

Regulatory and Scientific Challenges in Biosimilar Development: Nonclinical Considerations

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What is a Biosimilar?



What is a Biosimilar Drug?

- Each country/region has own definition
 - Individual countries/regions may have different definitions in different documents
- Generally, a biologic product highly similar to an already licensed biological product (originator, reference, or innovator product) in terms of quality, safety, purity, potency, activity, efficacy, etc
 - Not expected that all structural aspects are identical to originator product
 - Unlike small molecule generics where active ingredient(s) identical
 - Biosimilar amino acid sequence should match originator, but there will likely be differences in post translational modifications
 - Despite any differences, biosimilar should behave the same as originator



FDA Definition

- FDA definition (version for healthcare providers)
 - “Biosimilars are ... highly similar to an already FDA-approved biological product, ... and have been shown to have no clinically meaningful differences from the reference product. Minor differences in clinically inactive components are allowed. But there must be no clinically meaningful differences between the biosimilar and the reference product ... in terms of the **safety, purity, and potency** of the product.”



Biosimilar Terminology

Global terms used for biosimilars are ... somewhat similar, but not highly similar

Various Terms for Biosimilars	
Country/Organization	Term
US, Australia, China	Biosimilar
EU	Similar biological medicinal product
Japan, Korea	Biosimilar product
WHO	Similar biotherapeutic product
Canada	Subsequent-entry biologic
Mexico	Biocomparable
Brazil	Biologic product (vs new biologic product)
India	Similar biologic



Brief History of Biosimilars

- First therapeutic biologics approved in 1980's
 - Recombinant human insulin (Humulin) approved Oct 1982 by FDA



http://www.humulin.com/_Assets/img/vial_hru100.jpg

- First biosimilars approved in Europe by EMA in 2006
 - For somatropin (human growth hormone)
 - Omnitrope, Sandoz, Apr 12
 - Valtropin, BioPartners, Apr 24 (withdrawn in Aug 2012 for commercial reasons)



<http://www.musiktherapie-foren.de/wp-content/uploads/2015/09/omnitrope-label.jpg>

Brief History of Biosimilars (cont)

- First biosimilar mAb approved by South Korea in July 2012
 - Remsima from Celltrion, a biosimilar of infliximab
 - Approved and marketed in almost 70 countries as of Mar 28, 2016
- First biosimilar approved in US on Mar 6, 2015
 - Filgrastim-sndz (Zarxio)
- FDA just approved first biosimilar mAb (2nd biosimilar overall)
 - Infliximab-dyyb (Inflectra), on Apr 5, 2016



<http://cached.imagescaler.hbpl.co.uk/resize/scaleWidth/620/offlinehbpl.hbpl.co.uk/news/2MM/Inflectra-Remsima-infliximab-biosimilar-20150225021551373.jpg>



Why Can't Biosimilars be Generics?

- Active ingredient in small molecule products is typically a single simple structure which can be exactly reproduced
 - A generic
- Biotherapeutic products are a mixture of complex structural isoforms, many/all of which have biological activity
 - Protein production involves many steps, with many variables
 - Cell lines, media, culture conditions, purification, etc
 - Differences impact final product, sometimes substantially
 - Final proteins produced have differences in glycosylation, oxidation, deamidation, etc
 - “The process is the product”
 - Manufacturing a complex biologic to be exactly the same is not possible
 - Cannot exactly recreate the mixture of proteins

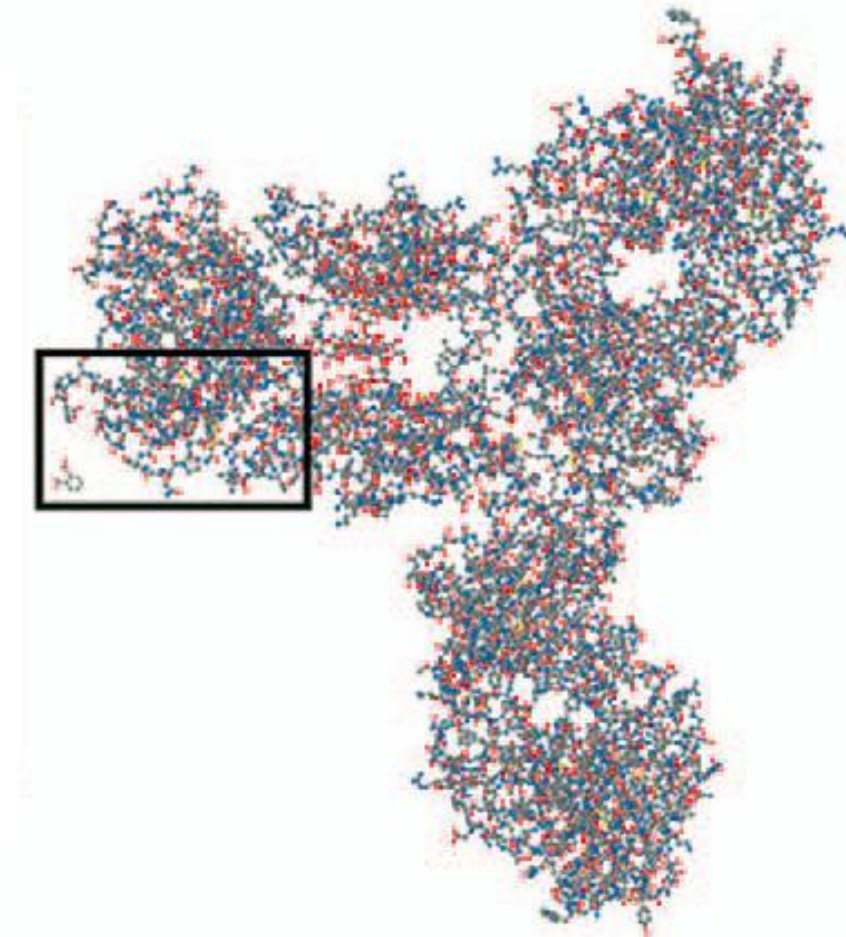


Why Can't Biosimilars be Generics (cont.)?

