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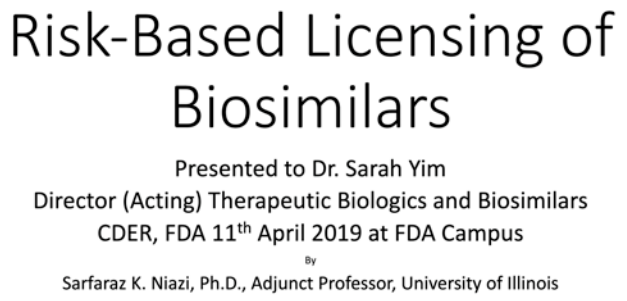
Peter Stein, MD
Director, Office of New Drugs, CDER
Sarah Yim, M.D.
Acting Director (Acting) OND Therapeutic Biologics and Biosimilars Staff (TBBS)
Sandra Benton, Senior Policy Coordinator
Office of New Drugs - CDER - FDA
White Oak Building 75, Room 6640
Silver Spring, MD 20993

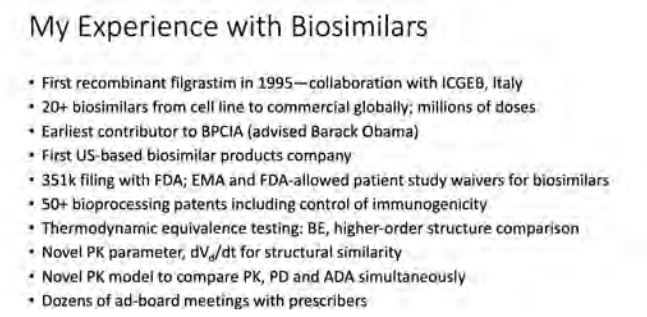


Dear Peter, Sarah and Sandy:

Thank you very much for this opportunity to meet with all of you in person to share my views on how a risk-based approach to licensing of biosimilars can help in making biosimilars more accessible. I have included in this letter, all of my presentation slides that I had shared with you to elaborate on my pending Citizen Petitions relating biosimilars.[1,2]

1. A Creative Approach

The FDA has a long history of bringing creative regulatory solutions to reduce regulatory burden without compromising the safety and efficacy evaluation. In March 2019, the FDA issued a risk-based guidance on managing clinical trials,[3] along with similar guidance on quality management,[4] and cGMP.[5] The risk-based approach to establishing safety and efficacy of biosimilars, as proposed here, is based on questioning the utility of the studies required and removing any redundancy, to expedite faster entry of biosimilars to the US markets.



