Biosimilars

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Disclosure

- The speaker has no financial or nonfinancial conflicts of interest for this topic and no disclosures for this program.
- The speaker will not be discussing the off-label use of any products.

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Objectives

- At the conclusion of this program the successful learner will be able to:
  - Compare and contrast a small molecule drug from a biological drug
  - Compare and contrast how a reference biologic drug compares with its biosimilar
  - Describe where a pharmacist would identify a biosimilar product and the legal implications of a biosimilar achieving interchangeable status with a reference product
  - Describe the nocebo effect and how to prevent it from occurring
  - Apply the knowledge from the objectives above to specific patient care scenarios in the self-assessment questions

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What is a biologic product?

- Biologic product means a blood component or derivative, (anti)toxin, vaccine, antibody, protein (except chemically synthesized polypeptides), or virus product.

Small Molecule Drug	**Biologic Product**
Low molecular weight	High molecular weight
Organic or chemical synthesis	Living cell synthesis
Easily characterized structure	Difficult to characterize structure (tertiary folding, etc)
Homogenous API	Heterogenous mixtures that may include variants
Less likely to cause immunogenic responses	More likely to cause immunogenic responses

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Biologics catch fire in US

- The OGs of biologics
  - Insulin, interferon, HGH, erythropoietin, Granulocyte-CSF
- Orphan Drug Act of 1984
  - Created favorable regulatory and sales environment
- ~50% of drug spending but 2% of drug utilization
  - Markedly more expensive than small molecule drugs
- Biologics are very expensive and with no small molecule Active Pharmaceutical Ingredient to replicate, generic equivalents are not possible

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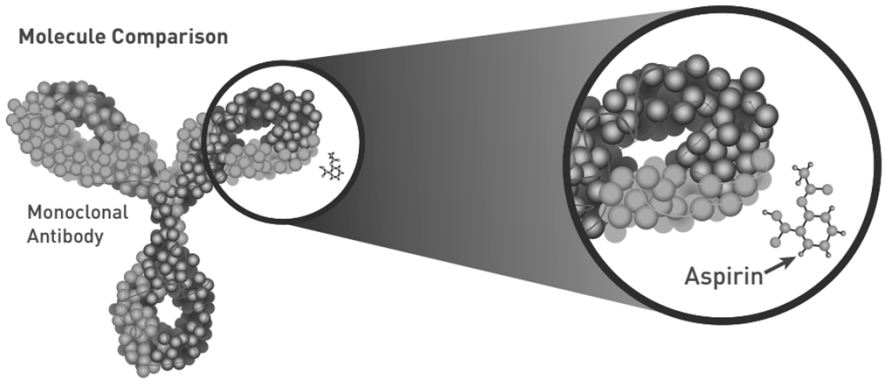
How much more complex is a biologic?



Not every atom or secondary or tertiary protein folding is mission critical. Small differences from batch to batch in non-critical areas are ok for biologics but the company needs to identify the critical structures for efficacy and safety and show the batches are not different there.

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Biosimilars to the rescue

- A biosimilar is a biologic product that is:
  - Structurally highly similar to a reference (innovator/originator) biologic product
  - No meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency of the product

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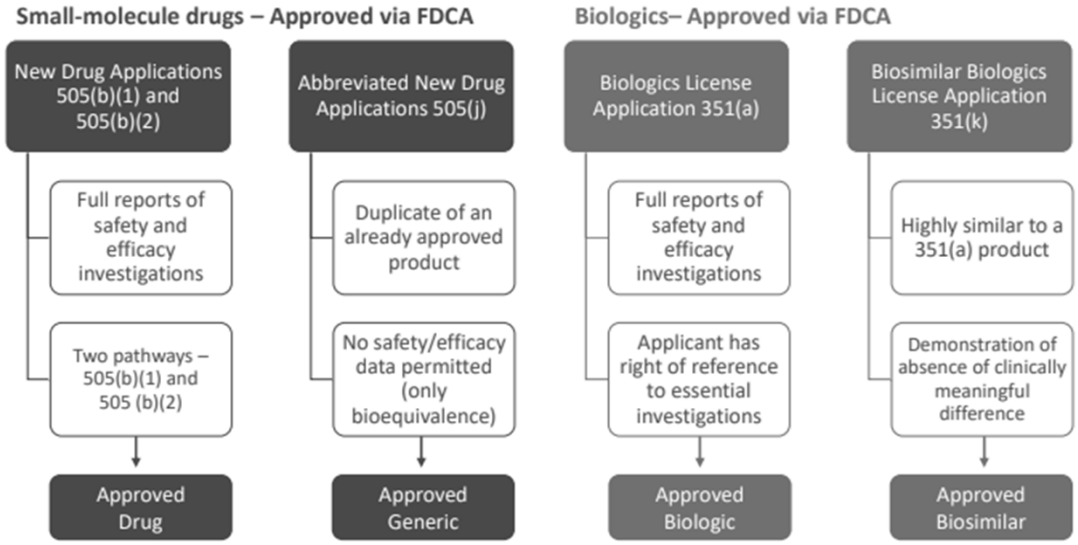
The FDA Approval Process