- In addition, biosimilar manufacturers may want to produce proteins using a more efficient process vs originator process (done many years before)
 - Reduces costs
 - May use different formulation
 - May even use different cell line vs originator
- Thus, the mixture of proteins produced by different manufacturers (originator and biosimilar products) will not be identical
 - But they must be highly similar and act the same
 - If they are “better”, then they are not a biosimilar, they are a biobetter, and are considered a new molecular entity requiring a full development package (nonclinical and clinical)



Structure Complexity: Biologics vs Small Molecules



Comparison between aspirin molecule and IgG mAb.
Aspirin has 21 atoms; MW = ~180 daltons
IgG mAb has ~20,000 atoms; MW = ~150,000 daltons
Insulin (not shown) has 788 atoms; MW = ~5,800 daltons

Mixture of Proteins: School of Fish Analogy



Each fish represents a molecule of a protein with certain CMC characteristics

Originator protein mixture

School of Fish Analogy – Similar Enough?

Which Molecules are Important for Efficacy? And Safety?



Proposed biosimilar

Originator protein
mixture

School of Fish Analogy – Similar Enough?

Which Molecules are Important for Efficacy? And Safety?

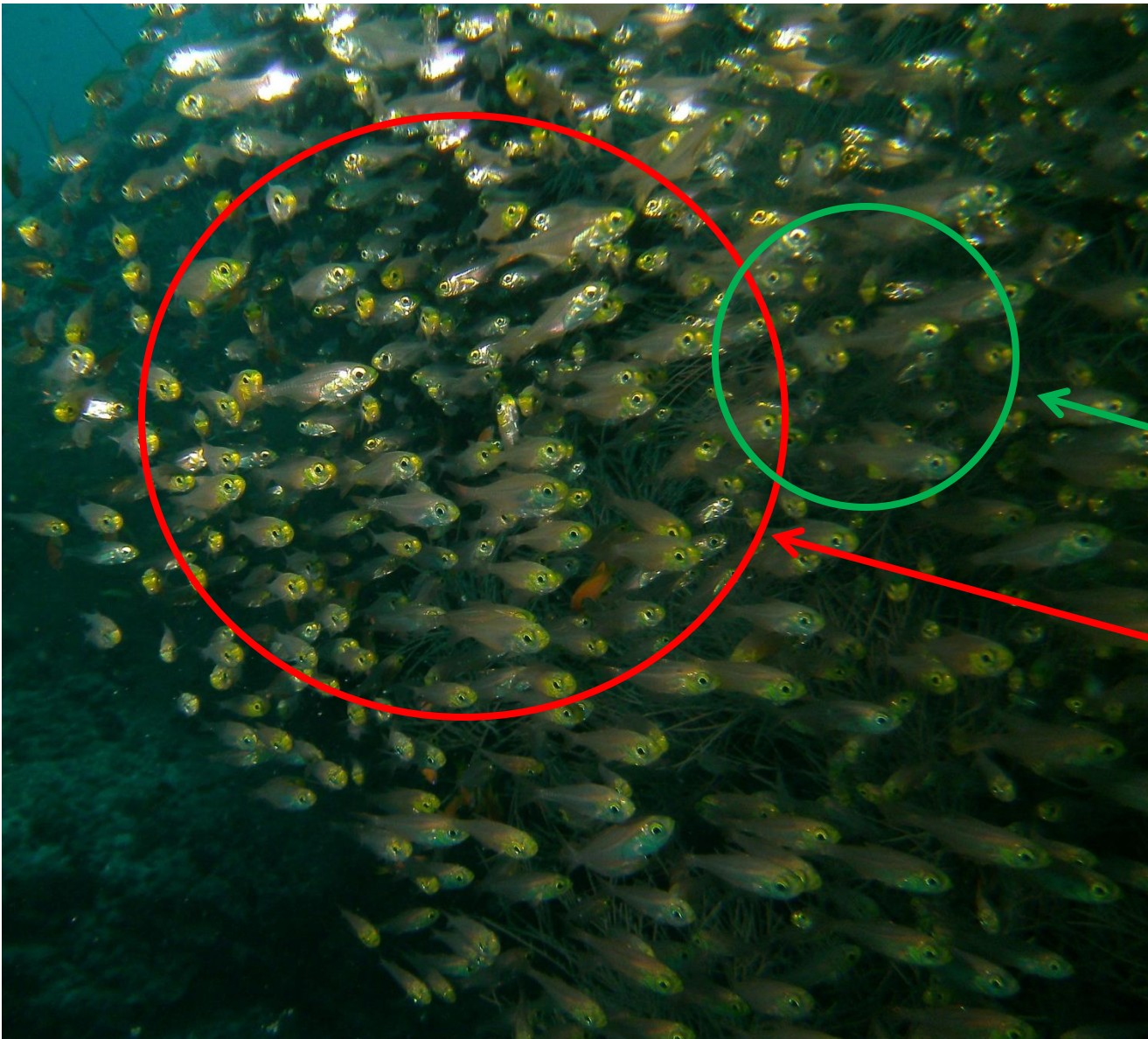


Proposed biosimilar

Originator protein
mixture

School of Fish Analogy – Similar Enough?

Which Molecules are Important for Efficacy? And Safety?



Proposed biosimilar

Originator protein
mixture

Why Make Biosimilars and Why The Big Push Now?

- Biosimilars are expected to have lower development cost, lower cost to patients, which should increase access to these medicines
 - Enhanced CMC package allows reduced nonclinical and clinical development efforts, compared with originator molecule
 - Can be manufacturing efficiencies using more current methods
 - Less expensive production

