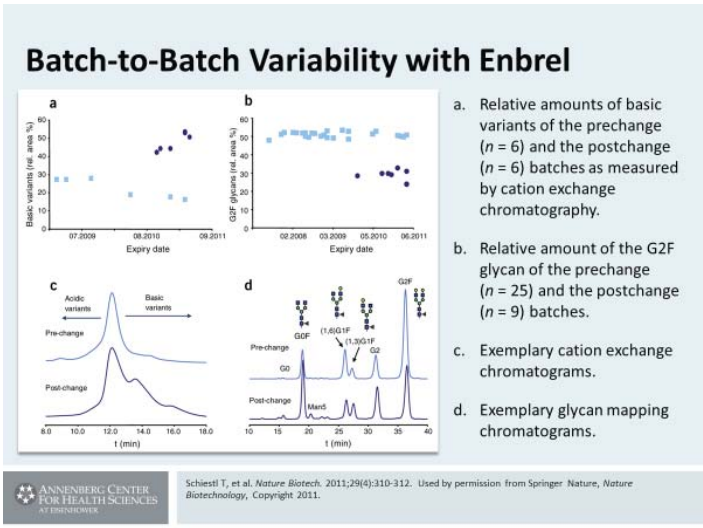


Ultimately, you get this final biologic that's a complex protein with sugar molecules on it and a variety of charges. The biologic product is so complicated that nobody can duplicate it, not even the originator company, and so these biologic products vary over time. Part of that variability will be due to changes in the source materials that are used, if there was a change in the cell line or the purification procedure. There's going to be batch-to-batch variability.

One batch is not going to be identical to the next batch, and the manufacturer needs to show that the product is comparable. It can't be identical because nobody can duplicate these structures completely perfectly.

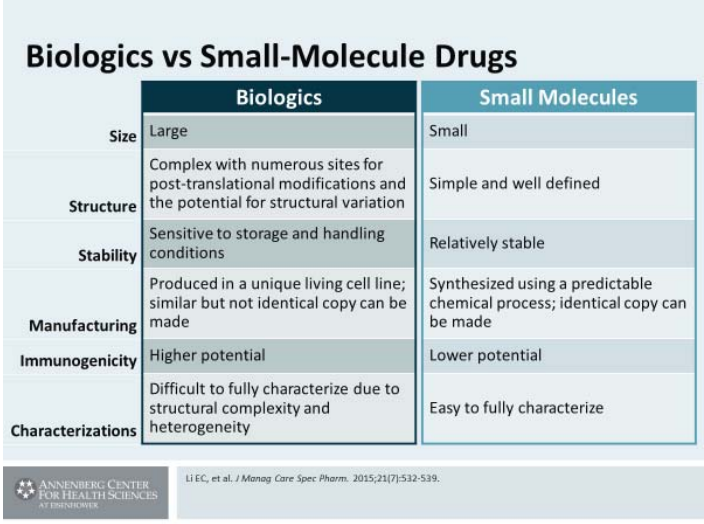


Batch-to-batch variability has been carefully assessed for different batches of the product etanercept. Here you could see a variety of studies, including differences in the percentage of basic variants, differences in the glycoprotein structure, and these vary from batch to batch, and even over time patients might go . . . at one time they might be on one batch and then switch to a different batch. Changes in the production process can lead to differences. In section C there, you see the change in the basic variants that happens after a change in the production process.



I think when we think of biologics, you think this is a single drug, but, in fact, if you run it through a separation column, you find that it's a mixture of different structures with different glycoprotein structure. From batch to batch, those structures might change. Now, all of these batches are called Enbrel, despite there being this variability.

Let's consider how biologics differ from small molecules. Well first, it's the size. The biologics are enormous and the small molecule's really quite small, certainly in comparison. The structure's very different. The small molecule has a simple, well-defined structure. A biologic has a complex structure that has folding, and carbohydrates added to the protein structure. The protein sequence for biologics will be the same from batch to batch, but how that protein folds, and what post-translational modifications are done to it, can vary. Small molecules are relatively stable, whereas biologics, which are large protein molecules, are sensitive to the storage and handling conditions.

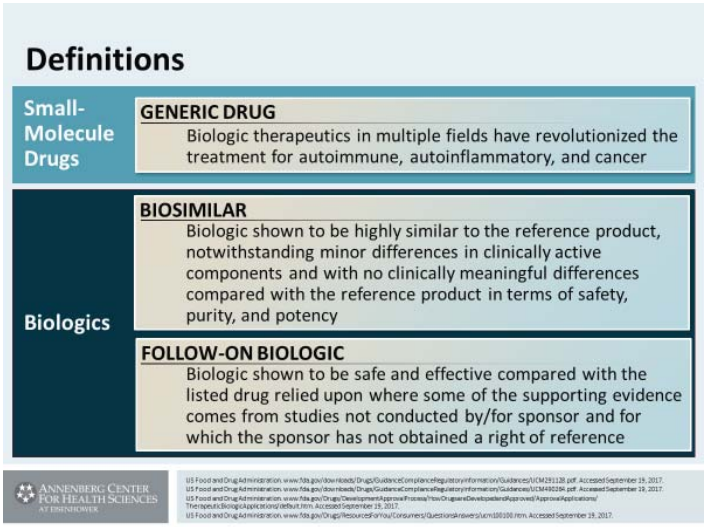


	Biologics	Small Molecules
Size	Large	Small
Structure	Complex with numerous sites for post-translational modifications and the potential for structural variation	Simple and well defined
Stability	Sensitive to storage and handling conditions	Relatively stable
Manufacturing	Produced in a unique living cell line; similar but not identical copy can be made	Synthesized using a predictable chemical process; identical copy can be made
Immunogenicity	Higher potential	Lower potential
Characterizations	Difficult to fully characterize due to structural complexity and heterogeneity	Easy to fully characterize

The manufacturing process is different. Small molecules are synthesized by a predictable chemical process and so you can make the same thing over and over again. As we saw with biologics, they're produced in living cells and by a complex process, complex purification afterwards. You can't make identical copies from batch to batch with this approach. Immunogenicity can be different. With small molecules we

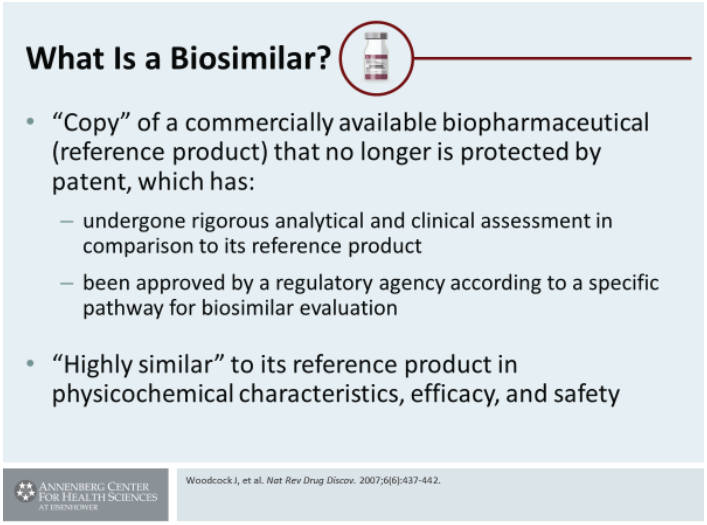
don't have to worry much about immunogenicity, with biologics we do. To characterize: these small molecules are relatively simple to fully characterize, whereas biologics would require a host of studies to fully characterize the molecule.

Let's define some of what we're talking about. With the small molecule drug, when you make a generic of that, it's basically chemically identical to the branded drug. The blood levels that you achieve when giving those drugs has to be within a certain range and the chemical is identical for all practical purposes. With biologics, it's much more complicated. You have 2 options. You can make biosimilars to the biologics, and you have to show that they are basically identical to the reference product, with no clinically meaningful differences compared to the reference product in terms of the safety, purity, and potency. I think of it almost like making another batch of the innovator. It's not going to be identical, but it's going to be so similar that there's not going to be any clinically meaningful difference.