[1] https://www.regulations.gov/document?D=FDA-2019-P-1236-0001
[2] https://www.regulations.gov/document?D=FDA-2018-P-1876-0001
[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633316.pdf
[4] https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf
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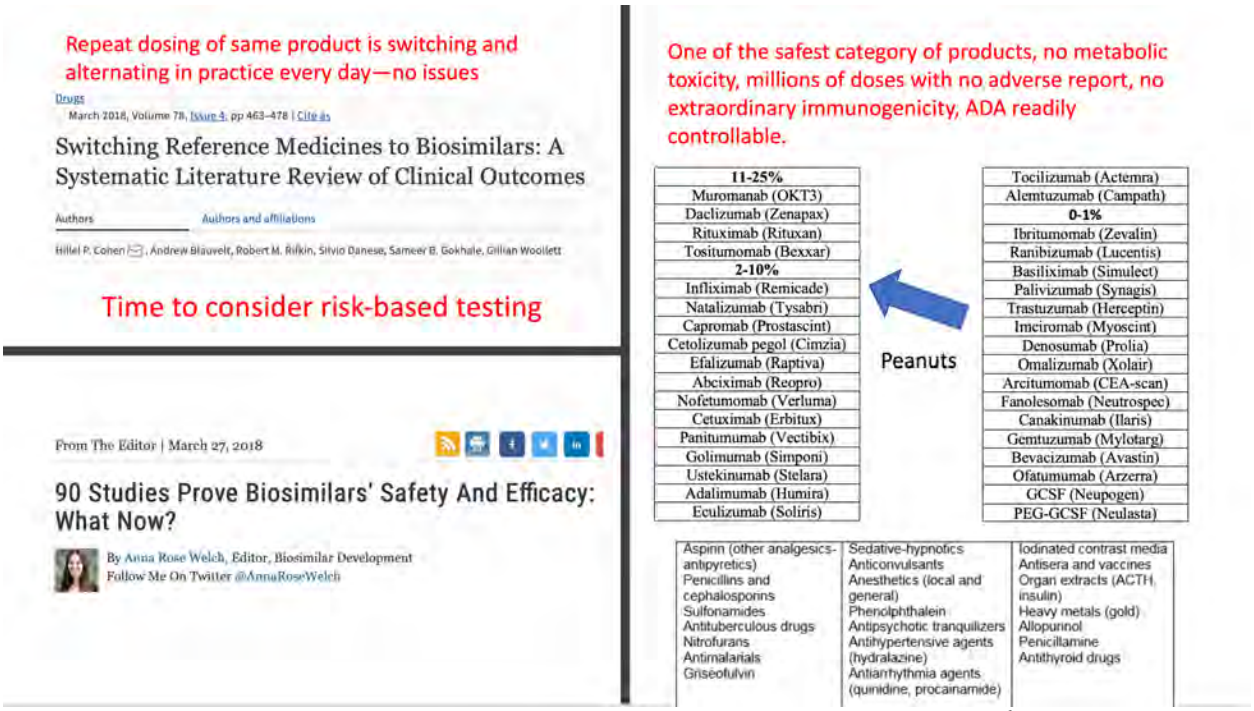
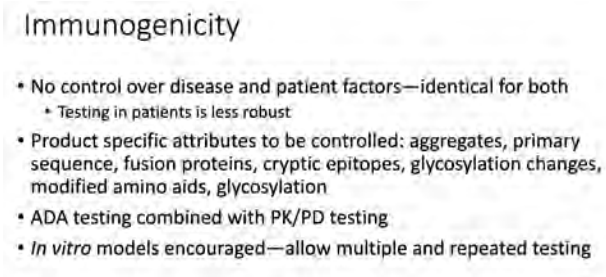
2. Safety of Biosimilars



Historically, biosimilars have to be one of the safest categories of drug products[6] with the exception of the reported PRCA in the use of erythropoietin[7] that was associated with a formulation and route of administration change, before the BPCIA that would have not be allowed this change.

The overall risk of immunogenicity of biosimilars is not extraordinary when compared to chemical drugs and even to foods. A large number of biological protein drugs have little immunogenicity. The main risk in the use of biosimilars or the originator product is the development of anti-drug-antibodies, a risk that is readily identified in simple studies.

2.1. Immunogenicity

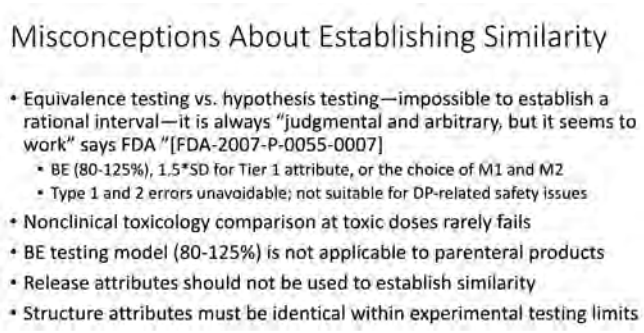


The FDA strongly recommends that at least one clinical study conducted to compare the immunogenic potential of a biosimilar candidate with a reference product. The testing for immunogenicity is complicated because the responses are highly dependent on the disease and patients, making it difficult to isolate the dosage form factor, which the purpose of the immunogenicity study. Immunogenicity studies in healthy subjects can be useful but never definitive in the absence of the disease and the patient factors. The product specific attributes contributing to immunogenicity are widely known and should form the first line of assuring safety of products. Ideally, the immunogenicity studies are conducted in phase IV, REMS stage in actual use in

[6] https://www.ncbi.nlm.nih.gov/pmc/?term=biosimilars+adverse+reaction&cmd=DetailsSearch
[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2730535/

patients; however, to develop more confidence in this approach, the FDA may start with the list of drugs as provided above where the immunogenic response is minimal. Selection of products allowed initial waiver should include low incidence products and not include products that have a wide range of immunogenicity record that indicates a lesser robustness to waiver. A good example of the practice of this suggestion is provided by EMA where they have allowed immunogenicity testing waivers to biological products like teriparatide which is treated as biosimilar in EMA but a PDUFA product in US, based on the historical record of reported immunogenicity, relative simplicity of the molecular structure and lack of PTMs.[8] It will be appropriate for the FDA to allow the developers to present arguments to waive immunogenicity testing, at least in the development phase and these arguments may include public data, scientific rationale, *in vitro* testing and other relevant documents.