Reference Biologic Development



Biosimilar Development



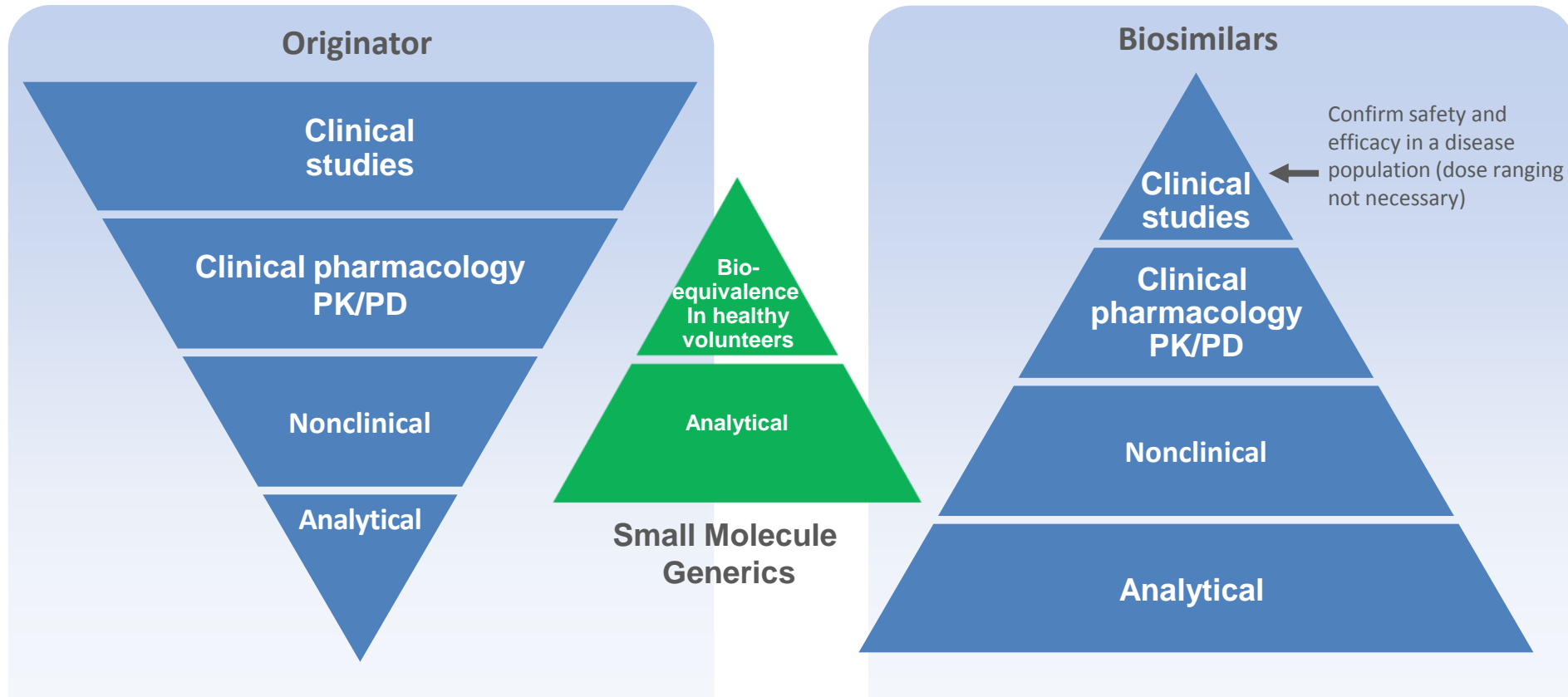
From
http://www.hospira.com.au/en/about_hospira/biologics/developing_biosimilars

- Many biotherapeutics are now coming off patent, opening the door to biosimilars



Relative Effort in Development Pathway

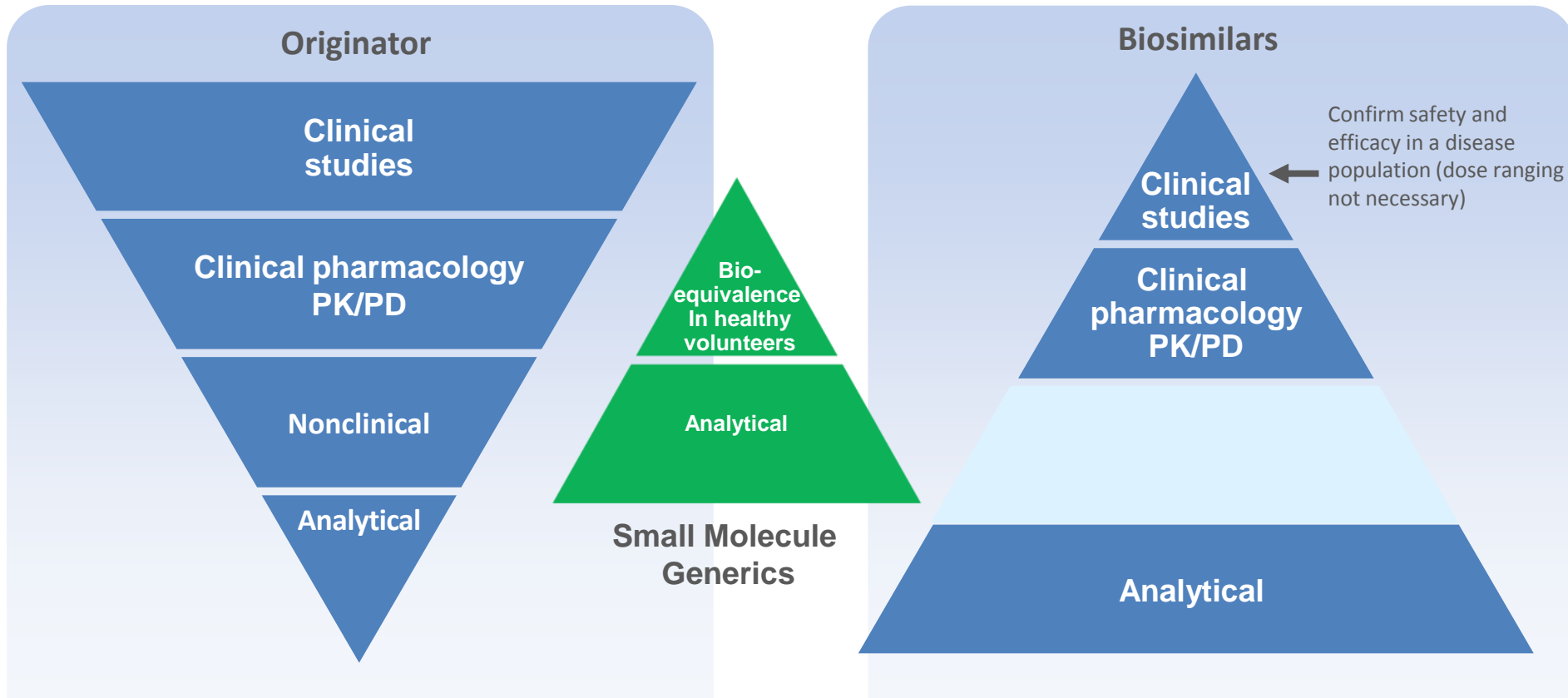
Originator vs Generic vs Biosimilar: Traditional



Modified from Berghout A. *Biologicals*. 2011;39:293-6; McCamish M. Presented at EMA Workshop on Biosimilars; London; October 2013; and MacDonald J, APEC Biotherapeutics Workshop, Seoul 2013.