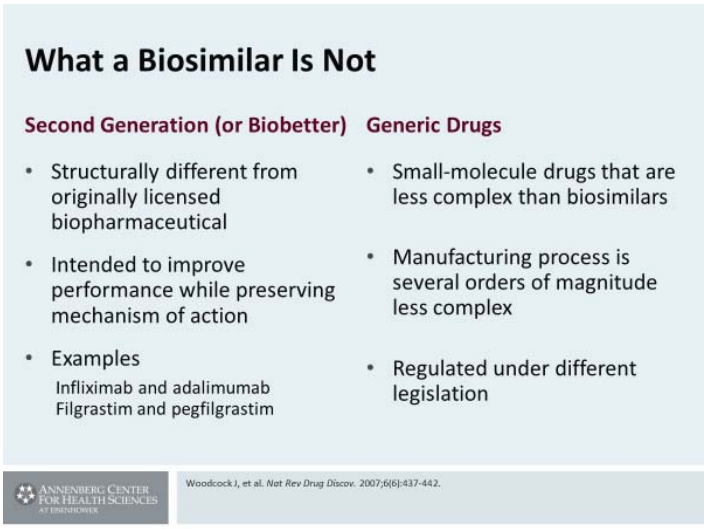


Follow-on biologics are different. Those, you would have to show, are safe and effective compared to the original drug.

Now, we're going to be focusing on biosimilars. What is a biosimilar? It's basically a copy—as near as you can make one—of the commercially available reference product. A reference product is no longer protected by patents, and these biosimilars undergo very rigorous analytical assessments to make sure they're similar to the reference product and, in addition, they undergo some clinical assessment to absolutely prove, as best you can, that it's going to perform basically like another batch, as the reference products would. They're approved by the regulatory agencies according to a specific pathway. The biosimilar is highly similar to the reference product in its physicochemical characteristics, it's efficacy, and its safety.



Now, biosimilars are not biobetters or second-generation biosimilars that are different from the original. The second generations are structurally different. They're intended to perform better, maybe using the same mechanism of action. For example, you have had infliximab and then add adalimumab. Both are TNF inhibitors, but they're very different drugs. They're not biosimilars. Biosimilars are also not generic drugs. In the same way that small molecules differ from large molecules, generics differ from biosimilars. The small-molecule generics are so much less complex that they're basically identical and they're regulated under a different pathway.



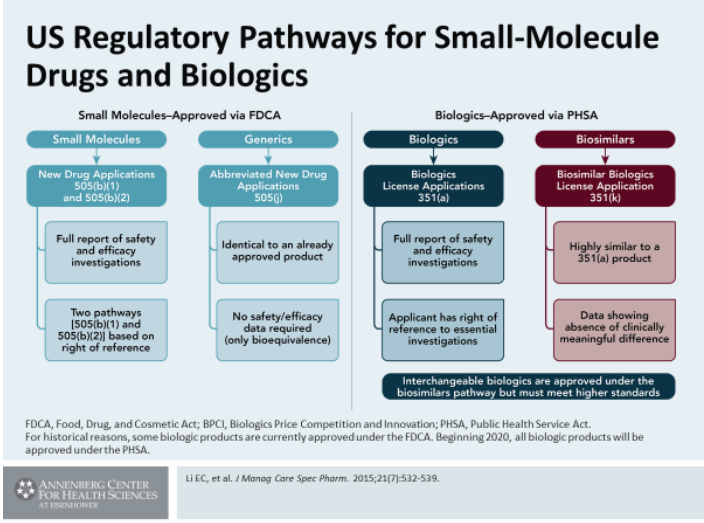
Okay. Let's summarize. Now we've learned about biologics and the differences between generic drugs and biosimilars. Let's go over the key points. First, biologics are so large and so complex that nobody can duplicate them, not even the innovator company. Even with an innovator molecule, there's going to be variation from batch to batch. Now, biologics have revolutionized the care of patients with inflammatory disease and that batch-to-batch variation is something that, as far as I could tell, has not affected our use one iota. We just accept that there's batch-to-batch variation. Maybe we didn't even know there was batch-to-batch variation and we use biologics.

Biosimilars are similar to the innovator biologic and that similarity is supported by an enormous pile of evidence, far more than we have for similarity of the different batches of the innovator. When I say that a biosimilar, to me, is basically like another batch of the innovator product, it's almost more than that because they get so much more data showing that it's similar to the innovator— actually more data than I get for different batches of the innovator product.

3 US REGULATORY REQUIREMENTS

Leonard H. Calabrese, DO: This is the yellow line in which we will discuss the rigorous scientific requirements for developing a biosimilar and how those requirements parallel the requirements that the manufacturer of a biologic must meet each time there is a change in the manufacturing process of a biologic.

So, I'd like to start with just kind of comparing and contrasting the regulatory pathways for small-molecule drugs, which we're all pretty familiar with, and biologics. On the left, we show small molecules. These are oral medications, and the application is applied to the FDA, and a rigorous clinical pathway is engaged in. The drug is ultimately approved. Over time, when the patent expires, people make generics of these drugs. Generics are literally carbon copies of the original small molecules. They're identical. They merely have to demonstrate that there's a unique similarity. No safety or efficacy data is required. And we have many of these generic drugs, as you well know.

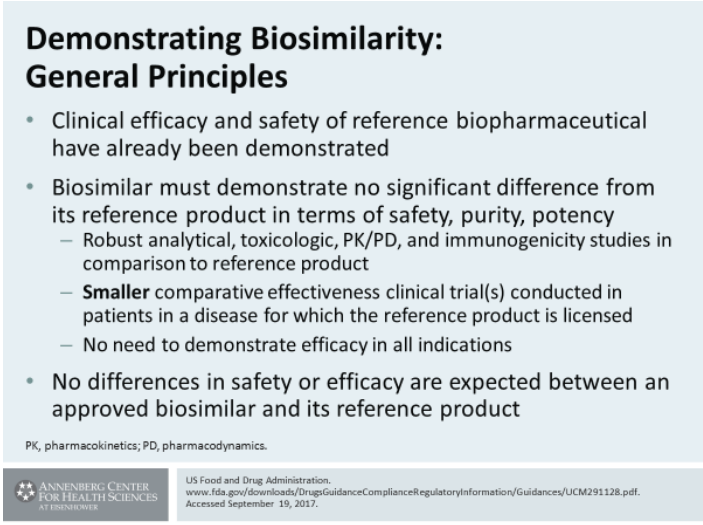


Biologics and biosimilars are different. Biosimilars are not generics. Biologics are these recombinant proteins, many of which are monoclonal antibodies, that go through a rigorous pathway of basic and clinical trials that demonstrate both pristine chemistry as well as efficacy in target diseases. Each disease for which they are approved requires a significant trial and ultimately this drug is approved and has reached the marketplace. We have had biologics in the field of rheumatic and immunologic diseases for over 20 years, and many other specialties for less than that.

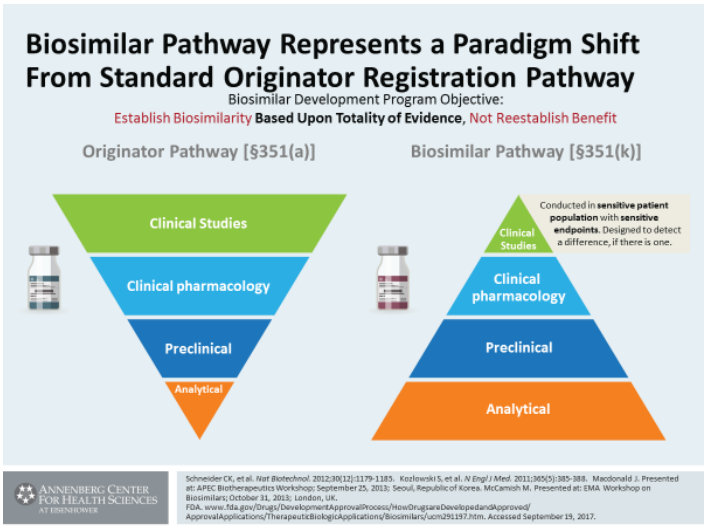
Biosimilars are not generics. As we will go on to explain, there is an abbreviated pathway for approval that must demonstrate what we call them to be highly similar to the originator product. So there needs to be an originator biologic. This has to be demonstrated to be highly similar. There can be no clinically meaningful differences. And then, ultimately, this reaches approval. There is a concept of interchangeability,

which we'll come back to later, which is a very . . . even higher bar.

So, the process of demonstrating biosimilarity; there's 3 basic principles. First, there must be an originator compound, where there's clinical efficacy and safety that has been demonstrated to reach regulatory approval. The biosimilar must come along and demonstrate no significant difference from its reference product in terms of safety, purity, and potency. And then finally, as I'll go on to demonstrate, there are no differences in safety or efficacy between an approved biosimilar and its reference product. Note that I said that it is not more efficacious, nor is it safer, it is highly similar.