3. Establishing Similarity



The FDA created equivalence testing when the generic drugs were allowed to enter the market without efficacy testing; bioequivalence was considered sufficient to equate clinical efficacy because the generic products are pharmaceutically and chemically equivalent. The FDA chose an interval of 80-125% that was challenged in my Citizen Petition[9], to which Dr. Woodcock responded after nine years that while there is a need to establish more novel approaches to establishing bioequivalence, the current system seems to work well.[10] Applying this model to biosimilars, using the same PK parameters as AUC and C_{max}, is further questioned because the BE model is intended to study differences in the absorption, a disposition phase that is either absent (in IV) or minimal (in SC).

Analytical similarity testing is the most significant part of development of biosimilars; the FDA has recently withdrawn its guidance on statistical treatment of similarity data because of the inconsistencies that I had pointed out repeatedly in several papers and also in my Citizen Petition.[11] The critical quality attributes that were subject for similarity comparison came from both the drug substance and drug product, creating a dilemma that a product may be suitable for patients, yet it will fail analytical similarity—a good example is the protein content. A fresh look at the risk analysis tells that analytical similarity testing should primarily apply to molecular structure that is responsible for the activity and immunogenicity. The primary, secondary, tertiary and quaternary structures are determined by the expression system, while other attributes are dependent on the process and formulation of the product. A different set of similarity assessment is needed for the structural elements and other critical quality attributes such as protein content, bioactivity, impurity, and physical properties based on industry-established limits, the USP specification or based on the values observed in the reference product (e.g., PTMs).

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[8] https://www.ema.europa.eu/en/documents/product-information/terrosa-epar-product-information_en.pdf; https://www.ema.europa.eu/en/documents/product-information/movymia-epar-product-information_en.pdf

[9] https://www.regulations.gov/document?D=FDA-2007-P-0055-0002

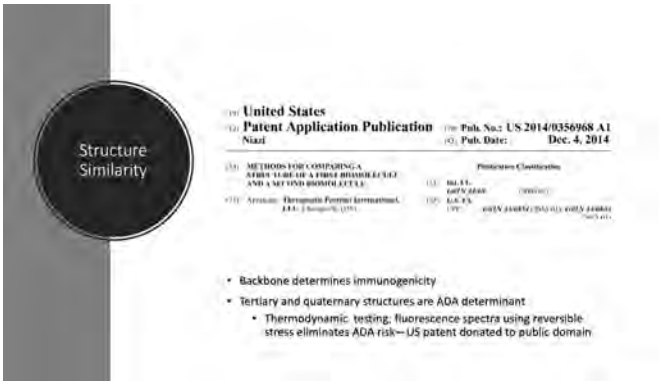
[10] https://www.regulations.gov/document?D=FDA-2007-P-0055-0007

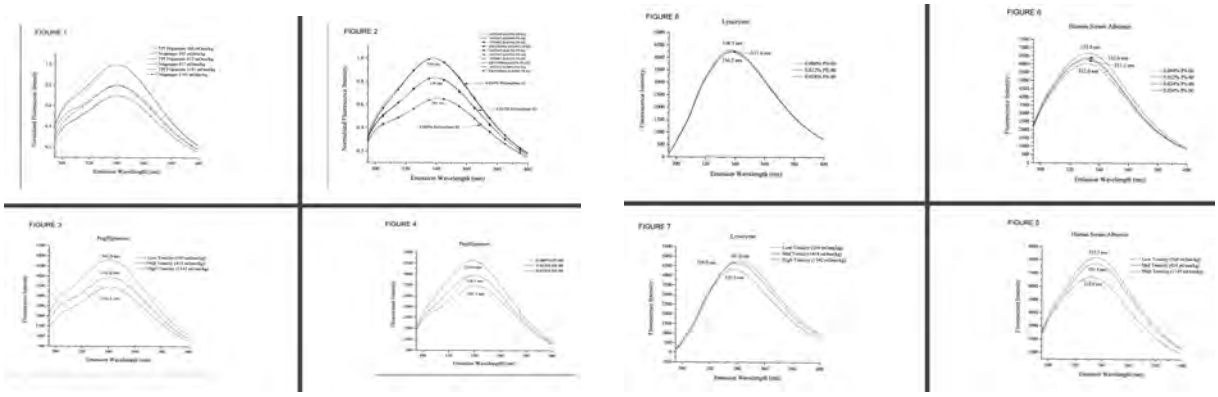
[11] http://www.regulations.gov/document?D=FDA-2018-P-1876-0001

