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Biosimilars and the Regulations in China

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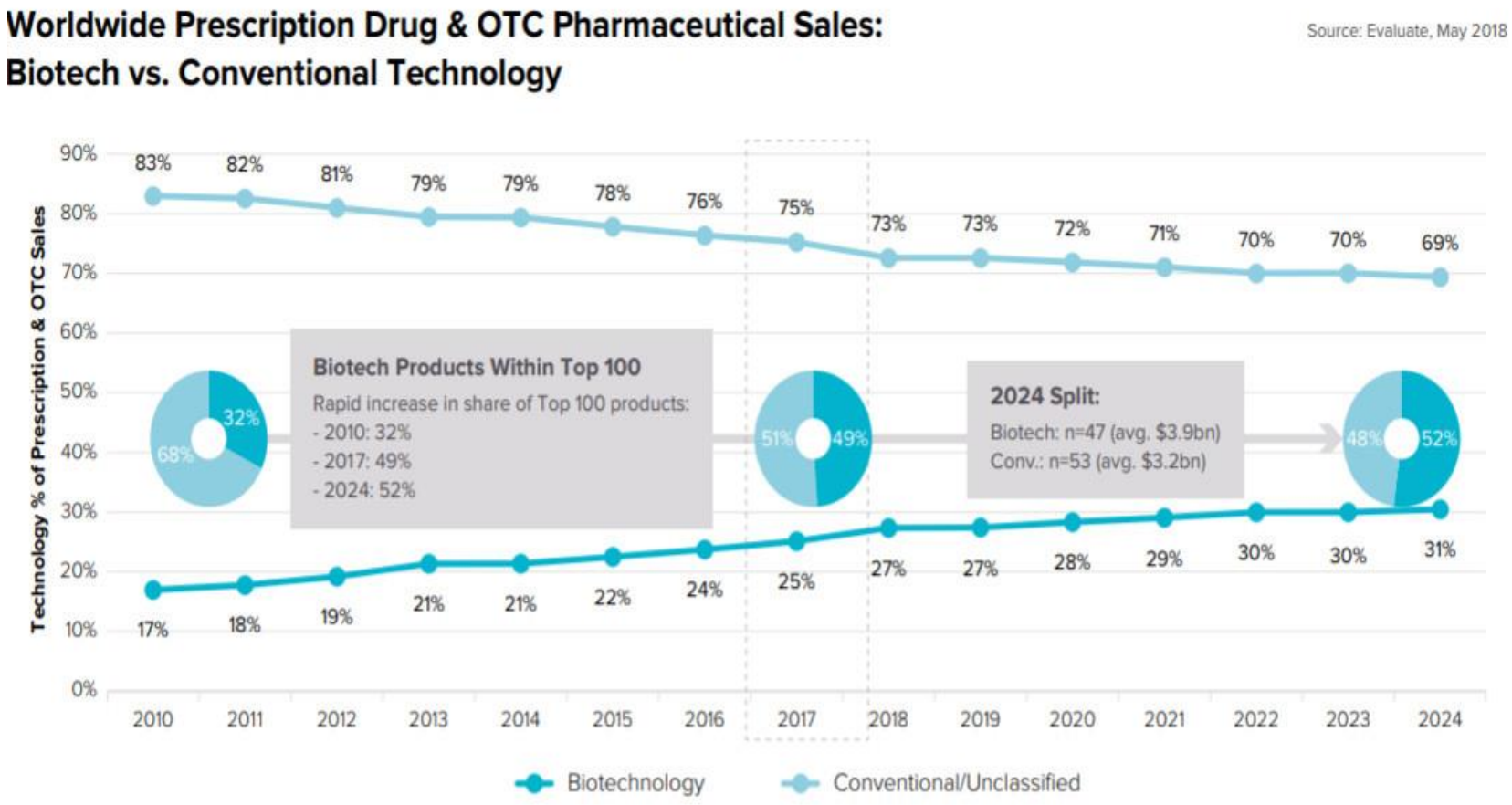
- Regulation Research Background
- Biosimilar Regulations Overview
- Key Considerations on China Regulations