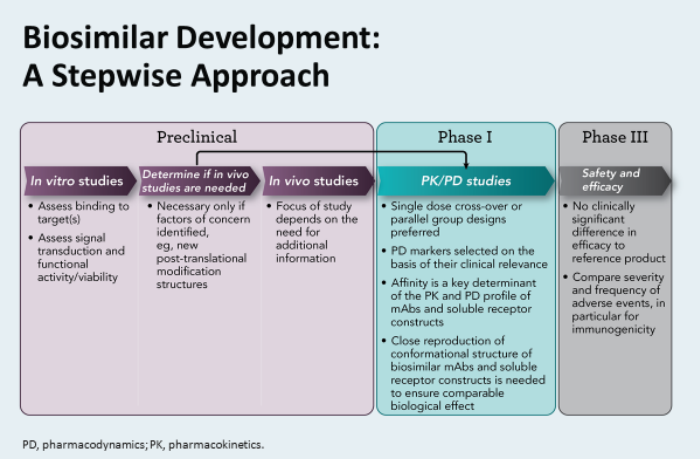
This next slide really nicely summarizes the approval pathways, both for the originator compounds, established biologic, and the biosimilar pathway. And as you can see, on the left, there is an inverted pyramid. The biologic is produced, there is rigorous analysis, there are some preclinical studies that demonstrate safety and lack of toxicity. We then understand the clinical pharmacology by going into phase 1 trials, and then the bulk of the studies are these rigorous and dramatically large clinical studies that now are done in thousands of patients (generally at hundreds of sites throughout the world).



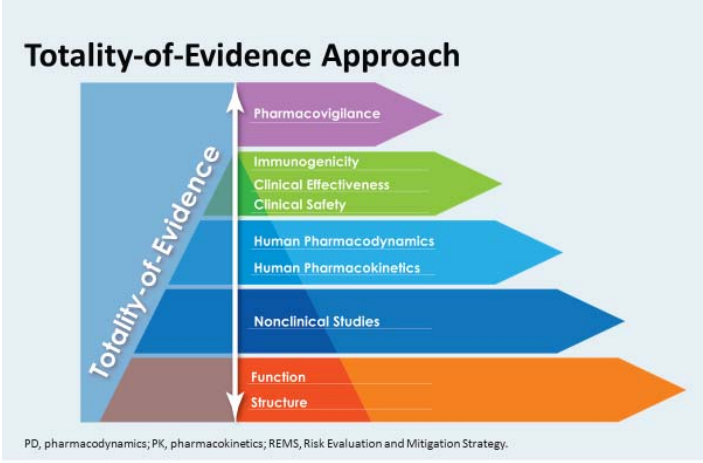
The biosimilar pathway, on the right, is an inverted pathway, where the regulatory approval process . . . that you have an originator, demonstrate that you have a molecule that has the same amino acid sequence, and then demonstrate through a series of analytic and preclinical studies that it behaves the same way, both immunochemically, immunophysically. All the properties that go to demonstrate this high degree of similarity. Then, small clinical trials are done to demonstrate highly similar pharmacokinetics and pharmacodynamics. And then a small clinical trial in a representative disease may be enough to push this molecule over the finish line of biosimilarity.

The stepwise approach for biosimilar development is shown nicely on this slide. The preclinical stage is the most robust. These in vitro studies assessing all the sophisticated chemical analytics to demonstrate binding ability to function as the originator molecule. If all of these studies, both chemical and immunologic, are highly similar, then there's a determination whether in vivo studies are even needed. They may not be. In vivo studies then will be done and to determine whether they are highly similar. From there, if all of the preclinical packaging shows this highly similar fingerprint, then it goes into human studies, looking at PK/PD, demonstrating this virtual highly similar picture to the originator. And then,

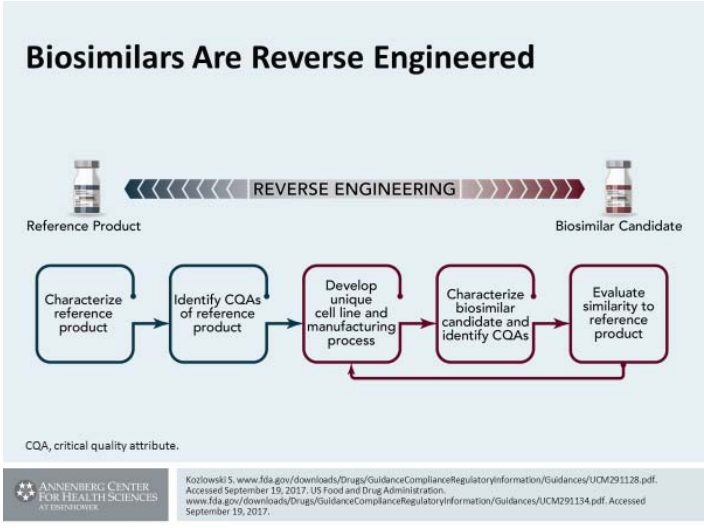
finally, a clinical trial, as I mentioned, of small architecture, to demonstrate equivalence in efficacy and safety.



The term that is often bandied about . . . and if you pay attention to the biosimilar literature . . . is the "totality of evidence" approach. And that's what the regulatory agency is looking at. It's not looking at just whether it's pharmacokinetically similar, whether there's a clinical signal, whether there's a safety signal, or whether the physical chemistry or immunochemistry are similar. It is all of these things put together in a package that provides a basis for direct comparison against the authorized or licensed reference product. On the basis of that, the totality of evidence will be judged up or down.



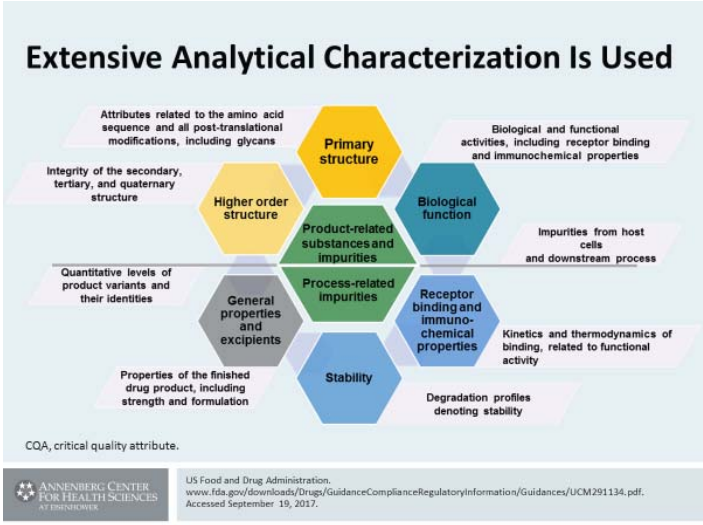
Another term that is often used in the biosimilar world is reverse engineering. I think this is interesting. I'd like to spend a minute on this. If one takes the challenge of developing a biosimilar, the first thing you should ask is, "What is available in the private domain? How can they just copy these originator drugs that took so long and so much money to produce?" Well, in the public domain is the primary amino acid sequence of the originator biologic. But that's about where the reliable information ends.



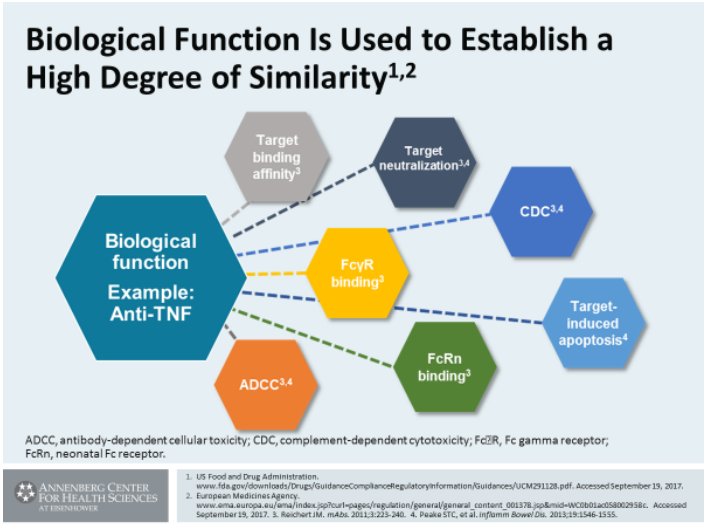
Based upon that, then a system—a biologic system—has to be developed to make a recombinant protein of identical amino acid sequence. That means it has to have a vector produced

that contains DNA to encode this. That means that a cell line has to be chosen. And even if we know the cell line of the originator, we will not have the exact same cell line as we make our biosimilar. We also can test the originator to find out what its binding properties are, what its other physiochemical and immunochemical properties are. And we can test whether ours are highly similar. And then, finally, we can move into a clinical trial and compare it pharmacokinetically and pharmacodynamically to the originator, and then do a clinical trial to demonstrate similar efficacy and safety.