The animal toxicology testing is a controversial topic because it may not provide any useful information. The toxicology studies are appropriate for new drug entities but not for biosimilars where analytical similarity testing has established that the primary, secondary, tertiary ad quaternary structures are similar. The current protocols of animal toxicology studies require testing at a dose to demonstrate toxicity that is often an extension of pharmacological response that will be in the non-linear end of the curve wherein it will be difficult to demonstrate any difference.

3.1. Thermodynamic Similarity Testing

While the secondary, tertiary and quaternary structures of a protein molecule are dependent on the primary structure, the safety and efficacy can be highly dependent on derivative structures because of the mode of action that invariably involves receptor binding that can be altered by all structure differences. A common test to establish structural similarity is the forced degradation comparison that can define the subtle structural variability; however, this





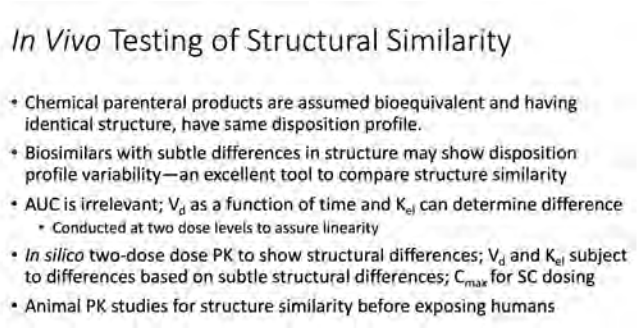
testing is conducted at the level of challenge that can miss out more subtle differences. I have developed and used a thermodynamic approach wherein the protein solution environment is altered resulting in a reversible spectroscopic shift—the shift is then compared between the biosimilar candidate and the reference product. Thermodynamic challengers include temperature, polarity, dielectric property, surfactant concentration, pH, physical stress, electromagnetic exposure and any other stress that is capable of inducing a reversible change in the structure of the molecule.

To allow biosimilar developers to use this technique, I have donated the invention to public domain.

3.2. *In Vivo* Structure Similarity Testing

Protein drugs are degraded in the body to innocuous protein fragments and amino acids; the activity and adverse effects of protein drugs lasts only until the full structure is maintained in its entirety; how the body views a protein molecule and how it is distributed and degraded in the body may provide another testing method—the concept *in vivo* structural similarity testing. It is noteworthy that the BE testing of small molecules is intended to identify only absorption

differences since the small molecules are identical in structure and therefore, subject to the same forces of distribution and elimination.



However, there is a need to redefine the PK profile analysis. Biological products are mostly administered through parenteral route, except those administered through eye; products administered by IV route are assumed bioequivalent, so theoretically, there shouldn't be any difference in the PK profile, except for the differences in the disposition profiles that are more appropriately characterized by distribution volume and elimination rate constant, and not the currently proposed parameters of Cmax and AUC; where a product is administered by SC route, and there is a likelihood of variable absorption, these differences would be picked up in the distribution volume. While there is limited utility of Cmax, it is highly unlikely that a direct relationship between Cmax and efficacy can be established—this parameter can serve as a support parameter but not subjected to statistical testing. The distribution volume is related to diffusion into tissues and receptor binding and the elimination rate constant is relevant to metabolic apparatus as it acts on the protein injected.

Further, the FDA must declare that PK studies for drugs like ranibizumab and aflibercept that are administered by intraocular route and do not appear in blood, should not be conducted. This guidance should apply as an overarching guidance.

One of the widely debated issue in structural similarity pertains to the clinical efficacy as affected by glycan patterns; it is well-established that glycans do not alter the disposition kinetics, even though the efficacy can be affected.[12] A confirmation of the distribution and elimination attributes will help establish safety and efficacy of products where the glycan profiles may not be identical.