YEEHONG RESEARCH
亦弘研究

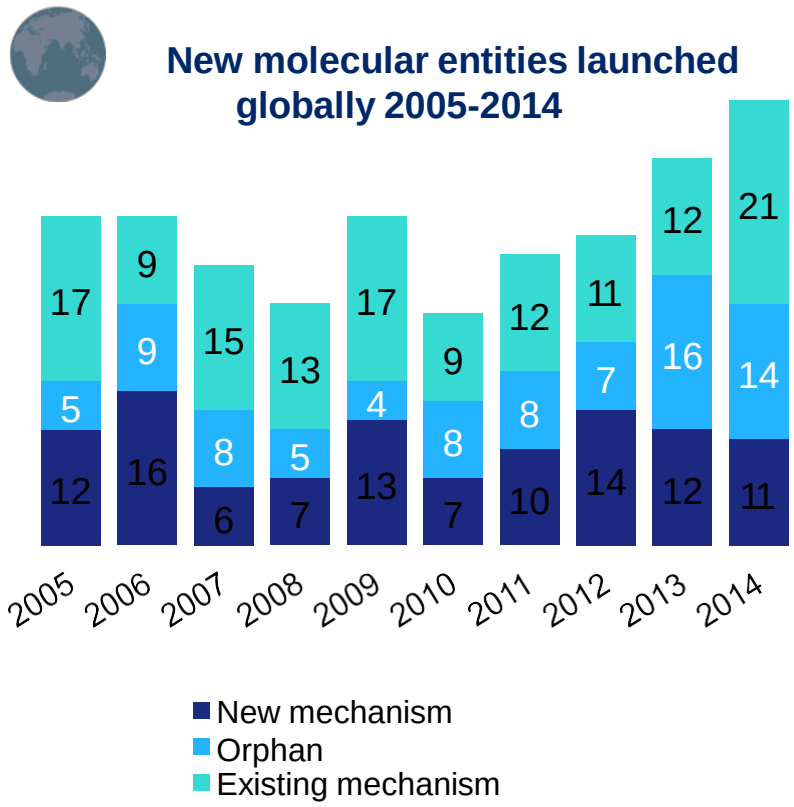
REGULATION RESEARCH BACKGROUND

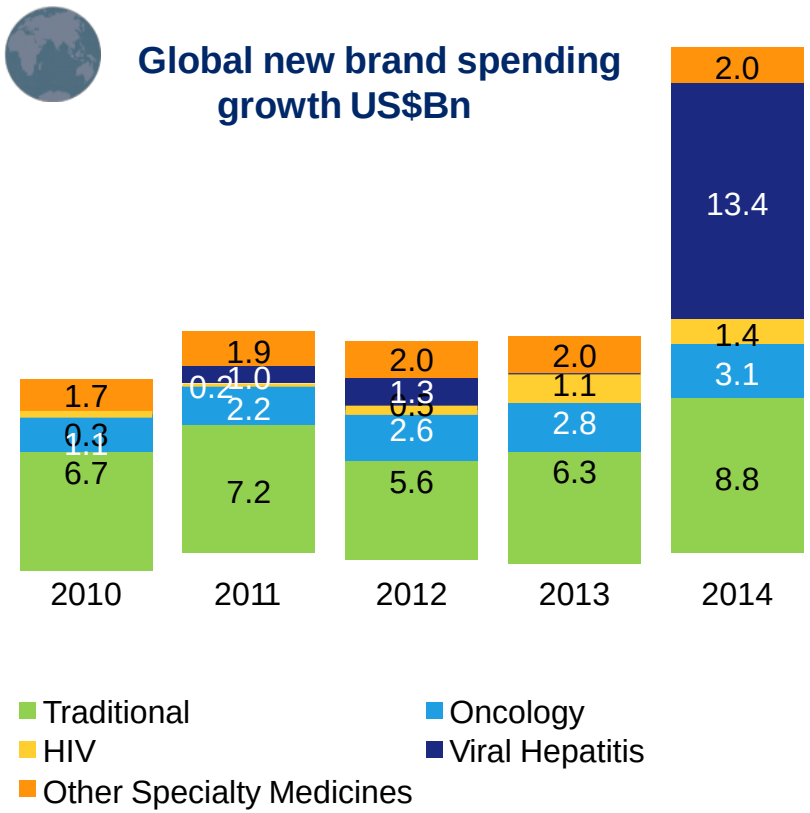
The market share of Biotech Products is increasing rapidly



The impact of new therapy on health care budget

Significant advances in treatment can have a profound impact on healthcare budgets.