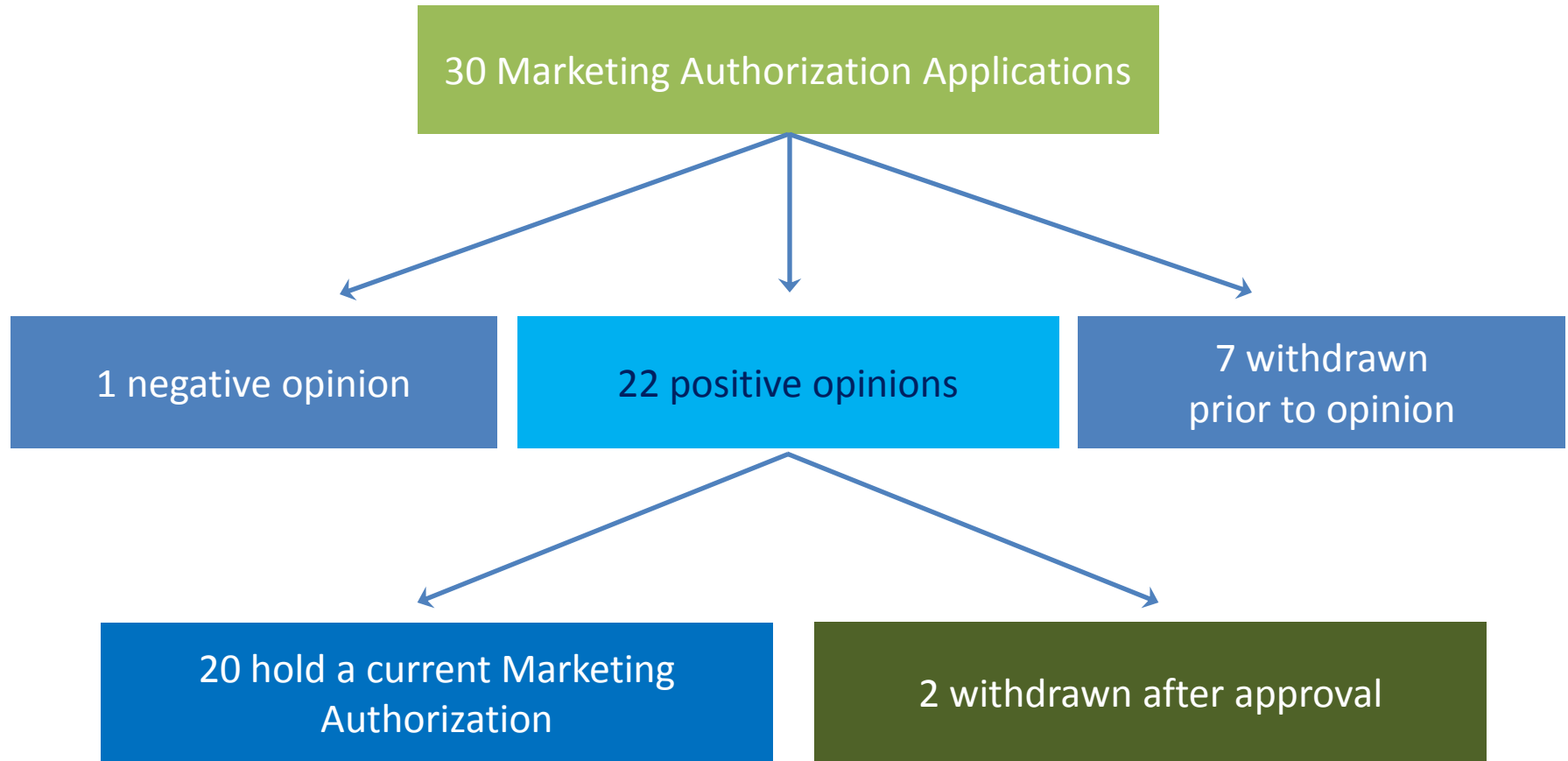
Relative Effort in Development Pathway Originator vs Generic vs Biosimilar: Revised



Modified from Berghout A. *Biologicals*. 2011;39:293-6; McCamish M. Presented at EMA Workshop on Biosimilars; London; October 2013; and MacDonald J, APEC Biotherapeutics Workshop, Seoul 2013.



Current Biosimilar Landscape in EU



Biosimilar Landscape in US (FDA)

- As of 30 September 2015, there were 57 proposed biosimilars participating in biosimilar product development program
 - 33 in FY 2013
 - 48 in FY 2014
 - 7 Biologics License Applications (BLAs) submitted as proposed biosimilars
 - First biosimilar approval March 2015
 - Zarxio
 - First biosimilar mAb approval Apr 2016
 - Inflectra

From Review of Biosimilar Biologic Product Applications by Eastern Research Group, Feb 24, 2016

- <http://www.fda.gov/downloads/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/UCM488846.pdf>



Evolution of Biosimilar Regulation

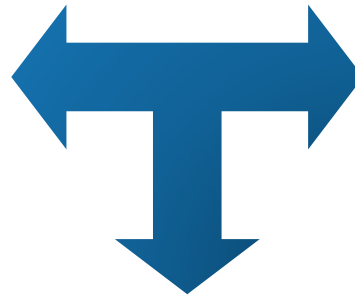
Two Choices From Existing Regulatory Systems

Regulate as Generics

Relies on being able to produce an identical product – not possible for a biologic, so generic regulatory route is not appropriate

Regulate as Novel Products

No safety issue in doing so, but in order to get the full range of labeled indications developers would have to repeat the nonclinical and clinical program of the originator product



Solution

Biosimilars concept as pioneered in the EU provides a tailored pathway so that not all nonclinical and clinical studies have to be repeated, but drugs receive a rigorous review



Global Regulatory Landscape

- Regulatory guidelines have varied globally
 - Temporally
 - Content

Evolution of biosimilar regulations, 2004-2014

				Taiwan						
				Malaysia	WHO	Saudi Arabia				
				Turkey	Japan	Brazil	Singapore	Mexico		
	EU			Australia	Korea	Canada	Peru	India		Iran
2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
				Argentina		S Africa	Chile	Venezuela	Peru	Jordan
								Egypt	Colombia	
								USA		
								Italy		
								PRC		