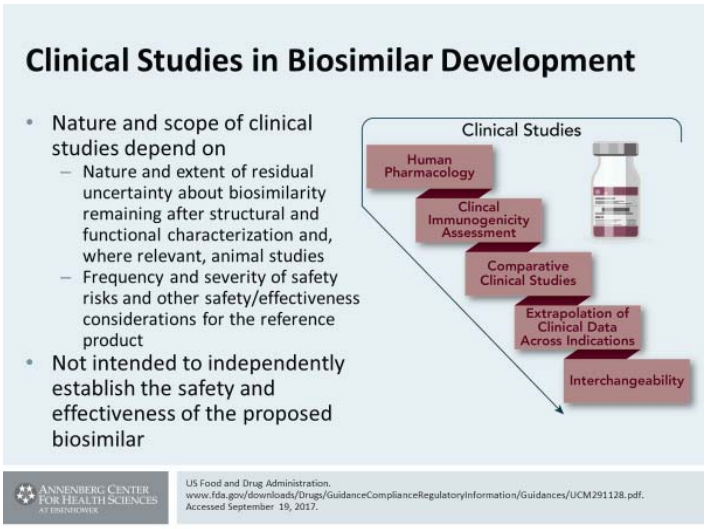
This diagram demonstrates the profound complexity of the extensive analytical characterization required to approve a biosimilar, requiring not only knowledge of primary structure, but higher order structure. Proteins have primary, secondary, tertiary, and sometimes quaternary structures. There are biologic functions, which I'll mention in a minute. And then the drug, as it is packaged, has to have an environment that'll allow it to be constant, and excipients are added—just as they are to the originator—that will stabilize it. All in all, this produces our totality of evidence.



This diagram demonstrates the biologic similarity that has to be demonstrated. And for these molecules, which are largely immunoreactive, assays things such as target binding, the ability to neutralize, can it activate complement, mediate, complement-dependent cytotoxicity, what is its FC binding characteristics, and a number of analytic assays. So, there's a tall measure of these ex vivo immunobiologic functions that have to be looked at.



So now as we look at the clinical studies in biosimilar development, here we start with human pharmacology, looking at PK/PD, looking at the immunogenicity assessment, something we'll talk more about later. This is vital for biosimilar approval process. Then we do comparative studies to demonstrate a comparative level of efficacy and safety. And then we will extrapolate—a term that will be defined later—as to its approval process across other drugs. And, finally, try to achieve the high bar of interchangeability, which remains to be discussed.

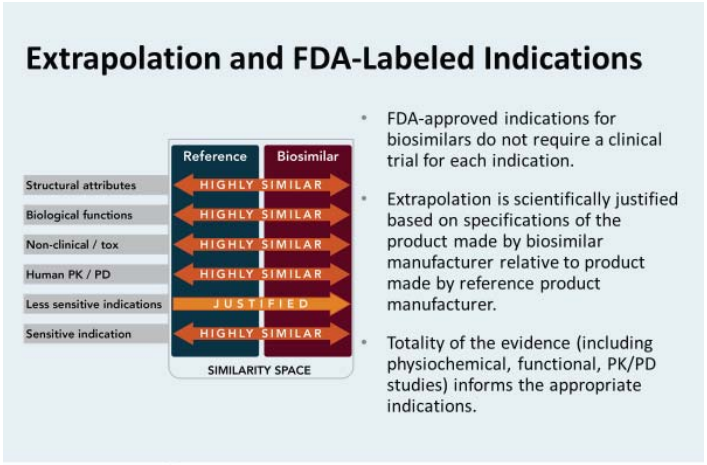


So, in summary, biologics, including biosimilars, are complex drugs that cannot be made generic. The process of biosimilar development and approval is based on a complex and robust ex vivo research program, supplemented by an appropriately sized clinical trial. And finally, approval of biosimilars is based on the totality of evidence.

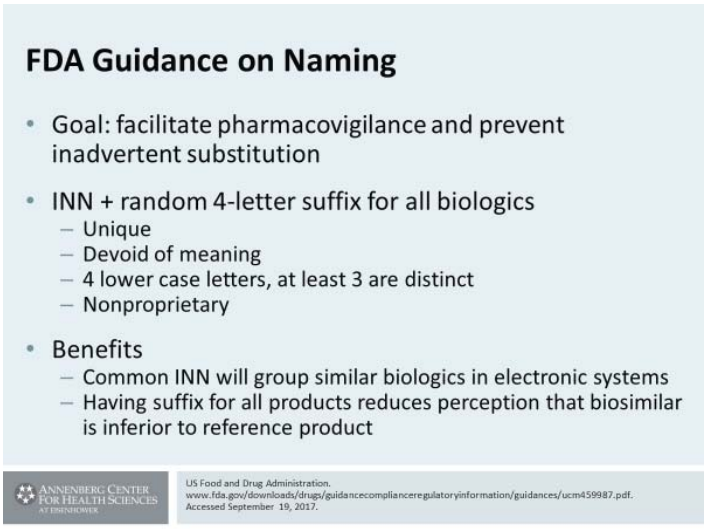
4 EXTRAPOLATION, NAMING, SUBSTITUTION

Leonard H. Calabrese, DO: This is the blue line, in which we'll discuss the extrapolation of indications and how biosimilars are named. We'll review the additional requirements that a biosimilar must meet to be considered interchangeable with its reference product.

First, let's start out with this conception of extrapolation. In its simplest terms, extrapolation is just what the lexicon would suggest. A biosimilar once demonstrated to be physiochemically and immunochemically similar, and have the appropriate pharmacokinetics and pharmacodynamics, then is demonstrated to be clinically efficacious and safe in a disease. If the originator drug is approved for multiple diseases, it is accepted by extrapolation that approval in one disease will give it an approval in the other diseases, such as… a biologic such as adalimumab, which is approved for many diseases, including rheumatoid arthritis, psoriasis, spondylitis, and more. If I have a biosimilar that is demonstrated to be clinically efficacious in psoriasis, I may be given, by extrapolation, FDA approval for the other indications.



A second and somewhat confusing area of biosimilars is this naming process. Now, at first blush, this would seem to be an easy challenge. But think about it for a moment. So, already we have biosimilars that have been FDA-approved to several immunoactive drugs used to treat immunomediated, immunoinflammatory diseases, or IMiDs.