Source: IMS Institute for Healthcare Informatics, *The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective,* June 2015.

10 Best Selling Drugs in 2018 and Patent Expiration

Rank	10 Best Selling Drugs in 2018	Company	Patent Expiration	Biosimilars
1	**Humira (Adalimumab)**	AbbVie	US (2016), EU (2018)	Yes
2	Revlimid (Lenalidomide)	Celgene		
3	**Opdivo (Nivolumab)**	BMS		
4	**Enbrel (Etanercept)**	Amgen	US (2012), EU (2015)	Yes
5	**Keytruda (Pembrolizumab)**	MSD		
6	**Herceptin (Trastuzumab)**	Roche	US (2019), EU (2014)	Yes
7	**Avastin (Bevacizumab)**	Roche	US (2019), EU (2022)	Yes
8	**Rituxan (Rituximab, MabThera)**	Roche	US (2018), EU (2013)	Yes
9	**Remicade (Infliximab)**	Janssen	US (2018), EU (2015)	Yes
10	**Eylea (Aflibercept)**	Regeneron	US (2027), EU (2027)	No

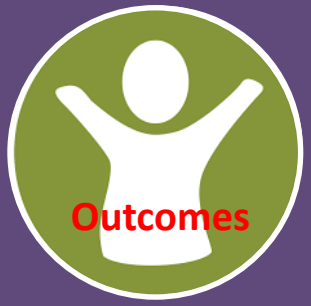
Source: Clarivate Analysis Cortellis, 2019/5/29

Potential Benefits of Using Biosimilars

Biosimilars provide stakeholders, including doctors, patients and payers, with more options for treatments.