	Final guideline implemented
	Draft version/concept paper

From Krishnan et al, Biosimilars, 2015



Regulatory Policies - EU

- EMA has published the first (2005) and greatest number and most detailed requirements for regulatory approval for biosimilars
 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/_general_content_000408.jsp#Productspecificbiosimilarguidelines
- Include overarching guidelines, and product-specific guidelines, and related guidelines in draft or final form, some of which have been superseded by newer guidelines
 - Over 25 in total at this time
 - I will not be covering them all in detail



Regulatory Policies – US

- The Biologics Price Competition and Innovation (BPCI) Act passed as part of Affordable Care Act
 - Signed into law Mar 23, 2010
 - Amended the Public Health Service Act, section 351, subsection k
 - Created abbreviated licensure pathway (the 351(k) path) for biological products shown to be “highly similar” to, or interchangeable with, an FDA-licensed reference product
- First draft FDA Guidance document on biosimilarity released in Feb 2012
 - Currently 7 guidance documents available
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>



Regulatory Policies – Japan

- Japan biosimilar guidelines published in 2009
- Some information is available only in Japanese
- See Nagia et al, Lancet Oncol 2015 for a summary of Japanese guidelines



Regulatory Policies – Rest of World

- A number of countries have published draft or final guidances
- RoW guidances generally (but not always) follow existing EMA or WHO guidances
 - WHO guidance formally adopted Oct 2009
 - http://www.who.int/biologicals/areas/biological_therapeutics/BIOOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
 - Draft WHO guidance on mAb biosimilars currently in process
 - Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)
 - http://www.who.int/biologicals/mAb_1st_draft_KG_IK_1_March_2016_clean.pdf



General Themes for Global Regulatory Guidances

- Some themes are consistent
 - Stepwise assessment of similarity, beginning with strong analytical (CMC) package
- One area that is less consistent is the need for nonclinical in vivo studies
 - EMA appears least likely to request in vivo studies if analytical package support similarity
 - US appears to be getting closer to EMA
 - Other countries appear more reluctant
 - Desire at least one in vivo toxicity study, even when clinical data are available from proposed biosimilar
 - “Comfort factor”



What is Needed to Show Biosimilarity?

- Goal of biosimilar development is to demonstrate no clinically meaningful differences from originator based upon totality of evidence
 - Not to re-establish safety, efficacy, and overall benefit which has already been shown
- Thus, need some combination of analytical, animal, and/or human testing
 - Analytical testing usually more extensive vs what originator did
 - Animal and clinical testing less extensive vs originator
 - Testing is often comparative
 - Proposed biosimilar compared with originator (reference product)
- Currently there is an effort to minimize or eliminate animal testing even more when scientifically justified
 - Might be possible to eliminate animal testing for some/many biosimilar programs



Nonclinical Studies for Development of Biosimilars

- What is really scientifically needed vs just a comfort factor?
- In 2014, the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) created mAb Biosimilar Expert Working Group in collaboration with UK Medicines and Healthcare Products Regulatory Agency (MHRA)
 - Goals:
 - Minimize unnecessary use of animals
 - Push for global harmonization in nonclinical space
 - Comprised manufacturers, CROs, and regulators
 - Europe, North America, and Asia represented
 - Reviewed global regulatory environment, surveyed current practice, determined drivers for nonclinical in vivo studies with biosimilar mAbs
 - Made recommendations for a data-driven approach to assess toxicity of mAb biosimilars



Nonclinical Studies for Development of Biosimilars

- Members co-authored article
 - Chapman K et al. Waiving in vivo studies for monoclonal antibody biosimilar development: National and global challenges, mAbs 8:427-35, ePub Feb 6, 2016, DOI: 10.1080/19420862.2016.1145331

MABS
2016, VOL 8, NO. 3, 427-435
<http://dx.doi.org/10.1080/19420862.2016.1145331>



PERSPECTIVE

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Waiving in vivo studies for monoclonal antibody biosimilar development: National and global challenges

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^mIntegrated Biologix, Switzerland

- Remainder of talk will focus on findings and recommendations from this manuscript, coupled with Pfizer's experience with nonclinical in vivo studies evaluating proposed biosimilar mAbs
 - Pfizer's nonclinical development occurred in 2011-2015 timeframe

Current Practice from Working Group Survey

- Working group collected information by questionnaire regarding 25 marketed and as yet unmarketed proposed biosimilar mAbs
 - Being developed 2010-2015
- An in vivo toxicity study had been carried out for all
 - 26 in vivo studies carried out for 25 products
 - 75% of in vivo studies in cynomolgus monkeys
 - Duration from single dose (two examples) to 26 weeks (one example)
 - Number of dose groups
 - From two test article-dosed groups (one group for biosimilar and one group for originator) to five dose groups (low-, intermediate-, high-dose groups for biosimilar; and low- and high-dose groups for originator)
 - Number of animals
 - Cynomolgus monkeys ranged from 10 to 36
 - Rats from 32 to 96
 - Mice from 36 to 138



Current Practice from Working Group Survey (cont.)

- No important differences detected between originator and reference products in any in vivo study
- Scientific arguments were made to waive in vivo studies
 - Were not accepted in any case



Experiences from Working Group Survey: Regulatory Interactions within EU

- EU currently appears to be actively promoting the initiation of clinical trials based on in vitro data only where appropriate
 - However, responsibility of implementing EU regulations lies with individual countries within EU
- Experiences from Working Group show that some member states within EU do not follow general EU guidances
 - Some national competent authorities, as well as some ethics committees, are requesting nonclinical in vivo studies when in vitro package is considered appropriate by manufacturer and by other countries within EU
- Additionally, acceptance by clinical investigators conducting proposed biosimilar clinical trials in absence of in vivo data (particularly safety data) remains challenging



Experiences from Working Group Survey: Regulatory Interactions in US and Japan

- Experience of Working Group is that US generally requires at least one nonclinical in vivo study
 - Does not necessarily need to be in monkeys
 - Does not necessarily need to be in pharmacologically-relevant species
 - Does not need to include both sexes
 - Can be single dose
- Japan requires at least a two-week repeat-dose in vivo toxicity study
 - Both sexes required
 - Does not necessarily need to be in pharmacologically-relevant species
 - Such studies have been requested by Japan even when there is significant human data available from other regions