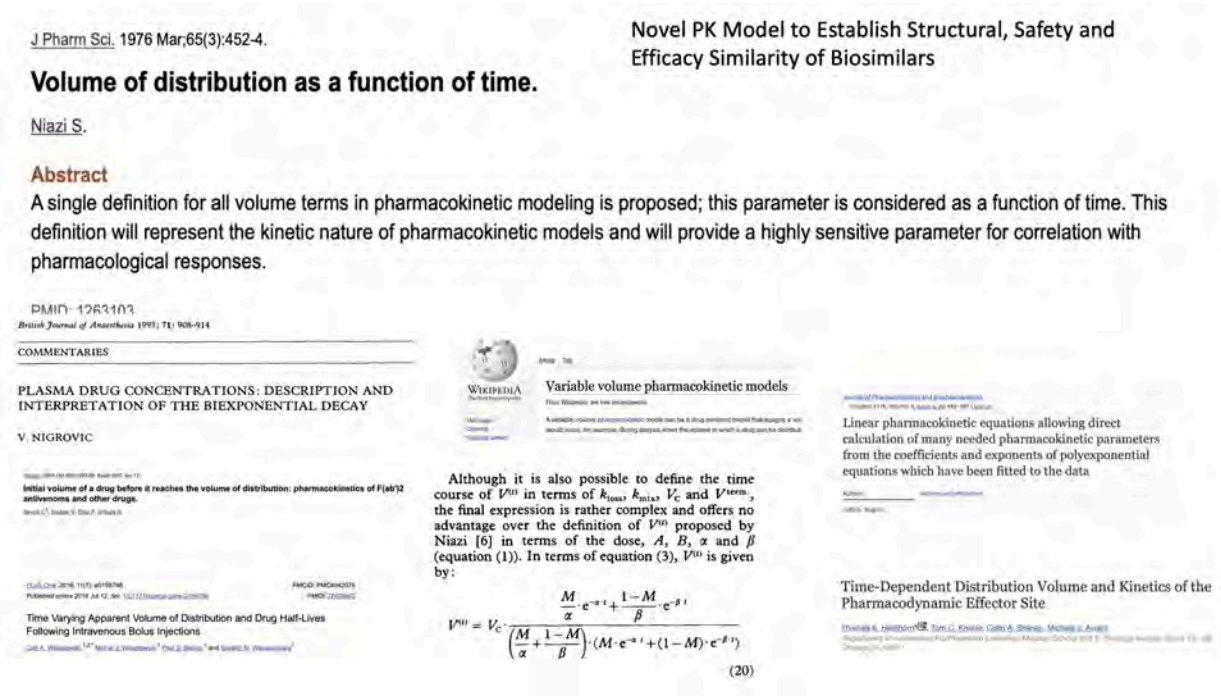
3.3. Distribution Volume as Pivotal PK Parameter

In 1976, I established a new PK parameter, distribution volume as a function of time; the most influential scientist John Wagner took it and derived many applications as did other scientists; the concept that I adduced combines thermodynamic forces with a kinetic force; while this parameter has served the purpose well, it is most appropriate to establish similarity of structure and molecular safety and efficacy of biosimilars. The concept is simple; when a drug is administered into general circulation, the distribution volume will be the volume of blood (not the central compartment; and considering both bound and unbound drug) that will soon expand as drug molecules equilibrate with other tissues and bind to tissues (receptors); calculated on the body weight basis, it is a thermodynamic parameter that can differentiate the nature of binding of biological drugs, more particularly in those instances where the rate of equilibration is also important. The distribution volume as a function of time is calculated on the body weight basis to reduce population variability.

I am proposing that the FDA consider using Vd and Kel as pivotal parameters and apply a simpler hypothesis testing model rather than creating an equivalence interval. A much smaller number of test subjects will be required to provide a highly sophisticated method of testing structural

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634315/

similarity. To make these studies more meaningful, a lower dose study is also recommended to study the Vd and Kel in the linear portion of the distribution and elimination capacity.



3.4. Non-clinical Testing

Animal toxicology studies are widely criticized, both on humanitarian ground, but more for the lack of utility of these studies in the development of biosimilars. A better utility of animal testing is in comparing PK parameters at several doses that might help identifying any subtle changes in the molecular structure.

4. DP Release Attributes

Drug product release specification is intended to provide a safe and effective product to patients; in several instances, over decades, we have determined the practical limits of manufacturing parenteral products and I do not see why this wisdom cannot be applied to establishing DP release attributes.