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What clinical studies are required

- Generic drugs and biosimilars need to show similar AUCs to brand or reference drugs
- Unlike generic drugs, biosimilars also require pharmacodynamic and immunogenic clinical study data to prove similar effects in at least one reference FDA approved indication
  - Can use surrogate outcomes to prove effects
  - All indications are given to biosimilar once one is proven

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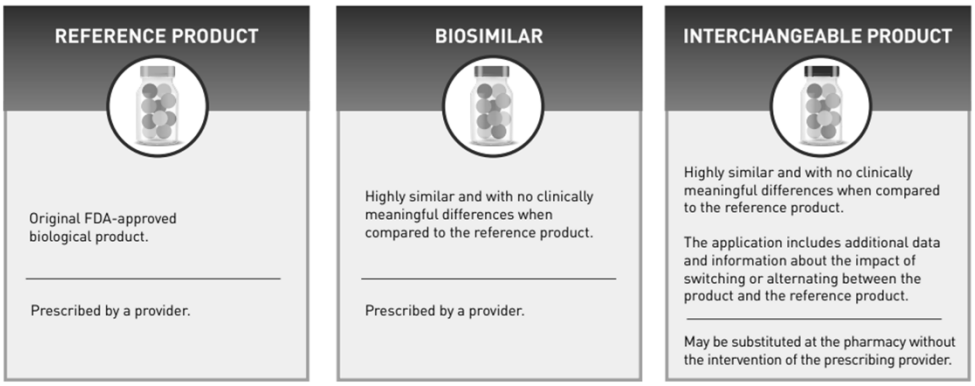
"Biosimilar" vs. "Interchangeable Biosimilar"

- Biosimilar means prescriber must write specifically for it and not the reference biologic



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Gaining an "interchangeable biosimilar" designation

- FDA used to require interchangeable biosimilars to conduct costly switching studies
  - Patients switched back and forth with reference biologic to ensure interchangeability
  - Studies conducted have not shown differences with interchangeable biosimilars and reference products or with other biosimilars not seeking interchangeable status
  - In June 2024, the FDA stopped requiring switching studies and will be more holistic in granting interchangeable designation (possible as early as 2026)

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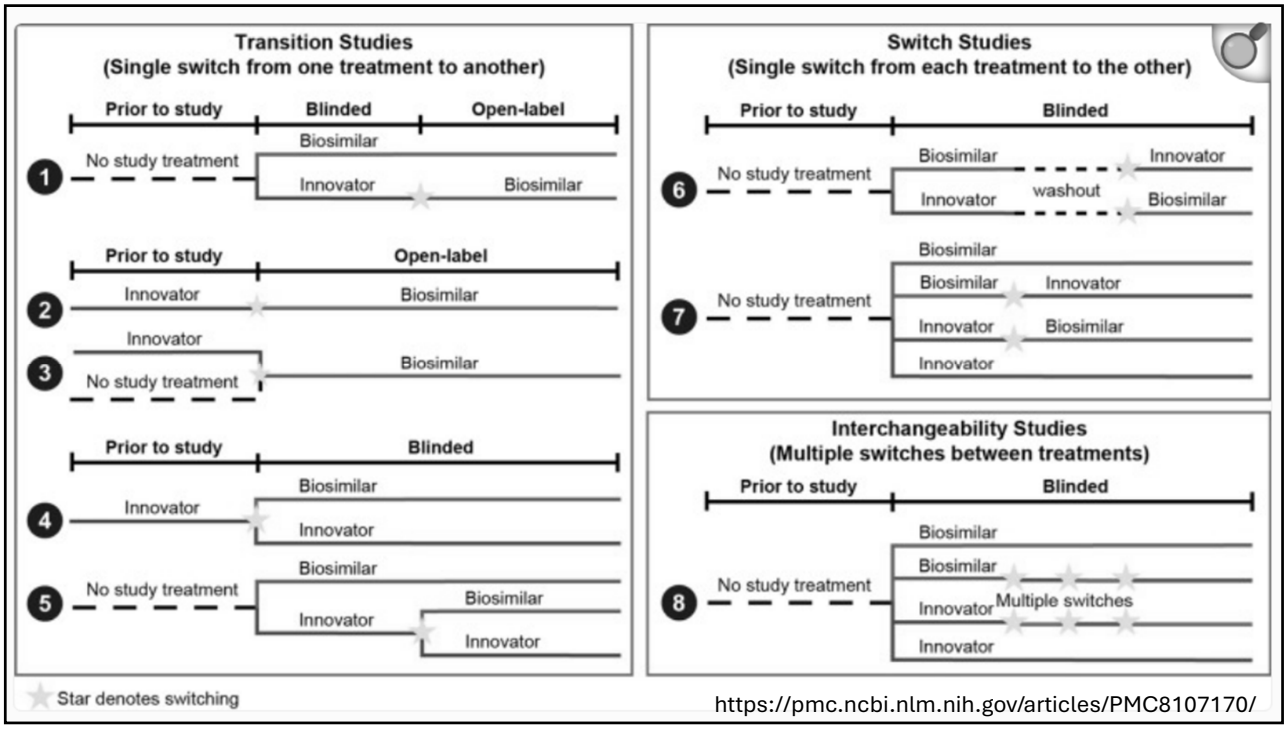