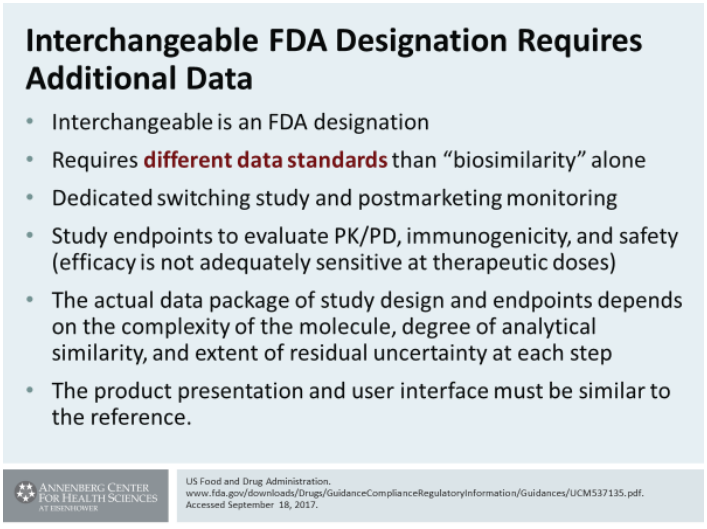


Adalimumab is a good example. There are 2 approved

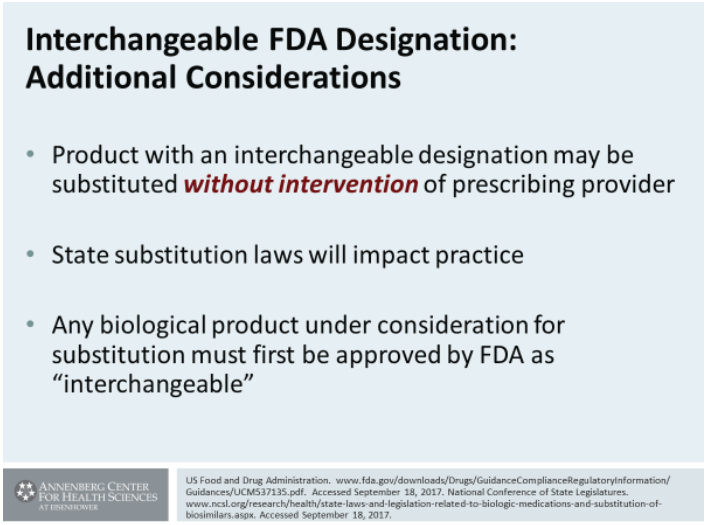
adalimumab molecules. So, how will we name them? Well, they will retain the name of the chemical compound of the originator, adalimumab. And then they will be given an identifier, and the identifier is a random 4-letter suffix that is applied. So, it may be -atto, -adbm, or it could be -xyac, etc.

When I first heard this, I was confused about this. I said, "Well, why isn't it named just for the company that developed it?" The response was actually rather clarion. Over time, that company may be sold or the product may be sold to another company. So, at the moment, it's important to be able to uniquely identify. We could envision 3 or 4 years from now that there may be 5 biosimilar adalimumabs and 6 biosimilar infliximabs. So, the pharmacy will have to keep track of them. The provider will have to keep track of them. And, ultimately, the patient will have to keep track of them. So, we need unique identifiers. So, what may be complex right now, will provide needed clarity as we move ahead.

The next term which causes concern for everyone who is trying to understand this field of biosimilars is this notion of interchangeability. Interchangeability is an FDA designation. As I will point out, it requires a different set of standards from clinical trials to be given this.



If a biologic was deemed interchangeable, the implications for clinicians and patients would be that the pharmacist, without pre-approval of the prescribing clinician, would be able to insert the biosimilar for the originators. So, if I was using the originator infliximab, and there is a biosimilar infliximab-abcd, the pharmacist would then merely insert this, as they would a generic for a small molecule. This has raised a lot of concerns in the provider community.



So, what are those additional considerations that we have to think about? Well, should a product be deemed interchangeable? If I am the clinician, I would want to be notified for this. And indeed, implicit in this is notification, but that could be post hoc. Now because we live in a federation and each state has its own laws, and states are now creating their own substitution laws, in advance of interchangeability, to regulate this. The pharmacist's substitution will have to abide by state laws, and there will have to be a framework. There will have to be product criteria, the clinician can… just like we can for small molecules, write, "dispense as written." We have to have laws about how this will be communicated. How we will keep our records. And how a health system may be, or may not be, exempted from this.

Pharmacist Substitution

State law gives pharmacists the authority to act independently of the prescriber to dispense the lowest-cost, equivalent medicinal product

Framework
Product criteria
Dispense as written
Communication with prescriber/patient
Record keeping
Hospital/health system exemption

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

I'm showing you on this slide—examples of active biosimilar substitution laws in multiple states. And these are now moving with great rapidity across the country. Looking at what time the pharmacist has to tell the clinician that they are substituting. What other provisos will be in this interchangeable designation?

Examples of Enacted Biosimilar Substitution Laws

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.

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State of Delaware. delcode.delaware.gov/title24/c025/sc06/index.shtml. Accessed September 19, 2017.
State of Florida. www.flsenate.gov/Session/Bill/2013/0365/BillText/er/PDF. Accessed September 19, 2017.
Commonwealth of Virginia. leg1.state.va.us/cgi-bin/legp504.exe?131+ful+CHAP0412. Accessed September 19, 2017.
Commonwealth of Massachusetts. www.foleyhoag.com/-/media/files/foley%20hoag/publications/alerts%20and%20updates%20misc/2014/foley-hoag-life-sciences-alert-chapter%20140-of-acts-of-2014.ashx?la=en. Accessed September 19, 2017.

If I wanted to summarize this (the common elements of interchangeability), I would say these are the 4 tenets. The biologic product under consideration must first be designated as interchangeable. I'm going to stop right here and anyone listening to us right now I will tell you, there are no interchangeable biosimilars that have been approved thus far. There is only a single study that has been designed that is now being launched. It'll be some time before this occurs. We don't need to worry about it immediately, but it's something on our radar screen.

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 substitution or switch was made. In some cases, state law requires patient consent prior to switch.

State-to-state variations possible

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National Conference of State Legislatures. www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Accessed September 19, 2017.

The second tenet is that the prescriber would be able to prevent substitution, just like we can for small molecules, by including the DAW, or "dispense as written."

The third common element is that this will not happen unbeknownst to us. The prescriber must be notified. Some communication has to occur.

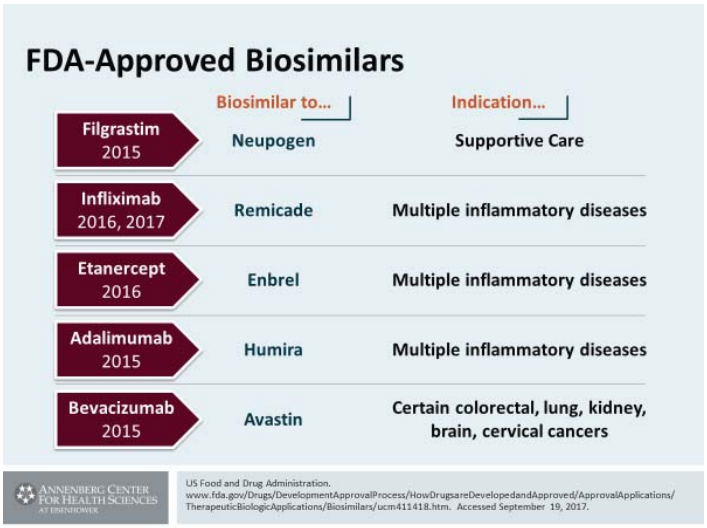
And finally, most importantly to me, the patient must be notified that a substitution or switch has been made. Now all of this will be shaded by the state-to-state variations, which are working their way through legislative processes.

In summary, an approved biosimilar can be expected to have the same efficacy and safety profile, meaning no clinically meaningful differences, as the reference product in the approved indications. Secondly, based on the totality of evidence, including all of the ex vivo and clinical studies, biosimilars can be approved to treat indications without clinical trials of that biosimilar, and recall that term is approval by extrapolation. Finally, the term interchangeability is a tall hurdle for biosimilar approval. As of yet, there are no approved agents with this designation.

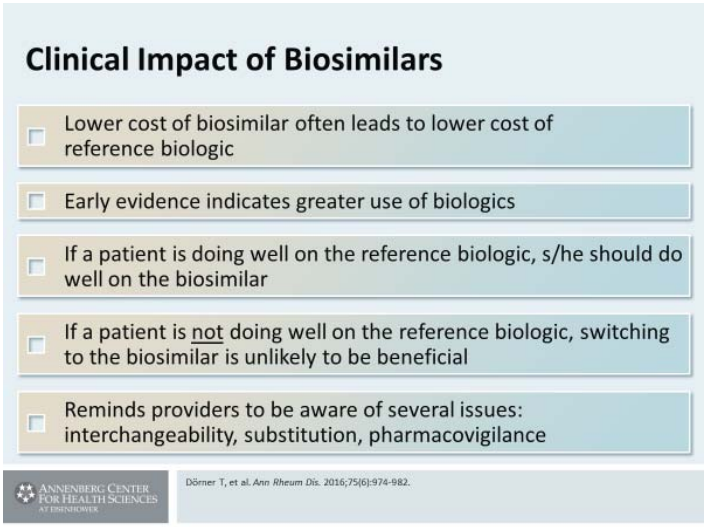
5 IMPLICATIONS FOR CLINICIANS

Steven R. Feldman, MD, PhD: This is the red line, in which we will discuss how biosimilars have begun to impact clinical practice, and patient access to treatment, with a biologic.