Potential Savings from the Use of Biosimilars

Providing more Affordable Options for Stakeholders

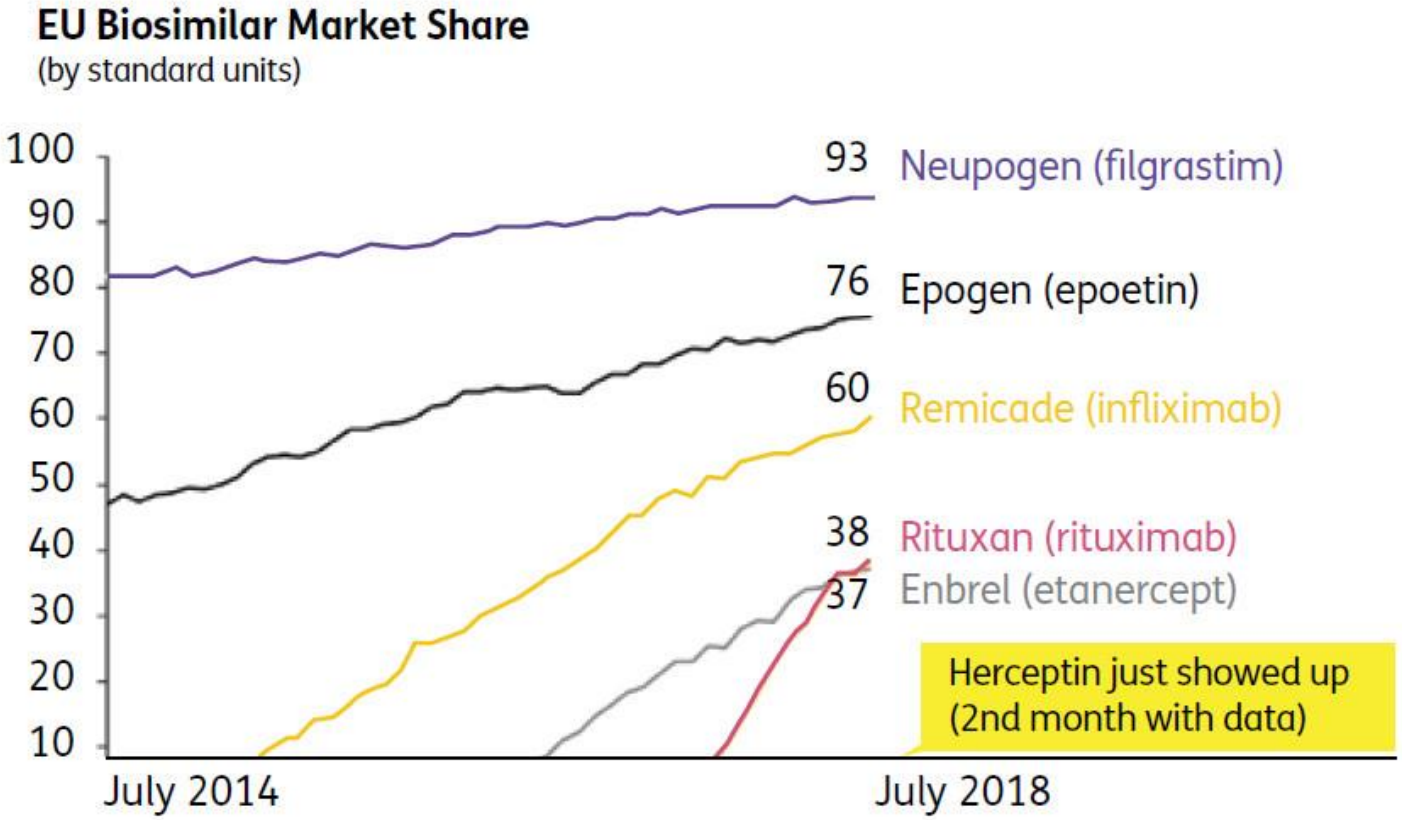


More Accessible and Improvement in Patient Outcomes

Reallocation of Resources to Other Areas of Patient Care

Market share of Biosimilars in Europe

Europe Market Overview: Biosimilars As Volume Share Of The Reference Molecule Market



Companies in Biosimilars Field

Sandoz, the generic drug division of Swiss drug giant Novartis AG, is determined to lead the biosimilar field

Amgen Inc, the world's largest biotechnology company, and generic drugmaker Watson Pharmaceuticals Inc will work together to develop and sell biosimilar versions of several biotech cancer drugs

Pfizer, the world's biggest pharmaceutical firm, will work with Biocon, India's largest biotech company, to bring "biosimilar" insulin treatments to market

Merck & Co is to develop its own version of Pfizer's ageing arthritis drug Enbrel with a South Korean manufacturer, Hanwha