https://pmc.ncbi.nlm.nih.gov/articles/PMC8107170/

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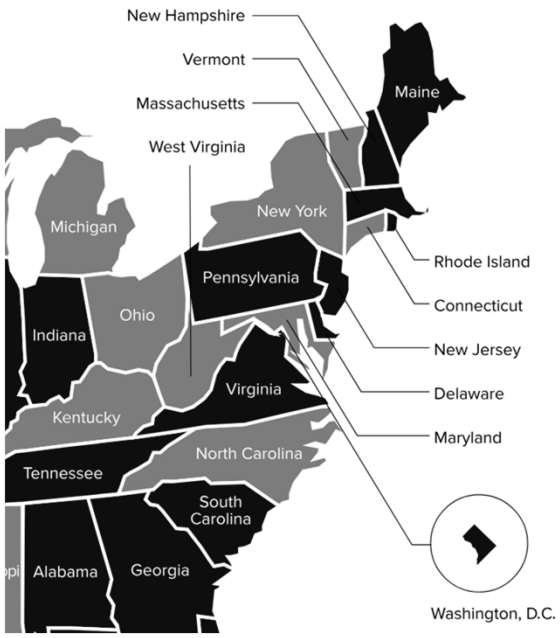
What Interchangeable Biosimilar Means Legally

- To check your state: https://interactive.digitalpfizer.com/biosimilars-map-us/index.html
- Pharmacists can interchange reference for biosimilar?
- Yes, in every state but
  - Dark blue = Yes
  - Light blue = Yes, if $$ less



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Does the pharmacist need prescriber approval?

Blue = No; Black = Yes

Does the pharmacist need to inform prescriber?

Blue = Yes; Black = No

After initial substitution, prescriber doesn't need to be informed for refills!

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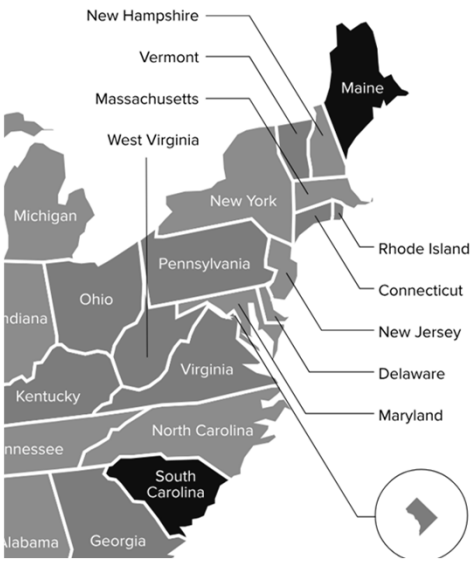
Can patients refuse a biosimilar substitution?

Patients and caregivers must be INFORMED that a change occurred

Gray = Not specified; Light blue = patient can refuse, Dark blue = patient must consent



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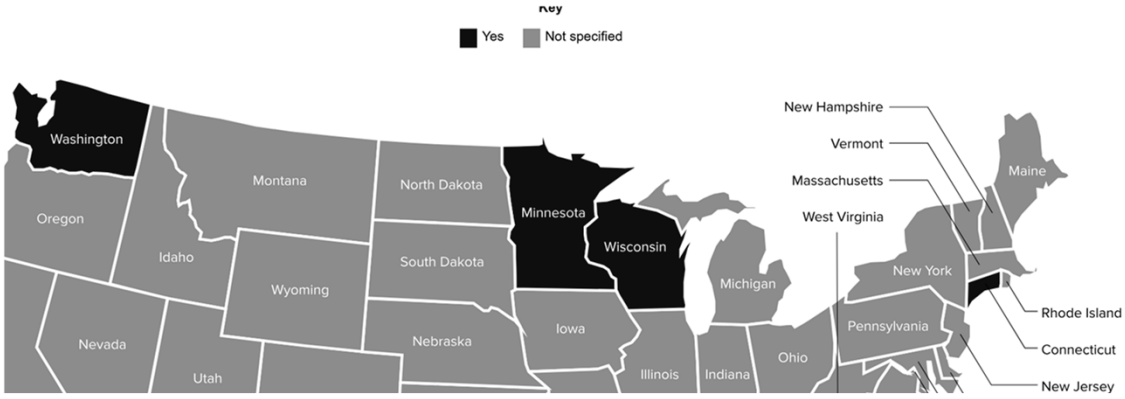
Must the pharmacy post a sign saying they can substitute with a biosimilar?