There are already a variety of FDA-approved biosimilar products. Filgrastim biosimilar was approved in 2015. It's a biosimilar to neupogen. Infliximab biosimilar to remicade has been approved. The FDA has also approved etanercept and adalimumab biosimilars. These drugs are used for a wide variety of indications, particularly inflammatory diseases.



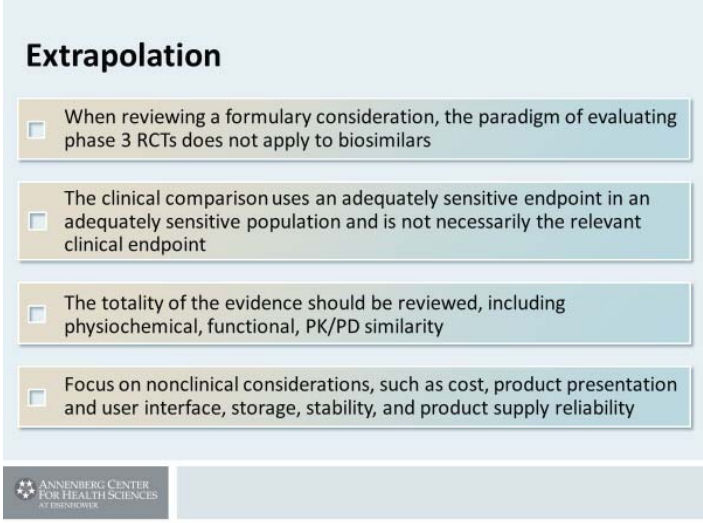
The clinical impact of biosimilars, to me, is somewhat limited. There is the thinking that biosimilars will come in at lower costs, but it's not going to be dramatically lower costs. That lower costs will often lead to lower costs of the reference biologic as well. There's some evidence that the development of biosimilars may lead to greater use of biologics. Now, if a patient is doing well on a reference product, that patient should also do well on the biosimilar. There's not a lot of change there. If the patient is not doing well on the reference biologic, switching to the biosimilar is not likely to be of benefit because the drugs are basically the same thing. Biosimilars are not going to help a patient who is not doing well on a reference product.



Now, there's several issues that we're going to want to discuss with regard to biosimilars, and that includes interchangeability, substitution, and pharmacovigilance, but as I consider these issues, I like to keep in mind that the biosimilar is basically, at least to my thinking, very much like another batch of the innovator product. With that in mind, we can understand the interchangeability substitution and pharmacovigilance, I think much more clearly.

Extrapolation is of concern to some people. This is the idea that an innovator product is tested for efficacy and safety in a wide variety of conditions. When a biosimilar is approved, it doesn't have to be tested in all of those indications. Perhaps it's only tested in one of them in order to show its similarity, but

then it's given approval to be used in other conditions, in other words, extrapolated to use in other conditions.

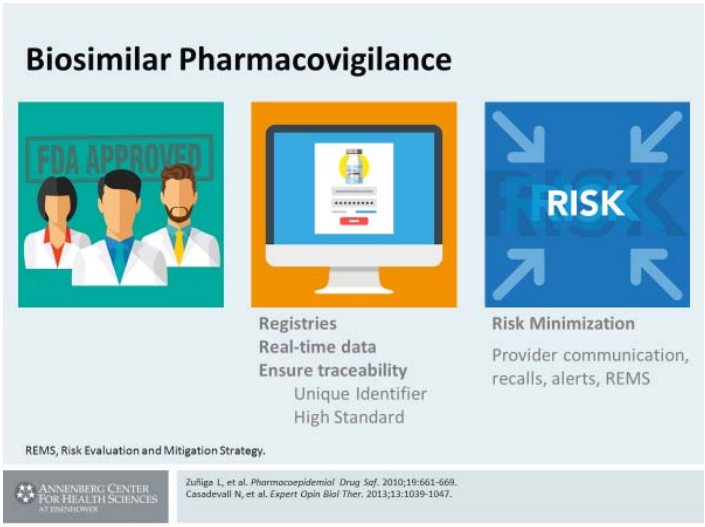


The innovator biologic will be approved for multiple different indications based on multiple randomized controlled phase 3 trials. A biosimilar does not undergo multiple randomized control trials in different indications. It may only be tested in one indication. If approved, its use may be extrapolated to other indications, the idea being that if you've shown the biosimilar to be similar to the innovator product, it should be good in all the diseases in which the innovator is good.

Now, to assure that the similarity in one indication should extrapolate to others, usually the indication that is most sensitive for detecting a difference should be the one tested. For example, if patients in one condition, say rheumatoid arthritis, are treated with methotrexate, along with the biologic, that might be a less sensitive way of detecting a difference between the biosimilar and the innovator than a disease like psoriasis where the biologic is used by itself, because the methotrexate might inhibit the development of antibodies against the drug.

Biosimilars are allowed to be extrapolated based on a totality of evidence. If the totality of evidence, which includes the physicochemical assessment of the structure of the biosimilar and its functional characteristics, how well it binds its target, and its pharmacokinetic and pharmacodynamic characteristics, how well it stays in the blood, and how well it actually functions in a particular disease. If all of that shows similarity, then the biosimilar would be allowed to be extrapolated for use in all the conditions that the innovator is indicated for. Basically, the ultimate decision about whether to use a biosimilar or the originator product would come down to other consideration that are predominantly the cost of the product.

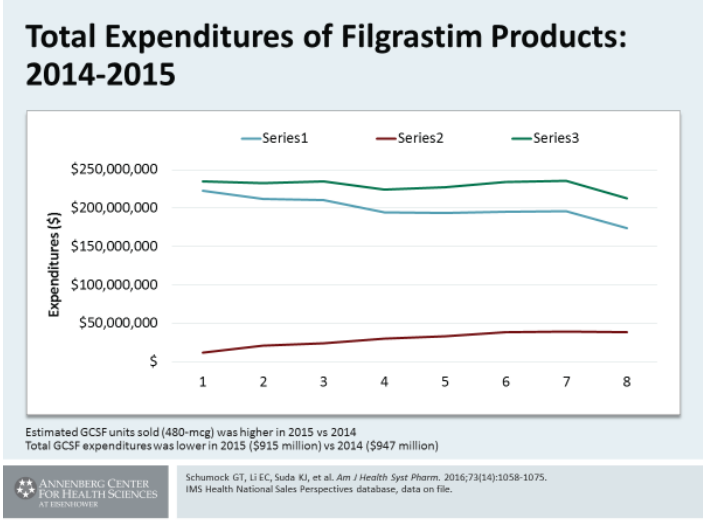
There's concern about telling whether a biosimilar will create some problem. There's attention paid to pharmacovigilance. The FDA may approve the biosimilar and then, once in use, you want to have data on the biosimilar to make sure it's performing as expected. You can do this with registries and all.



Now, some people feel the biosimilar should have to have a distinct name so that you can track it. To me, the biosimilar's basically like another batch of the innovator and we don't give each batch of the innovator a different name so that we can make sure that it's working the same as the previous batch. To the extent that we do give a biosimilar a different name and carefully monitor it, we are actually already at a higher level, a higher bar for making sure that the use of the medication is safe and effective, than we do for the different batches that

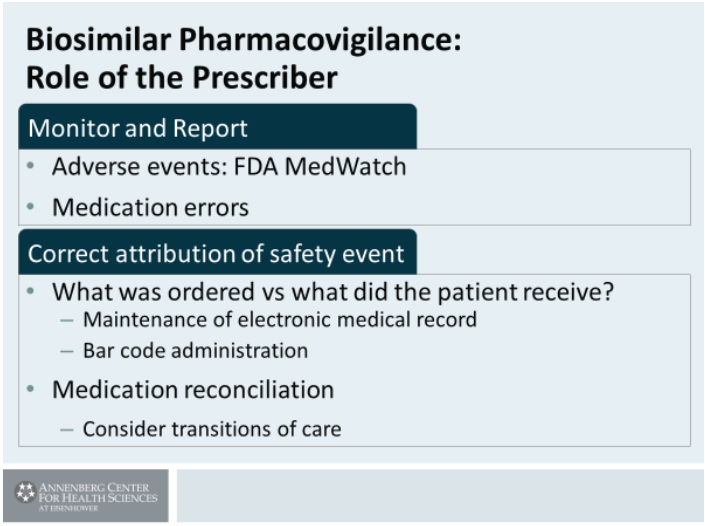
we're currently very happy with. The efforts to identify risk may include health care provider communications, recalls, alerts, and potentially even REMS programs. Those are risk evaluation and mitigation strategies.