Experiences from Working Group Survey: Regulatory Interactions Rest of World

- Experience with many countries in the rest of the world is that in vivo studies are interpreted as mandatory following the current requirement in WHO guideline (2009)
 - National guidelines based on WHO guideline often require in vivo studies
 - WHO recently released draft guidance “Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)”
 - Draft appears to accept reduced animal use
- Overall, the experience of the working group is that EU requires the least amount of in vivo data, US requires an intermediate amount, and rest of the world requires the most
- In some cases, companies have been asked to follow a nonclinical development pathway that is as extensive as for an originator product



Reasons for Conducting Nonclinical In Vivo Studies

1. Anticipation of a regulatory or institutional ethical committee request
 - Main reason for conducting nonclinical in vivo studies
2. Meetings with regulators not timely
3. Inconsistent approaches between geographic regions or within same region
4. Default practice to conduct nonclinical in vivo study
5. Assessment of identified or potentially unknown impurities
6. To address a lack of in vitro data or assess differences in in vitro data between originator and proposed biosimilar
7. To allow human trials at intended dose vs requiring dose escalation
8. Alternative formulations, novel excipients, different concentrations of known excipients
 - Might be legitimate reasons to conduct in vivo studies



Has Using In Vitro Data Alone Been Successful Thus Far?

- No
- From survey, no examples (0/25) where clinical trial entry was allowed using in vitro data alone
- 3 companies with 8 products presented a first-in-human package containing only in vitro data to regulators or ethical review committees
 - In some cases in vitro data showed identical glycosylation patterns
 - However, nonclinical in vivo studies requested on all these programs
- Sources of in vivo study requests
 - For 7 of 8 products, the National Competent Authority considered in vitro data insufficient
 - 3 of these 7 also had refusal from ethical committee
 - Remaining request was from an ethical committee







Pfizer Experience

- Pfizer has taken several biosimilars into human trials
- Will briefly discuss
 - Rituximab
 - Trastuzumab
 - Adalimumab
 - Bevacizumab
- Nonclinical in vivo studies did not identify any residual uncertainty
- Assessment of similarity could have been made without these studies
 - In agreement with Working Group findings



Rituximab: Pfizer Experience

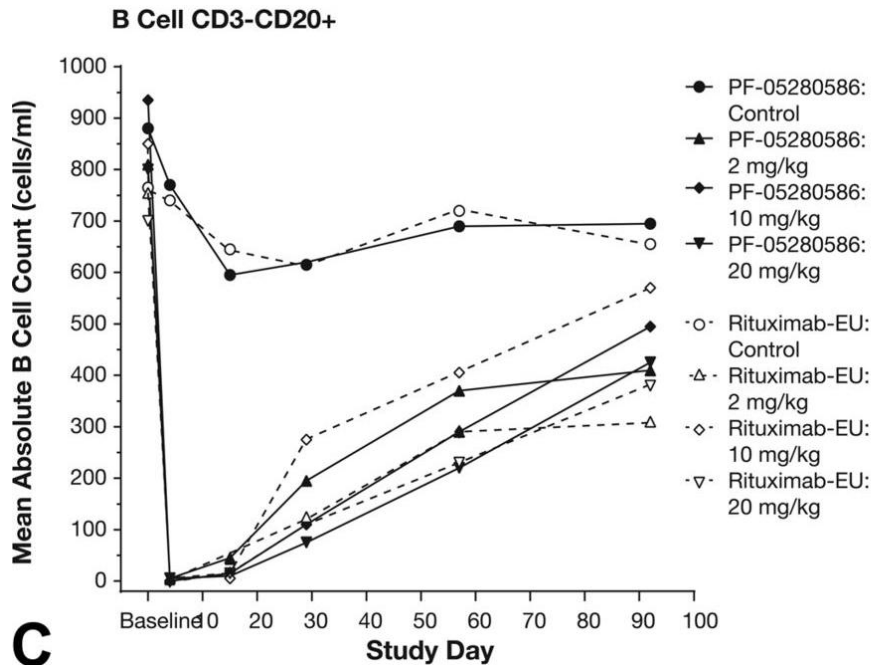
- Pfizer conducted two studies
- Both in cynomolgus monkeys
- Both GLP compliant
- Single-dose, non-terminal tolerability/PK study
- Repeat-dose, “standard” general toxicity study
- One regulatory agency required both sexes



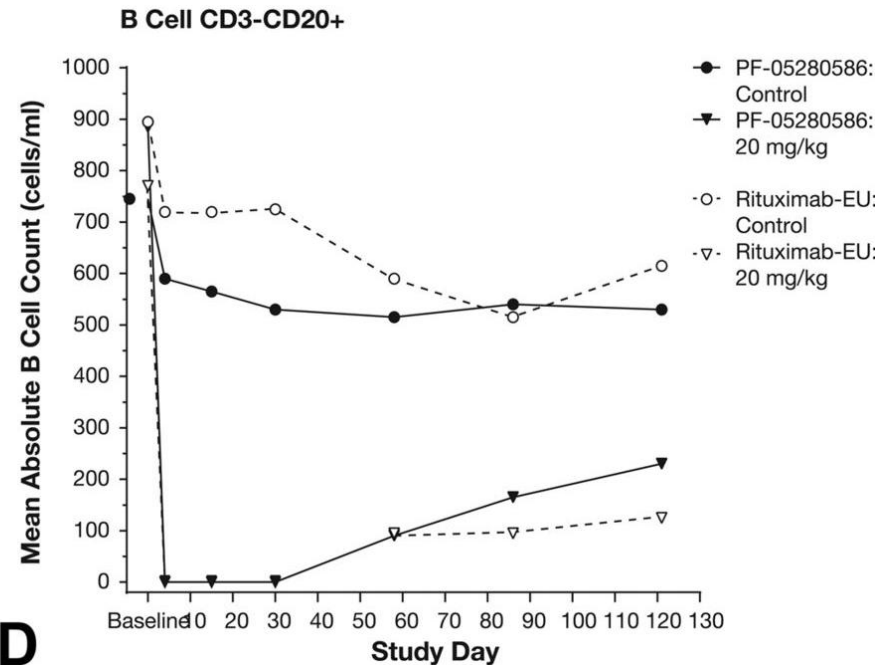
Rituximab: Peripheral Blood B Cell Effects