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In addition to the "Purple Book," does the state board of pharmacy need to provide interchangeable biosimilars on their website?

Black = No, Grey = Not Specified, Blue = Yes

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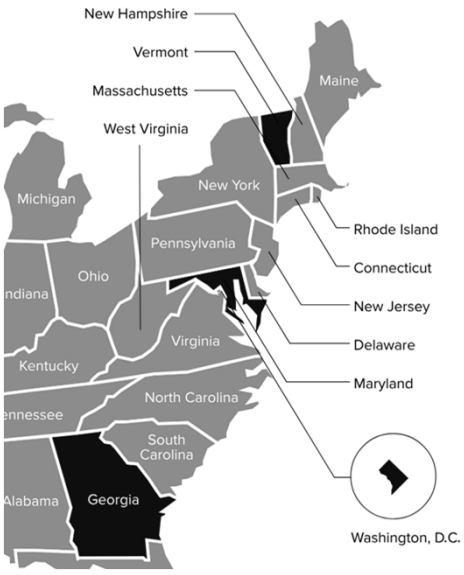
Must the lowest cost interchangeable biosimilar be used?

Grey = Not Specified, Blue = Yes



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Key Take Away!

- The Purple Book identifies biosimilars and interchangeable biosimilars
  - You can only auto-substitute the interchangeable ones
  - There may be a biosimilar that is not designated interchangeable that is much less expensive
    - The FDA is convinced that all biosimilars, interchangeable designation or not, are equally effective and safe
    - You could ask the patient if he/she wants the auto-substituted option with ___% savings or contact the provider and see about the other option with ___% savings

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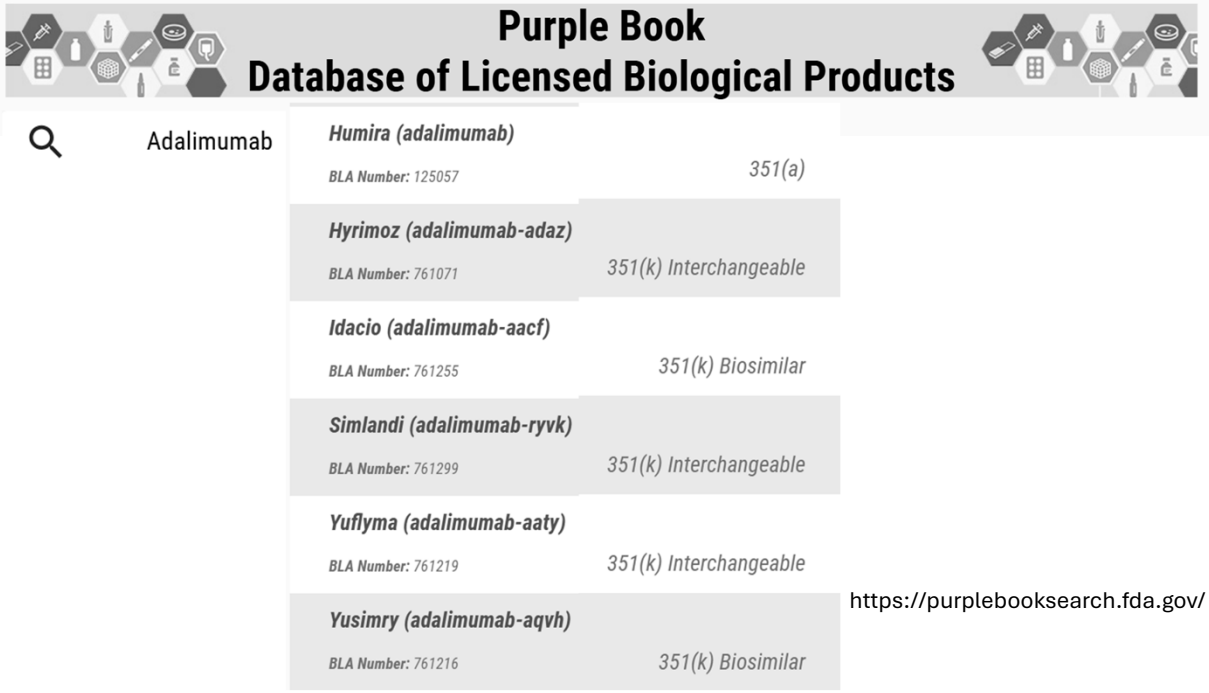