The primary reason people are excited about biosimilars is the potential that they will reduce the cost of therapy. Here we have total expenditures of filgrastim products. You can see that the amount expended on the biosimilar gradually increased. The amount that was spent on the innovator products gradually decreased somewhat, and the total cost came down some.

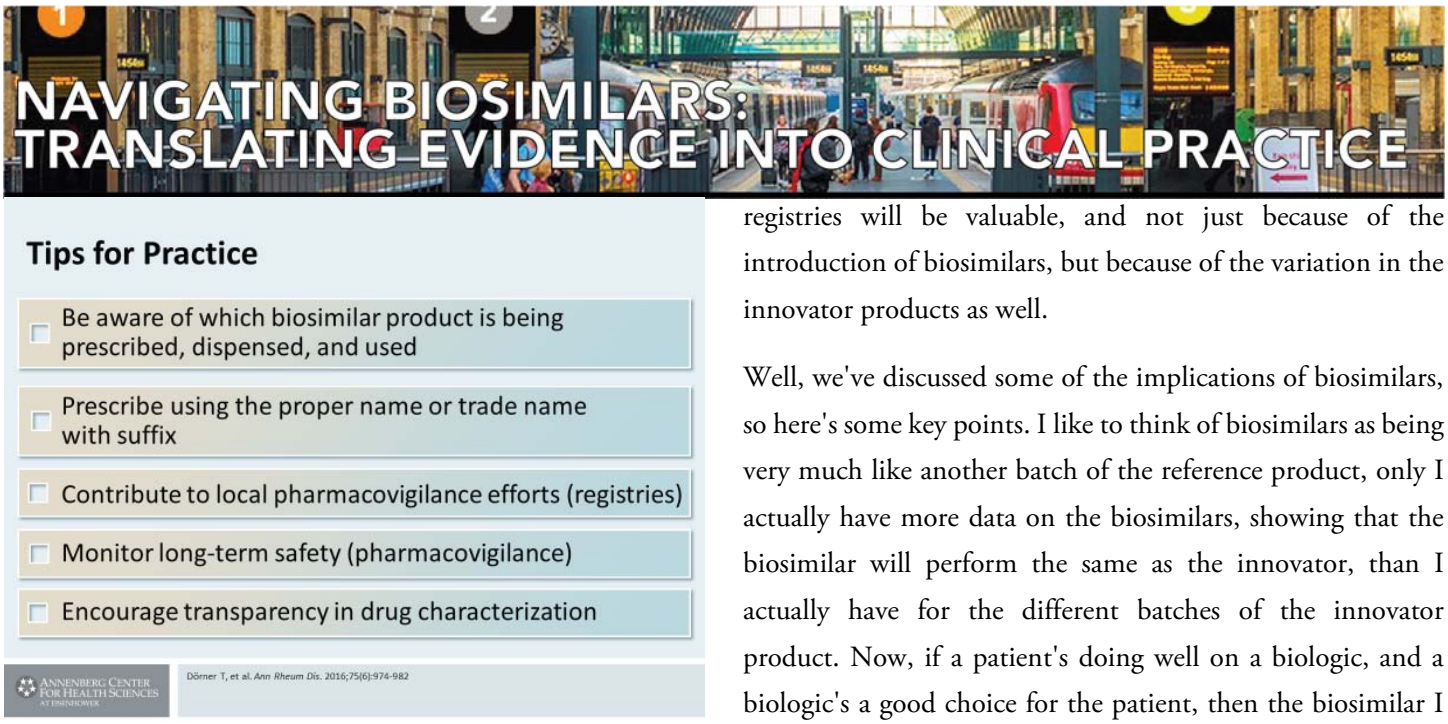


Now, the amount that it comes down appears not to be very large, but one of the main things is we might have expected that, over time, the expenditures for the filgrastim would have grown, and might have grown considerably. One of the advantages of biosimilars is that even if they don't reduce the spending on biologics, they may at least prevent rapid growth in the spending on biologics. That may be an enormous benefit.

As health care providers, we have some role in pharmacovigilance. The FDA MedWatch program records adverse events that are reported. There is tremendous under-reporting of adverse events. That program is only as useful as we make it. If we report adverse events when we see them, it will be more useful than if we don't. There's potential for medication errors that could be reported as well. If an adverse event occurs, it has to be attributed appropriately, and we'd want to know what the patient actually received. You'd have to know whether it was the innovator or the biosimilar, ideally what batch of the innovator or biosimilar was used.



Here are some tips that have been recommended. When a patient is on a biologic, you want to be aware of whether they're on the innovator, or which biosimilar they were prescribed, and which they were dispensed. You want to make sure you're using the right trade name that defines exactly which product they're on. You want to contribute to registries that will follow people over time. It's one of the best ways of collecting efficacy and safety data and monitor for long-term safety data, and encourage transparency in drug characterization.



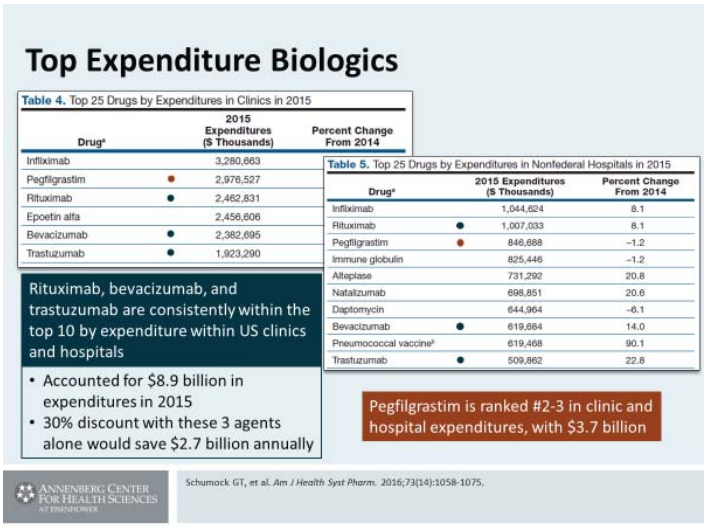
I think that those are all interesting and good tips, but here's the thing, we've been using different batches of innovator products for over a decade now, and we really haven't done any of these things, except perhaps the issue of registries. I'm still comfortable with my patient moving from one batch of an innovator product to another, and those minor variations that occur between batches are of no relevance to me. I think making sure that we get as many patients as possible into registries will be valuable, and not just because of the introduction of biosimilars, but because of the variation in the innovator products as well.

Well, we've discussed some of the implications of biosimilars, so here's some key points. I like to think of biosimilars as being very much like another batch of the reference product, only I actually have more data on the biosimilars, showing that the biosimilar will perform the same as the innovator, than I actually have for the different batches of the innovator product. Now, if a patient's doing well on a biologic, and a biologic's a good choice for the patient, then the biosimilar I believe should be fine as well, again because I have so much evidence that it is similar and that it performs similarly. At the same time, if a patient's not doing well on a particular biologic, switching to the biosimilar will not be helpful because you're basically giving the patient the same thing as the innovator, so if they're not doing well on one, they're not likely to do well on another.

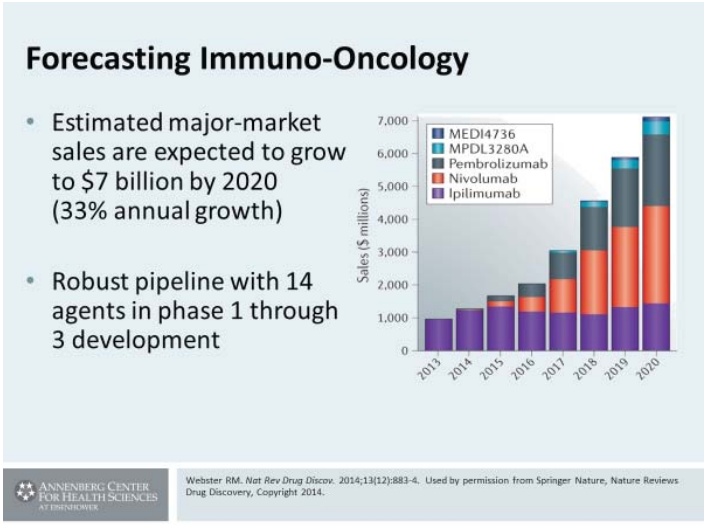
6 PATIENT EDUCATION

Leonard H. Calabrese, DO: This is the green line in which we'll discuss patients' perceptions about biosimilars and strategies to address these issues. This is a complex topic and one that is very dynamic right now. If we ask what our patients may or may not understand about biosimilars, we have to probe their attitudes, knowledge, issues of finances, access, and then ultimately their inquisitiveness about efficacy and safety.