DP Release Attributes

[Limits based on Reference Product]

Attribute	Safety	Efficacy
Protein Content		±10% of label
Bioassay		±15% of label
Known impurities		NMT 3%, no single >1%
Unknown impurities	0%	
Post-translational Modifications		±10% of reference
Glycan profile		±10% of reference
Aggregates	NMT Reference	
Particulates	USP Limits	
pH, Osmolality		±10% of label
Surfactant		±50% of label

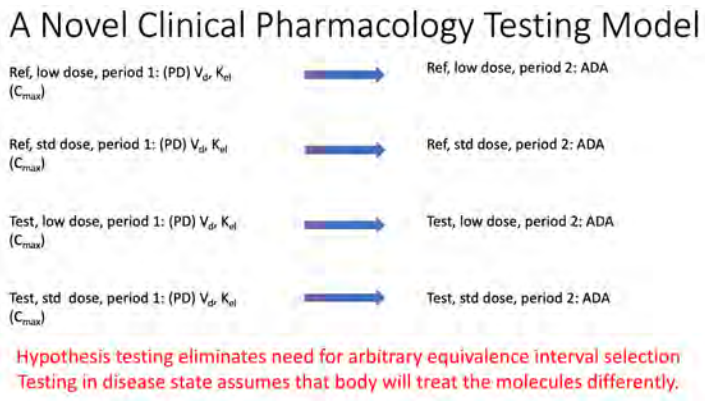
DP attributes determine the safety and efficacy because of their relationship with the process. Given below is a summary of various critical quality attributes and how these can be adjusted as needed and limits of release established.

Acceptable Ranges of Variability in Protein Products

Attribute	**Acceptable Range**	**Action Plan**
Molecular weight	Matches within experimental variation	None

Amino acid sequence	Matches, except terminal acids where allowed	None
Peptide Map	Matches within experimental variation	None
Secondary Structure	Matches within experimental variation	None
Tertiary Structure	Matches within experimental variation	Validate upstream and/or downstream
Disulfide bonds	Matches 100%	None
Glycans/Isomers	±10% of the average of the reference (3 lots)	Validate upstream/downstream
Forced degradation	Matches within experimental variation	None
Receptor Binding	Matches within experimental variation	None
Protein Content	±5% of label quantity	Validate formulation
Biological Activity	±15% of the label	None
Impurities, Known	±3%, no single more than 1%, no unidentified	Validate downstream process
Impurities, Unknown	None, except those known to be innocuous	Safety studies to validate
Aggregates	Not more than the average of the reference product (3 lots)	Validate downstream process; control fill and finish
Physical Attributes	±10% of the labeled amount (higher for surfactants)	Validate formulation and process
Particles	Meets USP test for subvisible particles	Validate formulation and process

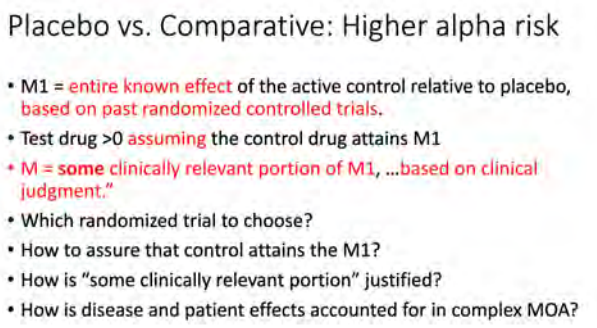
5. Minimizing Exposure to Healthy Subjects

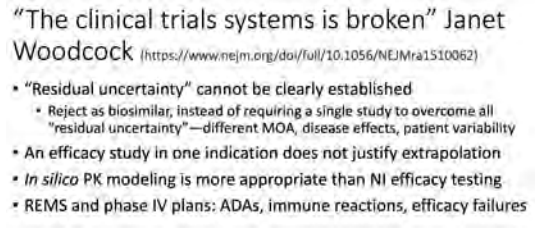


A basic tenet of the Hatch-Waxman is to minimize exposure to humans that translated into waiving clinical efficacy testing if a generic product meets other conditions. When testing biological drugs, the risk of exposure to healthy subjects is perhaps more severe, ranging from immunogenic response to creating ADAs for life and such reactions as PRCA as we have observed in the past. In my opinion, a single study with four arms run parallel at two doses will conclude structure, PK, PD and ADA evaluation. A simple ANOVA for hypothesis testing is sufficient that will reduce the size of population required.