https://purplebooksearch.fda.gov/

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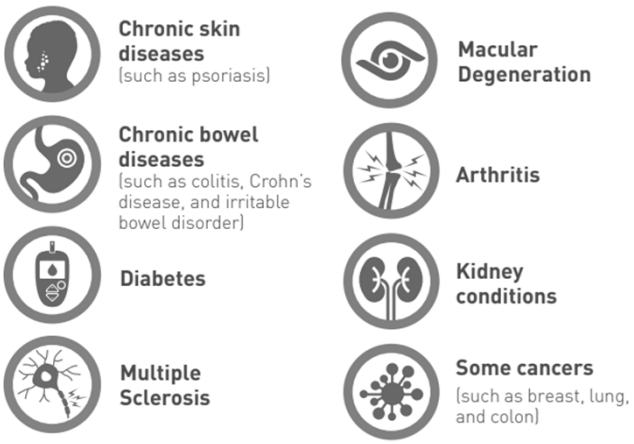
What diseases have the most biosimilars?



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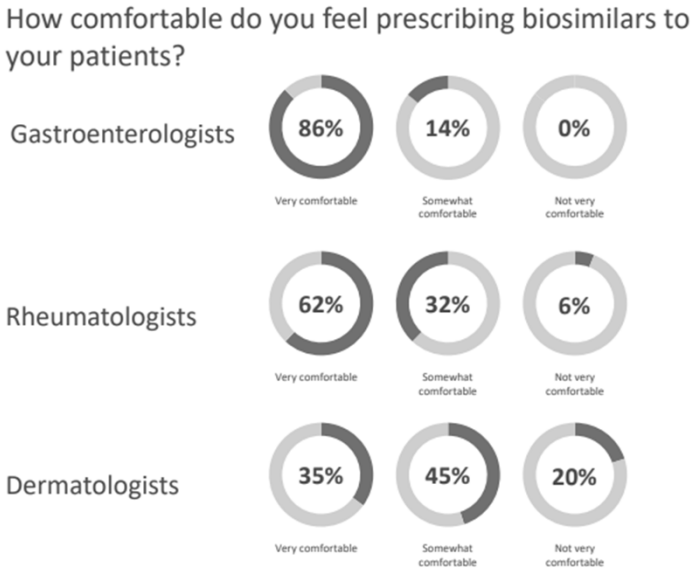
There is a learning and comfort curve



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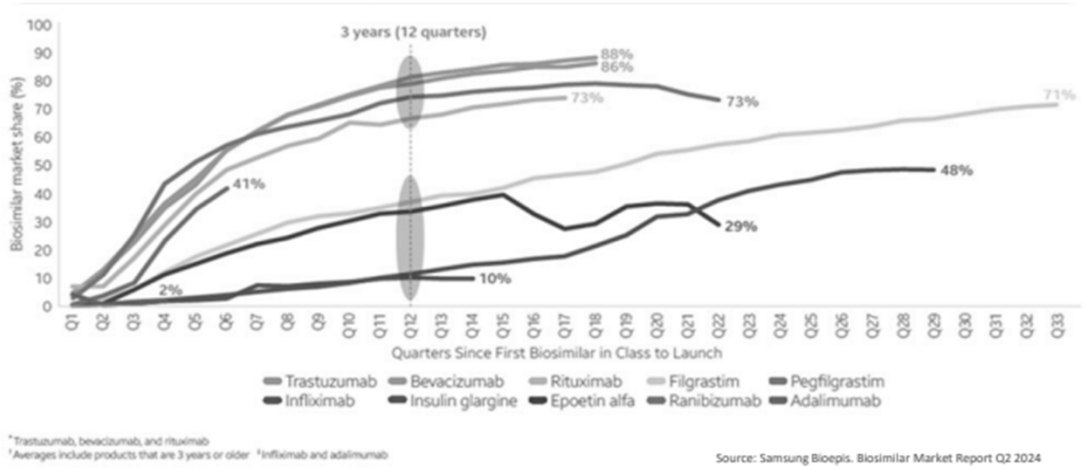
Biosimilars make a big splash, or not…



*Trastuzumab, bevacizumab, and rituximab
†Averages include products that are 3 years or older ‡Infliximab and adalimumab