To start out, let's look at some of the cost issues, because there is no doubt when we talk about biosimilars, the most important consideration in the development of biosimilars is the potential for cost savings. This is looking at top expenditure drugs, and as you can see, these are in the billions, with a "B." Many of these are oncologic, but the top drug is infliximab with TNF inhibitor. If there were a 30% discount with the top 3 agents, that could lead to savings of $2.7 billion. This is not an insignificant amount of money.

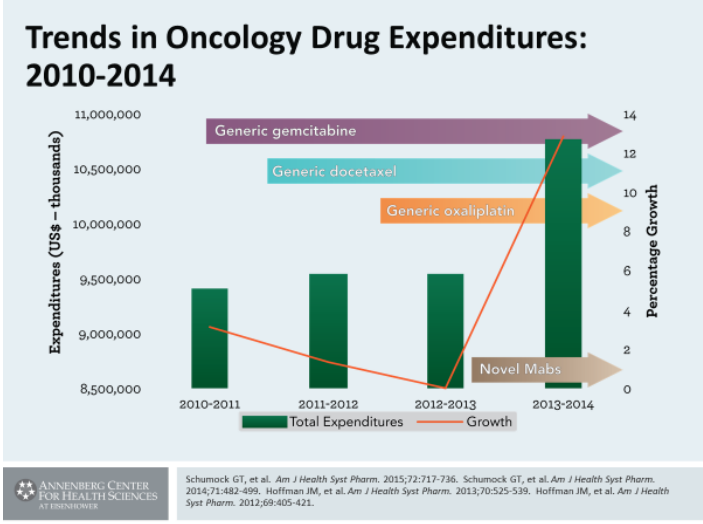


If we now do some forecasting, and base this now on immuno-oncology—probably one of the most exciting areas of the application of biologics—the expenditure is growing at greater than a linear rate. It's expected that this will grow to 7 billion by 2020. There is now a robust pipeline with many, many drugs that may expand this to even a greater degree.

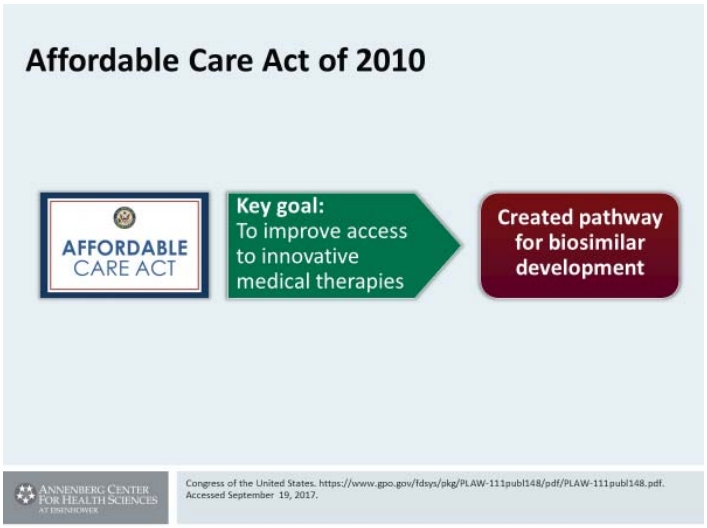


If we look at the immuno-oncology again, and look at the cost of all oncologic drugs, you can see that up through 2012, 2013,

there is quite a bit of stability there. But with the development of checkpoint inhibitor therapy, which was approved in 2011, there has been a spike in total drug expenditures that has been mammoth in degree. All of us who are in health care know that costs and regulating costs are a high priority.



In 2010, the Affordable Care Act was passed. This has many positive motivations. While it's under fire, it has done a lot for us to orient our thinking around affordability of care. The key goal was to improve access to innovative medical therapies and create pathways for biosimilar development. This was actually placed into the Affordable Care Act, and I think it was an important step.



Now, with that background, imagining that we have an increasing pipeline of biosimilars, what do we know about patients? How will they receive this information? How will they process it? What will their attitudes and beliefs be, and what will be their confidence in this?

Well, we're closer to the beginning than the end, but there have been several surveys published. This is one of the larger studies, but note the date. At that time, we had virtually no biosimilars. It showed that at that time, awareness was low. That same study compared patients who were aware or said they were unaware about biosimilars and then asked them what their perceptions and awareness were about safety, and efficacy, and price. To no one's surprise, the aware people had greater confidence and declared knowledge in these areas. So, with that as a backdrop, we need to have the dynamic, and ongoing studies of patients' knowledge and attitudes moving forward.

Patients Require Education

- 2014 US/EU survey (N=3198) shows
  - Overall awareness levels about biosimilars were lower than those reported for biologic therapies → indicating a need for patient education about biosimilars.
  - Patients who are diagnosed, as well as diagnosed advocacy and caregiver groups, have a higher awareness of biologics than the general population.
    - Biosimilar awareness was low across all groups.
- Partnerships with HCPs and advocacy groups may potentially develop and expand patient education.
- Important area to develop educational programs is within clinical trial participation, and particularly those studying biosimilars.

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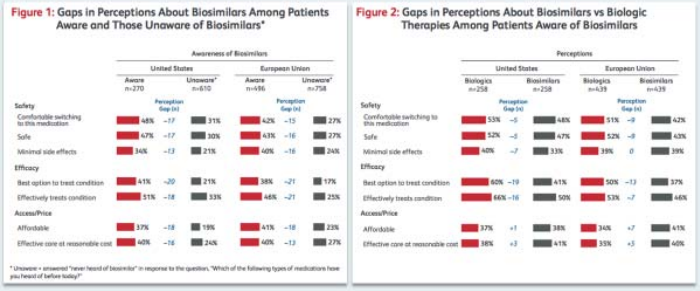
Jacobs I, et al. *Patient Prefer Adherence*. 2016;10:937-948.

Patients Perceptions About Biosimilars



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This is a checklist that I think really summarizes what an informed patient would be wanting to know about. If I had a disease, I'd want to know about the biologic therapies used for a specific disease. If you're telling me I'm getting a biosimilar, I'd like to know what it is. I think this totality of evidence, for some people, may have to be explained to them. Clearly, they need to know there's no meaningful differences in efficacy and safety, nor the delivery or administration. This will not affect access to treatment. I will tell you, out of all of these, the most important things patients want to know—this is my own experience reflecting back on this—is that how will this affect me through my insurance and my out-of-pocket expenses? Ultimately, it will be important for them to know what type of drugs they go on.

Checklist for an Informed Patient About Biosimilars

- Use of biologic therapies in the specific disease
- Definition of a biosimilar
- Totality of evidence required of a biosimilar
- Efficacy similar to innovator biologic
- Delivery/Administration of the agent
- Device use (if applicable)
- Access to treatment
- Insurance coverage and out-of-pocket cost
- Services available to support patient
- Clinical trials including standard biosimilar trial design
- Manufacturer identity

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Some additional key points about patient education, were that, recall again, this was an implicit and explicit goal of the Affordable Care Act. Secondly, that these biosimilars are highly similar, but not identical, not generic to the reference product. And finally, we need to encourage patients to partner with their providers, including the pharmacist, in making informed decisions, and shared decisions, about whether biosimilars will be best for them.

Key Points for Patient Education About Biosimilars

- A key goal of the Affordable Care Act of 2010 was to improve patient access to innovative therapies
- Biosimilar is highly similar to, but not identical to, its reference product
- Biosimilars are not generic biologics
- Encourage patients to partner with their providers, including pharmacist

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Finally, let me summarize by saying patient education will require a high degree of shared and informed decision-making,

on both sides of the fence, of provider and patient, to make this work. Secondly, while the science of biosimilars has yielded no red flags, and I'm very reassured by this, the paucity of active experience with these agents in the US has fueled concerns and misinformation at times. I'll tell you that as of this time, very few clinicians have actually used biosimilars.

Thirdly, there's even a greater uncertainty regarding biosimilars and how those cost savings will actually impact all parties. I think that this is the elephant in the room. Yes, these drugs will impart a cost savings, but who will receive those savings? We want to know that before we move forward.

And then, lastly, robust and ongoing education of all parties is critical to this decision-making process.

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