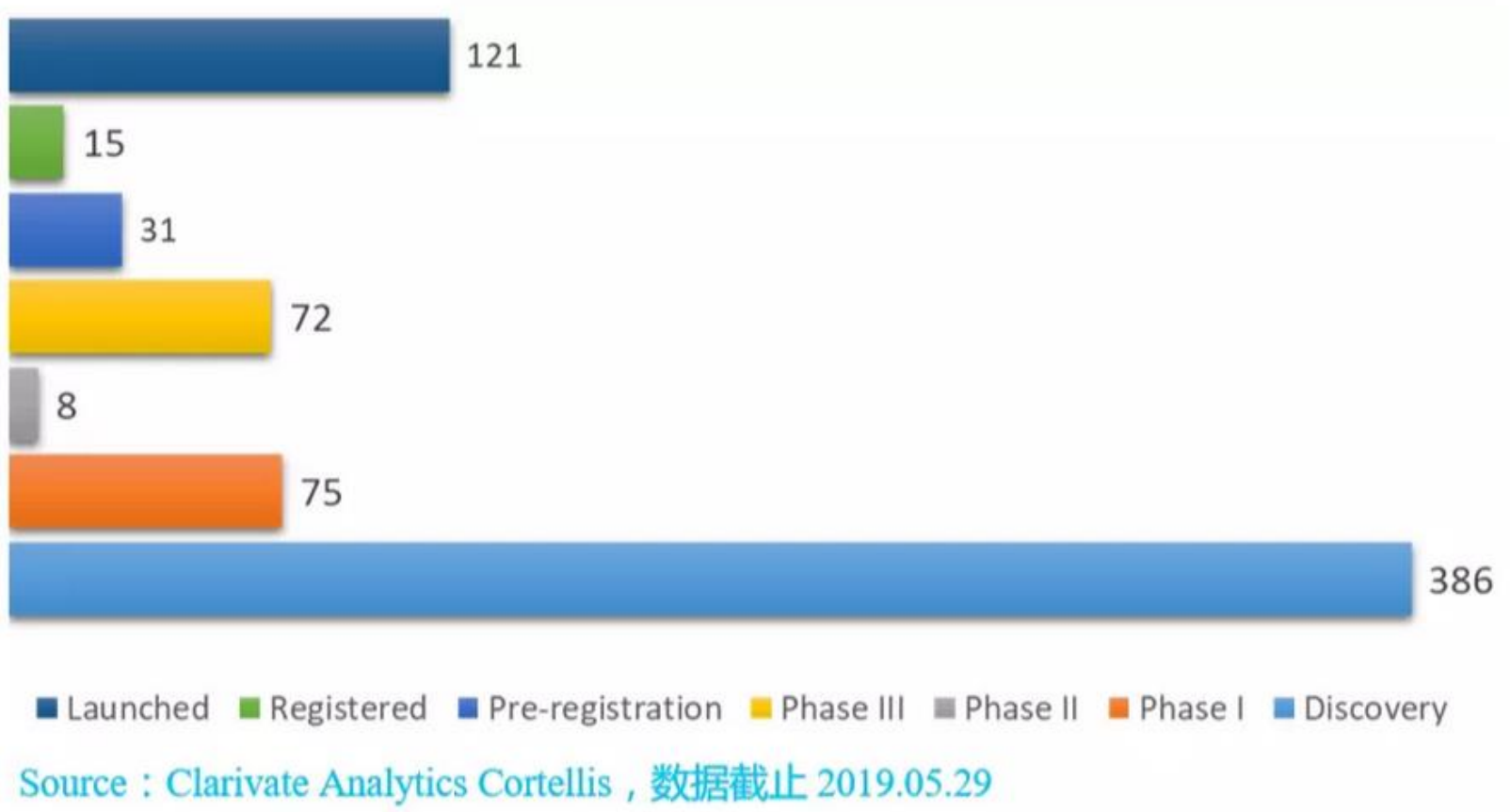
Korean electronics giant Samsung had entered into a biosimilars joint venture with US biotechnology company Biogen Idec

Celltrion, Inc., Incheon, South Korea,founded in 2002,

Focuses on the development of high quality biosimilar monoclonal antibody (mAb) and innovative biopharmaceuticals utilizing its accumulated R&D technology and production capabilities.

And also including Allergan, Biocon, Boehringer Ingelheim, Momenta, Mylan and Apotex etc…How to gain a competitive advantage will be crucial.

R&D Status of Global Biosimilars



Source：Clarivate Analytics Cortellis，数据截止 2019.05.29

Overview of Approved Products

Regulators	Up until	Approved Products	Sources
EMA	*December 2018*	*52 biosimilars from 20 reference drugs*	*European public assessment reports*
FDA	*December 2019*	*26 biosimilars from 9 reference drugs*	*FDA. Biosimilar Product Information*
Japan	*November 2019*	*21 biosimilars from 7 reference drugs*	*PMDA Website*
Korea	*November 2019*	*22 biosimilars from 8 reference drugs*	*MFDS Website (Korea)*
China	*December 2019*	***4, and 269 biosimilars under R&D***	*CFDA Website Thomson Reuters 2016*

FDA CDER approved Ten New Biosimilars In 2019

Products	INN	Mechanism	Notes
Avsola	infliximab-axxq	TNF Antibody	the fourth biosimilar to Remicade (infliximab)
Eticovo	etanercept-ykro	TNF Antibody	the second biosimilar to Enbrel (etanercept)
Hadlima	adalimumab-bwwd	TNF Antibody	the fourth and biosimilars to Humira (adalimumab)
Abrilada	adalimumab-afzb	TNF Antibody	
Ontruzant	trastuzumab-dttb	HER2 Antibody	the third, fourth, and fifth biosimilars to Herceptin (trastuzumab)
Trazimera	trastuzumab-qyyp	HER2 Antibody	
Kanjinti	trastuzumab-anns	HER2 Antibody	
Ruxience	rituximab-pvvr	CD20 Antibody	the second biosimilar to Rituxan (rituximab)
Ziextenzo	pegfilgrastim-bmez	GCSF analogs	the third biosimilar to Neulasta (pegfilgrastim)
Zirabev	bevacizumab-bvzr	VEGF Antibody	the second biosimilar to Avastin (bevacizumab)