Source: Samsung Bioepis. Biosimilar Market Report Q2 2024

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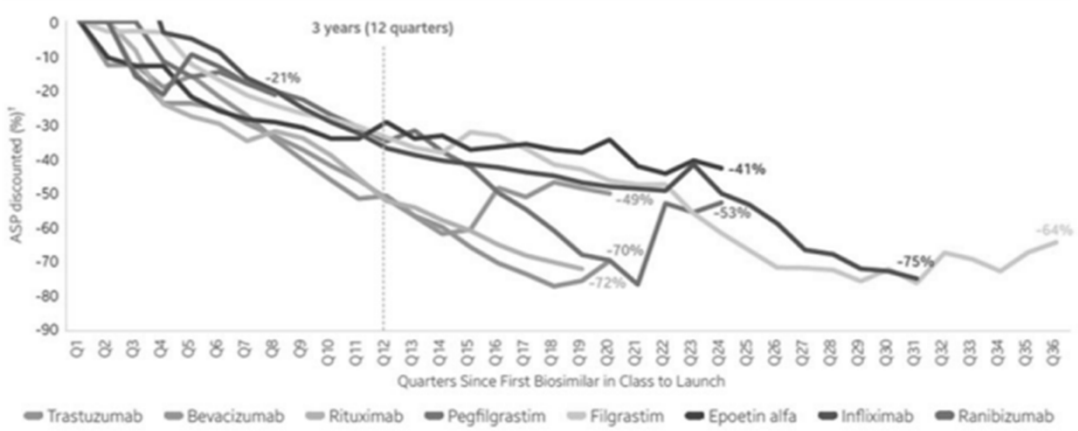
Biosimilars cut costs for themselves and reference biologics…



TA: Therapeutic area; ASP: Average sales price
*Trastuzumab, bevacizumab, and rituximab are included †ASP discounted % vs. reference product ASP when first biosimilar in class launch

Source: Samsung Bioepis. Biosimilar Market Report Q2 2024

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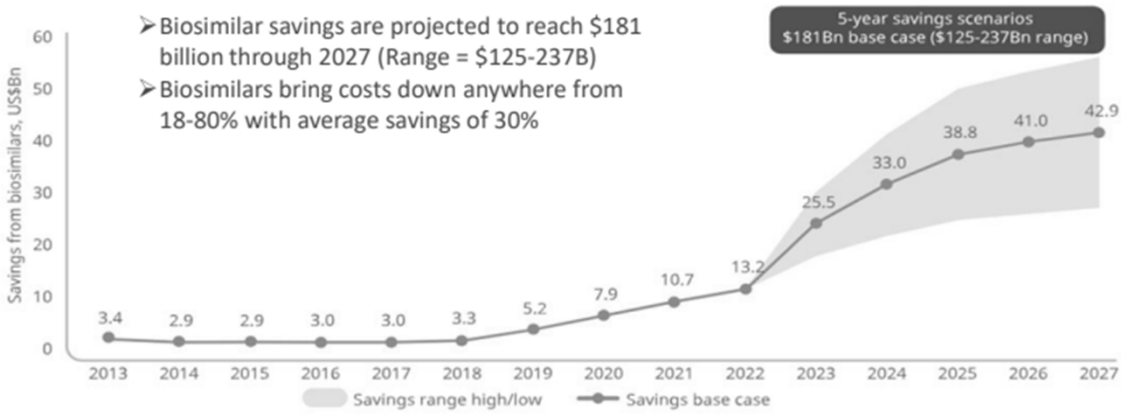
Future projected savings



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Explaining biosimilars to patients

- Patients are prone to the nocebo effect
  - The nocebo effect is either feeling an equally efficacious product is less effective than a brand or reference product or that they are experiencing new adverse events not seen with a generic or biosimilar product
  - Patient education is key to reducing the impact of the nocebo effect
- Prescribers may not fully understand how strong the regulations surrounding biosimilars are, or the large cost savings
  - They may convey to the patient information in ways that contribute to the nocebo effect
- Pharmacists are uniquely qualified to prepare patients to switch to a biosimilar
- FDA brochure:
  - file:///C:/Users/cmw02007/Downloads/Biosimilars-What-Patients-Need-To-Know.pdf

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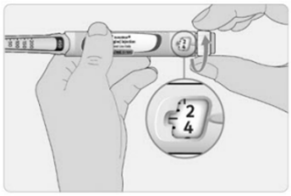
Pharmacist should also explain the delivery technology

- While the efficacy and safety of a biosimilar and reference product is the same, there can be differences in things like the autoinjectors
- Sharing those differences and being the Rosetta stone for the patient makes a big difference
- Here are three pens, one reference and two biosimilar
  - The location of wording, the clear window, how you put on and take off the needles are all the same
  - The colors of the pen, the name of the product, and how you prime the new needle is different
    - Some require 2 but one requires a 3 unit prime



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Pegfilgrastim vs Pegfilgrastim-pbbk

- The only difference is the color
- Same time out of fridge, volume, injection sites, and technique