- Marked to complete depletion of CD3-CD20+ B cells
- At all doses
- Similar for rituximab-Pfizer and rituximab-EU (originator product)

Single-Dose Study



Repeat-Dose Study



Rituximab: Summary of Nonclinical Results

- In all parameters examined, rituximab-Pfizer and rituximab-EU appeared similar
- Results also consistent with available data from the originator:
 - Clinical observations (well tolerated)
 - Systemic exposures
 - Expected depletion of B cells in peripheral blood
 - Expected depletion of B cells in tissues



Rituximab: Outcome

- Nonclinical package accepted in support of human trials in
 - US
 - Certain EU/Rest of World countries
 - Japan



Trastuzumab: Pfizer Study

- CHMP indicated no in vivo study needed
- FDA suggested conducting single-dose rodent study in one sex
- Pfizer therefore conducted one study
 - Single-dose PK study in mice
 - Males only
 - Pfizer selected mouse based on lack of anti-HER2 effects observed in any species
 - Mouse PK data available from originator
 - Rat data was not available
- GLP compliant
- Hurst et al. BioDrugs 2014, 28:451-459



Trastuzumab: Outcome

- Initial nonclinical package accepted in support of human trials in
 - US
 - Certain EU/Rest of World countries
- PMDA requested repeat-dose nonclinical toxicity study using both males and females prior to dosing humans in Japan
 - Suggested a non-comparative rodent study
 - Acknowledged it was not a pharmacologically-relevant species
 - No test article-related findings
 - Allowed trials to proceed in Japan



Adalimumab: Pfizer Study

- FDA requested 1-month toxicity study in cynomolgus monkeys
 - Comparative study (i.e. including originator, adalimumab-EU)
 - At highest dose used by originator in 1-month study (no other dose levels)
 - 157 mg/kg/week (380x dose multiple)
 - SC considered acceptable (innovator toxicity studies were IV, clinical route is SC)
 - Both sexes
 - Recovery phase not requested
 - Agency indicated their response may have been different if more CMC data provided
- Adalimumab-Pfizer- and adalimumab-EU-related effects limited to minimally decreased cellularity of lymphoid follicles and germinal centers in spleen
 - Findings appeared similar



Adalimumab: Outcome

- Nonclinical package accepted in support of human trials in
 - US
 - EU
 - Japan
 - Selected RoW



Bevacizumab: Pfizer Study

- FDA agreed to proposed 1-month toxicity study in male sexually-immature cynomolgus monkeys
 - Sexually immature to focus on physeal dysplasia
 - One sex
 - Males
 - Comparative study (i.e. including originator)
 - 10 mg/kg twice weekly (intermediate dose used by originator; no other dose levels)
 - No recovery phase



Bevacizumab: Nonclinical Results

- Expected pharmacologic response of physeal dysplasia seen microscopically
 - Similar incidence and severity with bevacizumab-Pfizer and bevacizumab-EU (originator product)
 - Due to inhibition of blood vessel formation
- No bevacizumab-Pfizer- or bevacizumab-EU-related findings in other parameters
- Overall, findings with bevacizumab-Pfizer and bevacizumab-EU considered similar