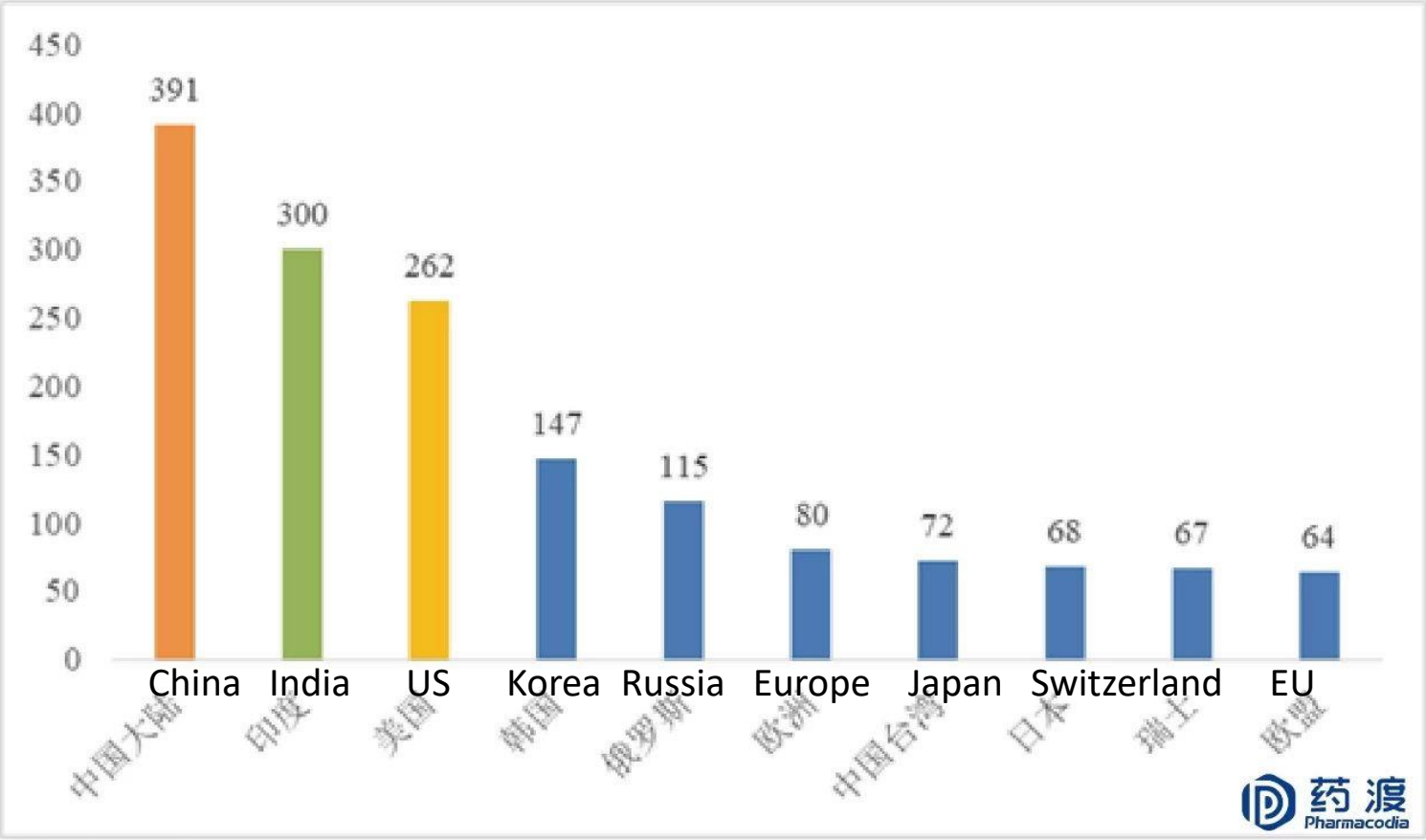
Source: FDA CDER: Advancing Health Through Innovation: New Drug Therapy Approvals, January 2020