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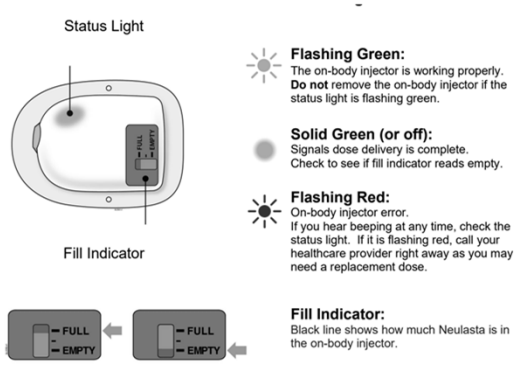
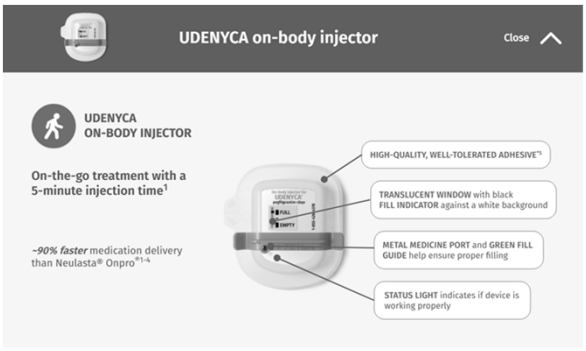
Pegfilgrastim (Neulasta OnPro) vs. Pegfilgrastim-cbqv (Udenyca On-Body)

- Same shape, one is white, one is tan
- Same injection sites
- Indicator lights and fill indicators are slightly different
- <u>One delivers 90% faster than the other!</u>





https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Neulasta/neulasta_patient_ifu_obi.pdf

https://udenyca.com/hcp/administration-options

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Case 1: Select Therapy

- A patient comes into your pharmacy and asks to speak with you. When you go to the counseling counter, the patient relays that rituximab therapy is just too expensive. You see this on the Purple Book:

1. Can you automatically interchange any of these options?
    - Yes (and which one) or No

Riabni (rituximab-arrx)	
BLA Number: *761140*	*351(k) Biosimilar*
Rituxan (rituximab)	
BLA Number: *103737*	*351(a)*
Rituxan (rituximab)	
BLA Number: *103705*	*351(a)*
Ruxience (rituximab-pvvr)	
BLA Number: *761103*	*351(k) Biosimilar*
Truxima (rituximab-abbs)	
BLA Number: *761088*	*351(k) Biosimilar*

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Case 1: Select Therapy

1. Can you automatically interchange any of these options?
   - Yes (and which one) or **No (none are Interchangeble Biosimilars)**
2. What can you do?
   a) You are powerless
   b) You can contact the prescriber and say the patient wants a biosimilar
   c) You can contact the prescriber with a specific cost effective biosimilar in mind

Riabni (rituximab-arrx) **BLA Number:** 761140	*351(k) Biosimilar*
Rituxan (rituximab) **BLA Number:** 103737	*351(a)*
Rituxan (rituximab) **BLA Number:** 103705	*351(a)*
Ruxience (rituximab-pvvr) **BLA Number:** 761103	*351(k) Biosimilar*
Truxima (rituximab-abbs) **BLA Number:** 761088	*351(k) Biosimilar*

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Case 1: Select Therapy

2. What can you do?
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Case 1: Preempting the Nocebo Effect

3. When your recommended rituximab-arrx biosimilar is prescribed, how can you preempt the patient from falling victim to the nocebo effect?

a) Reinforce that biosimilars are inexpensive but equally effective and safe versions of the biologic they were taking.
b) Go into the deep science and talk about tertiary protein folding difference but that they are not in the critical molecular areas.
c) Tell them about how the deep state is out to get them and that taking a biosimilar leads to brainwashing impelled prescribing of 5G linked vaccines that makes people “Libtards”.

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Case 1: The Future

4. You make the substitution to rituximab-arrx and three years go by with no issues. Then the efficacy starts to wane, and some flair ups occurs. What is the best course of action for the patient?

a) Switch back to the reference biologic rituximab
b) Switch to another biosimilar rituximab-pvvr
c) Switch to a biologic drug in another class

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Case 1: The Future

4. You make the substitution to rituximab-arrx and three years go by with no issues. Then the efficacy starts to wane, and some flair ups occurs. What is the best course of action for the patient?

a) Switch back to the reference biologic rituximab
b) Switch to another biosimilar rituximab-pvvr
c) Switch to a biologic drug in another class

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Case 2: Switching

5. A patient has been taking successfully taking adalimumab-ryvk for a year now but, due to a supply chain issue, you do not have it in stock. Can you automatically substitute it for adalimumab-adbm?

a) You would look at the Purple Book and if one of them is an interchangeable biosimilar, the answer is yes
b) You can always automatically substitute a biosimilar to another biosimilar regardless if one is interchangeable or not
c) Both of the products need to be interchangeable biosimilars to automatically substitute it
d) You are not allowed to swap out one biosimilar to another even if one of the other is an interchangeable biosimilar

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Case 2: Switching

5. A patient has been taking successfully taking adalimumab-ryvk for a year now but, due to a supply chain issue, you do not have it in stock. Can you automatically substitute it for adalimumab-adbm?