6. Additional Clinical Studies

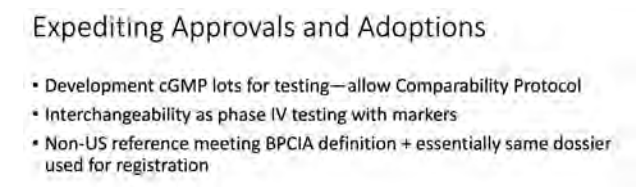
Each of the 18 products licensed by the FDA as biosimilars conducted extensive testing in patients in a two-way or one-way (non-inferiority) mode in large patient populations. To the best of my knowledge, none of these studies ever failed raising the question whether these studies were needed in the first place? What triggers a required in-patient study has never been made clear by FDA; the developers planning to use these studies to promote their products are often too eager to conduct these studies, raising the bar for other developers. When a new molecule is developed, a testing against a placebo is fully justified and the FDA decides whether the response compared to placebo is reasonably justified against the adverse events. While this too is a judgmental call, it is a reasonable approach. However, when comparing a biosimilar candidate with a reference product, the comparability bar is raised as both arms are active requiring establishing an equivalence criterion that is also judgmental but, in this case, there is no justified basis. Are we concluding similarity when the products are not similar (alpha error) and the studies are driven mostly by powering them to meet certain outcomes; in several instances, the FDA has pointed out that the studies are unreasonably powered, yet accepted the results?





Another objection to clinical efficacy testing of biosimilars comes in the use of a single clinical study to overcome all "residual uncertainties" allowing extrapolation of all indications. If it is concluded that there is a residual uncertainty, then it cannot be removed with just one study, given that there could be multiple modes of actions. In my opinion, such products should be rejected under 351k.

7. Making Biosimilars More Accessible



While the cost and time it takes to develop a biosimilar should never be a consideration when it comes to assuring safety and efficacy of biosimilars, the FDA has taken it on itself to promote approval and adoption of biosimilars. One step taken by the FDA to require a four-letter suffix to the common names of biological drugs has worked against establishing confidence in biosimilars. Moreover, as of March 2019, a final guidance on naming of biological products was revised requiring the suffix to apply only to biosimilars[13] stating:

[13] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf

> FDA no longer intends to modify the proper names of biological products that were licensed under the PHS Act without an FDA-designated suffix in their proper names.[7] FDA also does not intend to apply the naming convention to the proper names of transition biological products.[8]

It is widely debated and established that there is no pharmacovigilance issue as the label that provides the suffix details also provides other information that is totally adequate to trace the products. The only purpose the use of suffix has served is to misguide stakeholders about the safety and efficacy of biosimilars. Examples are provided here.

The issue of interchangeability has long been debated; reality is that a patient receiving repeated dosing of an originator biological product undergoes switching and alternating inevitably without any safety or safety concerns. Unfortunately, the BPCIA has tied down the hands of FDA, so my suggestion is that the FDA carves out simple protocols that can be executed post approval in a limited number of patients to qualify a change of status to interchangeable.

Other issues where the FDA can help is in letting the developers submit data based on smaller scale lots and exercise the Comparability Protocol to scale-up; this will allow smaller companies to enter the market quickly. [This is a similar approach allowed in the filing of 505(b)(2) products.]

The FDA is also known to be most stringent in allowing use of non-US comparator that is needed to create global dossier, but here too, the hands of the FDA are tied down by the BPCIA; my conclusion is that the FDA has the legal authority to allow use of a non-US comparator by placing certain restrictions on it, namely that it meets all requirements of BPCIA and also have been approved using essentially the same dossier as used to secure licensing of the product in the US.