4 Biosimilar Products have been approved in China

Time	Company	Product	Brand Name
2019/2/25	**Henlius 复宏汉霖**	**Rituximab**	汉利康®
2019/11/7	**Bio-thera 百奥泰**	**Adalimumab**	格乐立®
2019/12/6	**Hisun 海正药业**	**Adalimumab**	安健宁®
2019/12/9	**Qilu 齐鲁制药**	**Bevacizumab**	安可达®

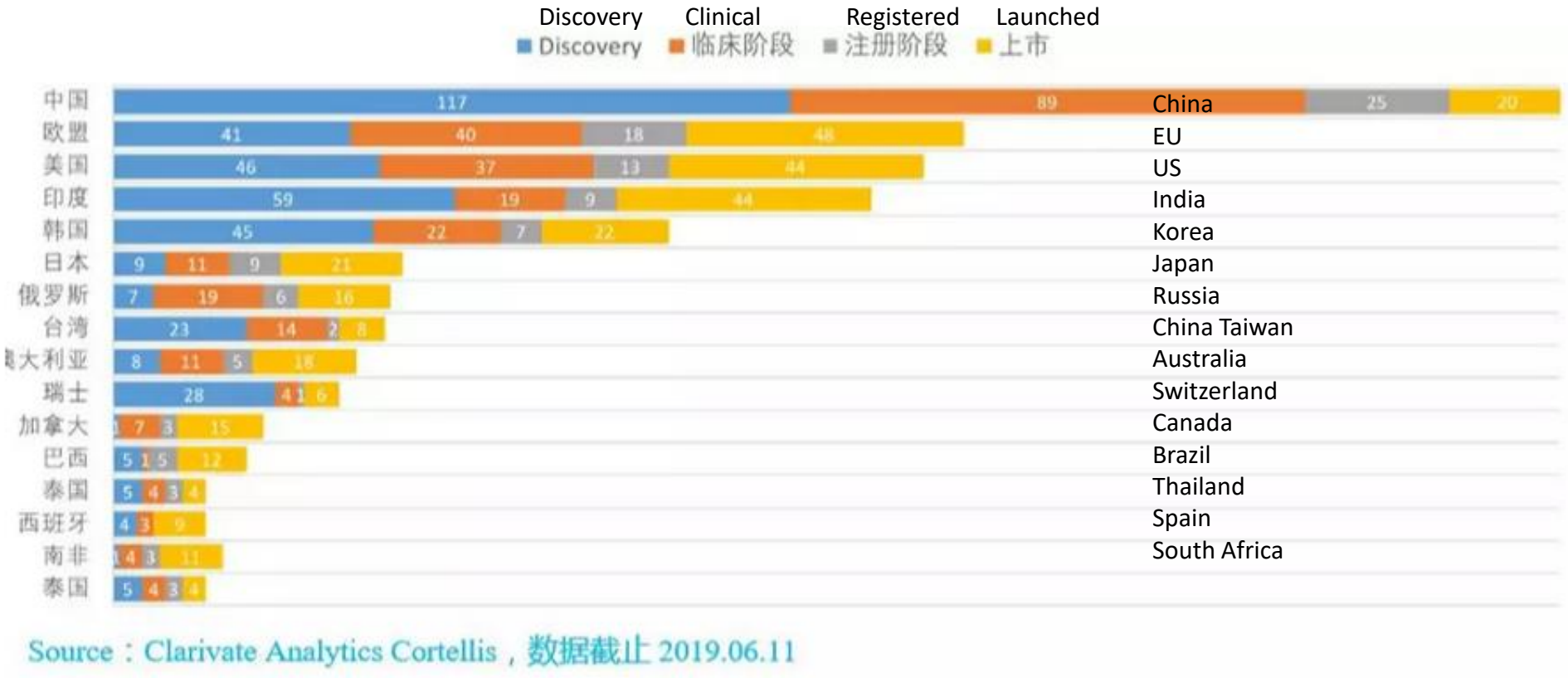
This also marks the breakthrough in the field of biosimilars in 2019 in China.

R&D Pipelines of Biosimilars in China Ranks First in the world



Source: Pharmacodia, 2019/12

The competition of biosimilars in China is the most intense



In terms of the number on the market, the EU has the largest number of biosimilars on the market (48), followed by the United States and India.

REGULATORY SYSTEM OVERVIEW

Research Goals

Our Objectives: To provide the comprehensive suggestions on developing biosimilar regulatory system in China and on establishing technical guideline framework to support the development of biosimilar industry.