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b) You can always automatically substitute a biosimilar to another biosimilar regardless if one is interchangeable or not
c) Both of the products need to be interchangeable biosimilars to automatically substitute it
d) You are not allowed to automatically swap out one biosimilar for another even if they are both interchangeable with a reference (you need to call the prescriber and get a new prescription)

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Case 3: Selecting Optimal Therapy

A patient is taking Lantus insulin glargine and comes in with a new prescription. You look at the Purple Book and see this:

6. You check the prices and see that insulin glargine-aglr is more expensive than Lantus, can you automatically substitute it?

Yes or No (and why)

Lantus (insulin glargine)	
BLA Number: *021081*	*351(a)*
Rezvoglar (insulin glargine-aglr)	
BLA Number: *761215*	*351(k) Interchangeable*
Semglee (insulin glargine)	
BLA Number: *210605*	*351(a)*
Semglee (insulin glargine-yfgn)	
BLA Number: *761201*	*351(k) Interchangeable*

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Case 3: Selecting Optimal Therapy

A patient is taking Lantus insulin glargine and comes in with a new prescription. You look at the Purple Book and see this:

6. You check the prices and see that insulin glargine-aglr is more expensive than Lantus, can you automatically substitute it?

Yes or No (and why)

It depends on the state. In CT, the answer is no. The cost has to be less before it is switched.

7. Follow up, if insulin glargine (Lantus) was $300, glargine-aglr was $260, and glargine-yfgn was $210, could you automatically substitute with the glargine-aglr?

Yes or No (and why)

Lantus (insulin glargine)	
BLA Number: *021081*	*351(a)*
Rezvoglar (insulin glargine-aglr)	
BLA Number: *761215*	*351(k) Interchangeable*
Semglee (insulin glargine)	
BLA Number: *210605*	*351(a)*
Semglee (insulin glargine-yfgn)	
BLA Number: *761201*	*351(k) Interchangeable*

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Case 3: Selecting Optimal Therapy

7. Follow up, if insulin glargine (Lantus) was $300, glargine-aglr was $260, and glargine-yfgn was $210, could you automatically substitute with the glargine-aglr?

Yes or No (and why)

Yes, in some states the price doesn't matter while in others like CT, the product has to be lower than the reference drug but does not have to be the lowest interchangeable biosimilar.

Lantus (insulin glargine) BLA Number: 021081	351(a)
Rezvoglar (insulin glargine-aglr) BLA Number: 761215	351(k) Interchangeable
Semglee (insulin glargine) BLA Number: 210605	351(a)
Semglee (insulin glargine-yfgn) BLA Number: 761201	351(k) Interchangeable

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General Question 1

8. How is a biosimilar different from a generic drug?

a) A biosimilar is a small molecule product while generic drugs are large molecule

b) A biosimilar requires both immunogenicity assessments and pharmacodynamic assessments while generic drugs do not

c) A generic drug requires both immunogenicity assessments and pharmacodynamic assessments while biosimilars do not

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General Question 1

8. How is a biosimilar different from a generic drug?

a) A biosimilar is a small molecule product while generic drugs are large molecule

b) A biosimilar requires both immunogenicity assessments and pharmacodynamic assessments while generic drugs do not

c) A generic drug requires both immunogenicity assessments and pharmacodynamic assessments while biosimilars do not

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General Question 2

9. Which of the following would not promote defining something as a biologic?

a) Expensive price

b) Monoclonal antibody

c) Made from living cells

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General Question 2

9. Which of the following would not promote defining something as a biologic?

a) Expensive price

b) Monoclonal antibody

c) Made from living cells

However, biologics are very expensive and make up ~50% of drug spend but only 2% of drug utilization.

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Conclusions

- Biologics are large molecule products made from living cells and are generally very expensive
- Biosimilars and interchangeable biosimilars are both similarly safe and effective as a reference biologic but only interchangeable ones can be automatically substituted by a pharmacist
- There are state specific laws about interchangeability of biosimilars
- The FDA is lessening requirements for switch studies before approving something as an interchangeable biosimilar
- Patients need counseling to preempt or counter the nocebo effect and to understand nuanced differences in the technology associated with the products

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What you have all been waiting for…

Session code:

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