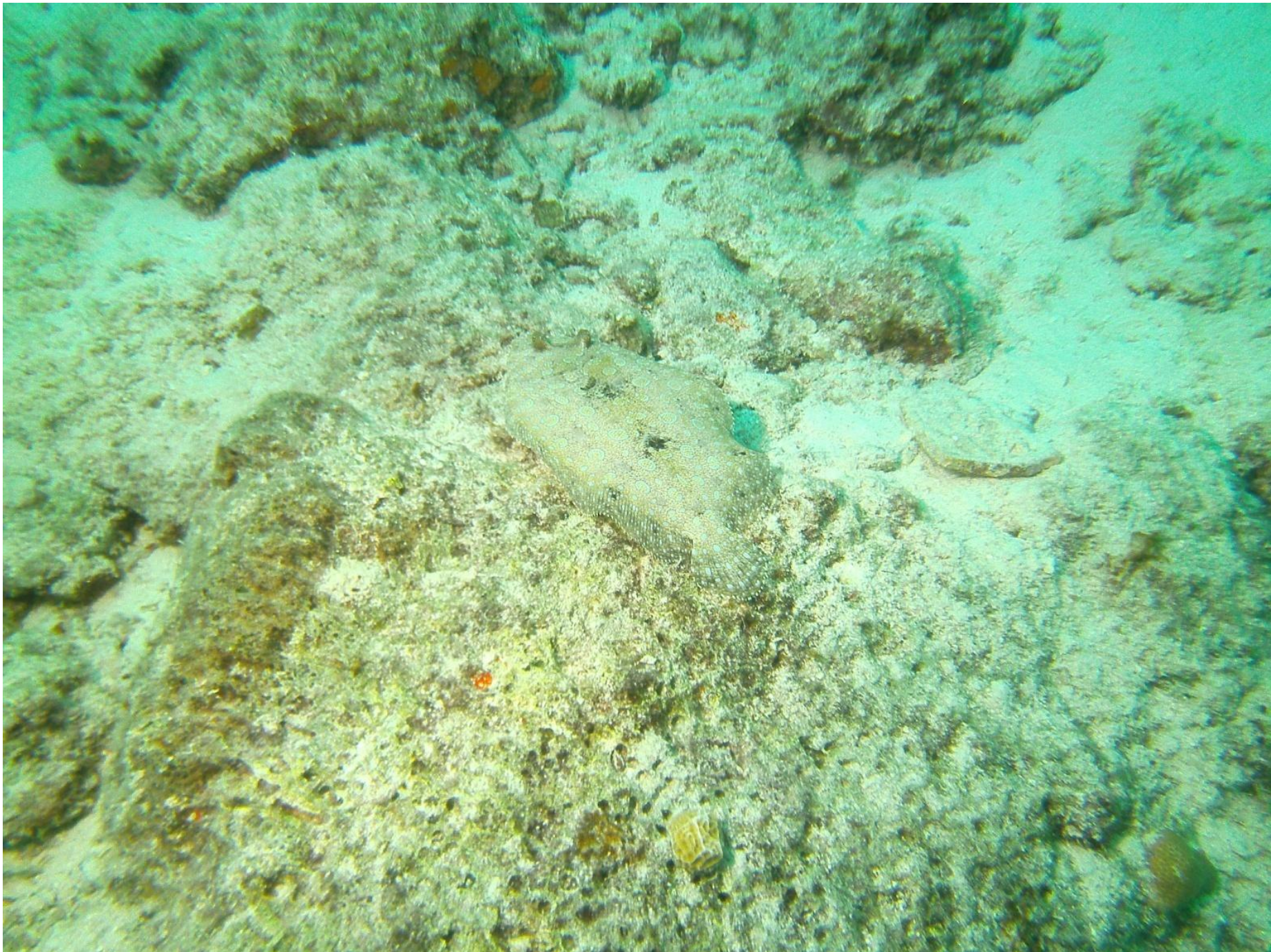


Bevacizumab: Outcome

- Nonclinical package accepted in support of human trials in US
- PMDA requested repeat-dose nonclinical toxicity study in female animals prior to dosing women in Japan
 - Allowed rat, a non-pharmacologically-relevant species
 - Non-comparative study design
 - No adverse test article-related findings
 - Minor findings seen that did not impact clinical program
- Data has supported clinical trials in US, EU, and Japan







Discussion

- Working Group not able to identify any case where nonclinical in vivo data provided useful information to a proposed biosimilar mAb program that had a strong in vitro data package showing a high degree of similarity
 - Pfizer data agrees with this
- Working Group believes that nonclinical in vivo studies do not usually add value in assessing the similarity of proposed biosimilar mAbs when in vitro data strongly suggests similarity



When In Vivo Studies Are Required, What Design Should Sponsors Use?

- Exact purpose of study should be carefully considered and number of animals minimized
- Mice or rats, rather than monkeys, are often suitable to assess the PK properties of mAbs
 - Even when there is no pharmacologic activity present in rodents, the interaction of the mAbs with FcRn can be assessed
- Testing in one sex should be considered wherever possible
 - But note some regions are requiring both sexes
- Assessment of recovery generally not necessary



When In Vivo Studies Are Required (cont.)

- Testing at one dose level is usually sufficient
 - Dose should match one of those used by originator
 - Should not saturate dose response so that differences between proposed biosimilar and originator can be more readily detected
- Relevant control for proposed biosimilar is originator material
 - Vehicle control group is not usually needed
- Testing of a single reference product is sufficient
 - Where there is a regulatory request to test a different version of the reference product, this can be achieved by CMC characterization and a clinical PK/PD bridging study



When In Vivo Studies Are Required (cont.)

- Example of rat study design
 - Specific design needs to be based on needs of program
 - Is toxicity assessment needed, vs just PK?
 - Are separate toxicity and TK groups needed?
 - Are both sexes needed?

Group	Subgroup	Dose in mg/kg/cycle	Number of Males	Number of Females (is one sex acceptable?)
Originator	Toxicity	Low or intermediate dose from originator study	5	0
	TK		3	0
Proposed biosimilar	Toxicity	Same	5	0
	TK		3	0

When In Vivo Studies Are Required (cont.)

- Example of cynomolgus monkey study design
 - Specific design needs to be based on needs of program
 - Are both sexes needed?

Group	Dose in mg/kg/cycle	Number of Males	Number of Females (is one sex acceptable?)
Originator	Low or intermediate dose from originator study	0	3
Proposed biosimilar	Same	0	3



Conclusions

- Working Group has written paper to provide an impetus to change practice of regulatory agencies and institutional ethical committees, and some regulatory guidances
 - Goal is to reduce animal use when in vivo data not scientifically necessary in development of biosimilar mAbs
 - Agrees with van Aerts et al. Biosimilars entering the clinic without animal studies. A paradigm shift in the European Union. mAbs, 6:1155-62, 2014
 - Paper by several members of the regulatory community from the EU, although not representing an official regulatory position
- Experience of Working Group and Pfizer is that there was no case where in vivo animal studies provided useful information for safety evaluation of biosimilar mAbs
- Working Group recommends reducing animal use in nonclinical biosimilar mAb development
 - Can be eliminated in many cases
- Regulatory agencies and ethical committees do not always agree



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Questions???



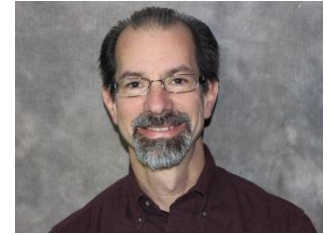
Thank you for your participation in the American College of Toxicology Webinar!

*We hope to see you at the
37th Annual Meeting of
the American College of Toxicology.*

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37th Annual Meeting
Baltimore, Maryland
November 6–9, 2016



Presenter Bio



Dr. Michael Leach is currently a Therapeutic Area Lead for Drug Safety Research and Development at Pfizer in Andover, MA, where he supports the Centers for Therapeutic Innovation Research Unit. Until recently he also supported Pfizer's Biosimilars programs and was accountable for the nonclinical strategies supporting Pfizer's Biosimilar portfolio that is currently in development. Dr. Leach is a board certified veterinary pathologist, and has worked as a toxicologic pathologist, investigative pathologist, and toxicologist during his career. Dr. Leach received his DVM from Purdue University in 1986, and his PhD in Comparative Pathology from the University of California-Davis in 1992. Prior to Pfizer, Dr. Leach previously worked at Schering-Plough, BASF Bioresearch Center (which was purchased by Abbott), and Wyeth (which was purchased by Pfizer). Dr. Leach is also a member of the multidisciplinary Biotherapeutics Advisory Council within Pfizer. During his career, Dr. Leach has been involved in the discovery and development phases of small molecules, novel biopharmaceuticals, and biosimilars. He is a member of the American College of Veterinary Pathologists, the Society of Toxicologic Pathology, and the Society of Toxicology. Dr. Leach has been an author or co-author on over 50 peer-reviewed scientific publications, as well as on a number of opinion and invited articles related to toxicology, pathology, and drug development, including biosimilars. Related to the current topic, Dr. Leach is a member of the NC3Rs/MHRA Biosimilar Antibody Expert Working Group.