8. Summary

1. A well-defined risk-based approach will allow availability of a transparent system that will allow innovations to take place of traditional, often archaic methods of testing. Any testing that is based on an equivalence interval or range, must have rational basis, more particularly if it is used as "one size fits all," contrary to FDA's teaching that it should not. While common wisdom teaches us that these statistical testing methods are useful and have worked for decades, I am of opinion that now is the time to question this method, at least when it comes to establishing similarity of safety and efficacy of biosimilars with the reference product. We discussed and I provided examples of situations where the use of equivalence may result in approval of unqualified products; while I am motivated to bring biosimilars to market faster, and at a lower cost to developers, I am seriously concerned that this statistical methodology may allow entry of unqualified products into market. I have provided alternate methods of evaluation that are more robust and reliable.
2. Analytical similarity should be established on the molecular structure, tested side-by-side with the reference product; these attributes are expression-system dependent and need to be as similar as experimentally possible, not through any equivalent interval or range method; it is this stage where the FDA should be able declare a product not qualifying as a

351k candidate. I have also provided a thermodynamic structure comparison method that I have donated into public domain; I shared with you that using this method, many products might fail similarity while meeting other equivalence-based testing. I strongly urge the FDA to consider this, as well as, many other novel methods of comparing structures of complex molecules that have become available over the past decade.

3. Dosage form factors are dependent on the process, upstream, downstream and formulation and manufacturing; these attributes, unlike the molecular structure, can vary between batches; with decades of experience, FDA has the wisdom to recommend the release limits without referring to the reference standard, except where a range and identity needs to be established like the identity of impurities, and PTMs. These attributes should not be part of the analytical similarity testing.
4. Animal toxicology studies provide determination of safety windows for new chemical entities; for biosimilars, these studies are conducted at a dose level where the comparative studies will never fail; I am proposing to remove all toxicology studies and replace them, where justified, with animal PK studies at several doses to establish structural similarity.
5. Clinical pharmacology studies form the backbone of biosimilar approvals; unfortunately, the use of protocols used for generic drug approval have rendered these studies of lesser value, compared to the risk of exposing healthy subjects to a potent drug. The bioequivalence concept does not apply to biosimilars—instead it is the Vd and Kel that can be related to how the body sees the molecular structure of the biosimilar product compared to the reference standard. I have provided a simplified, yet highly robust protocol to answer all questions relating to structure similarity, safety and efficacy with limited number of subjects. Immunogenicity studies needs to be rationalized based on the risk associated with a given product, and the protocol that I have provided should answer all questions relating to safety and efficacy.
6. Additional clinical studies that involve efficacy testing are not recommended for several reasons; first, a residual uncertainty, if found cannot be relieved by a single clinical study in one of the chosen indications; second, the M1/M2 chosen for these studies can easily result in approval of products that not biosimilar. In my opinion, if the FDA is not satisfied with the similarity profile, the product should be rejected as 351k candidate and the developed advised to seek the 351a route.
7. In my first-hand experience, the FDA does not enjoy a high trust among many stakeholders regarding the safety and efficacy of biosimilars. There are a variety of reasons and the FDA is doing a great job educating all stakeholders; however, using a suffix to differentiate, now only biosimilars, has harmed the status of biosimilars as I showed in many examples; I am totally convinced that the label that will identify the suffix will also identify the product through the rest of the information about traceability. I strongly urge the FDA with withdraw this guidance to prevent more damage to the adoption of biosimilars.
8. There is a need to revise the requirements of cGMP compliance of biosimilars, particularly the PPQ compliance at the time of filing and the use of commercial scale products; other similar approvals take a more practical approach and I recommend that the FDA allow PPQ after the filing and scaling up under the Comparability Protocol; these changes will enable smaller companies to enter the biosimilar markets with lesser burden.
9. It is highly commendable that the FDA allowed me to present my views, some of which may appear critical of the current practice of approving biosimilars and I am totally confident that the scientific leadership at the FDA has always come up with solutions that

are rational, transparent and futuristic. I am confident that the FDA will continue this trend as the biosimilars come to maturity.

I hope you find these comments useful as you embark on issuing new guidance for biosimilar developers. I am iterating my offer that I am available to discuss these and any other topics that the FDA may want to consider as the BAP gets ready to be revealed.

Sincerely,

Sarfaraz K. Niazi, Ph.D., SI, FRSB, FPAMS, FACB.
Adjunct Professor of Biopharmaceutical Sciences, University of Illinois and
University of Houston, Patent Agent, US Patent & Trademark Office.
20 Riverside Drive, Deerfield, IL 60015 | USA
Phone: +1-312-297-0000; Fax: +1-312-297-1100; www.niazi.com

Cc: Dr. Janet Woodcock, Head, CDER; Dr. Dr. Ned Sharpless, Acting Commissioner, FDA