Research Principles

- To increase the accessibility, to fulfill the clinical needs and to encourage the R&D of biosimilar in China.
- **To find out key factors in biosimilar regulatory system, to make recommendations which follows the law and rule of R&D and to provide the suggestions on building and perfecting the biosimilar regulatory system aiming at a whole life cycle supervision.**
- To take lessons from the supervision on chemical generic drugs in China, and to optimize the industry development path of biosimilars.
- To Coordinate the sustainable development relationship between the innovative biological products and biosimilars to promote each other.
- To encourage the biosimilar industry development, and to improve the global competitiveness of China biosimilar industry.
- To pay attention to the Operability and Robustness of the recommendations

Research Contents

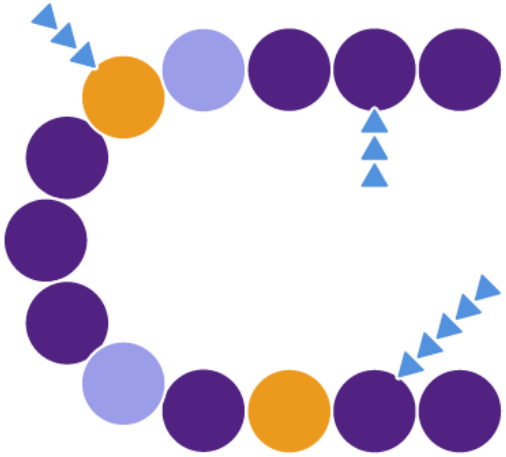
- Comparative research and analysis of biosimilar regulatory systems and technical guidelines of US, EU, Japan, Korea, WHO and China

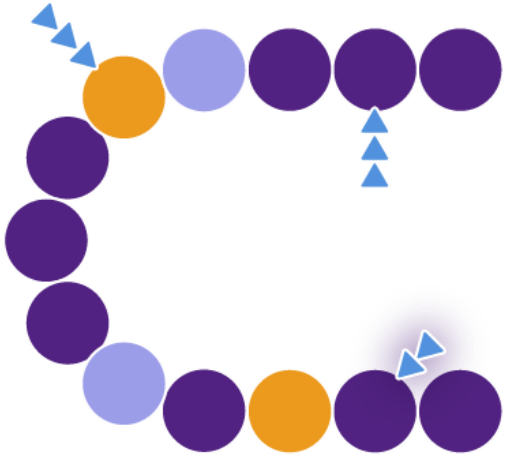
- Analysis of existing problems in China biosimilar R&D and legislation, and to find out key factors in biosimilar regulations and guidelines with the directional surveys.

- Research on the "***Purple Book***" in US with its positioning and roles, the principles of product collecting, the settings of drug information, etc., and to demonstrate the necessity and feasibility of establishment of China *Approved Biological Products Catalog*.

- To form the comprehensive recommendations on developing China biosimilar regulatory system and technical guideline system framework to support the development of biosimilar industry based on the comparative study and result of the survey.

Biosimilars are not exactly the same as the original drugs





Reference medicine

Biosimilar medicine

Different cell lines

Different manufacturing processes

… SIMILAR enough as the reference products

…. But NOT IDENTICAL to the reference products.

Impact of small differences in either biological or manufacturing process could lead to different clinical efficacy and safety for patients[1,2]

What is a Biosimilar?

A biosimilar is a biological drug manufactured by a different company, and demonstrated to be highly similar to a biologic drug that was already authorized for sale (known as the reference biologic drug).

WHO: A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

EU: Similar to a biological medicine that has already been authorized, the so-called reference medicinal product.

US: A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product in terms of the safety, purity, and potency of the product.

Canada: A biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product.

What is the “biosimilar concept”?

- Biologics are complex and its not possible to produce an identical copy as biological production introduces variability
- Therefore biosimilars cannot be regulated as generics
- Developing a biosimilar is like re-creating an old masterpiece in present day

The reference product

Objective- to demonstrate that there are no clinically meaningful differences (not to demonstrate *de novo* efficacy and safety)

Via iterative comparative testing the biosimilar developer pieces together a product as similar as possible to the reference product

Different cell lines and manufacturing processes will result in a ‘highly similar’ product but not completely identical

The biosimilar

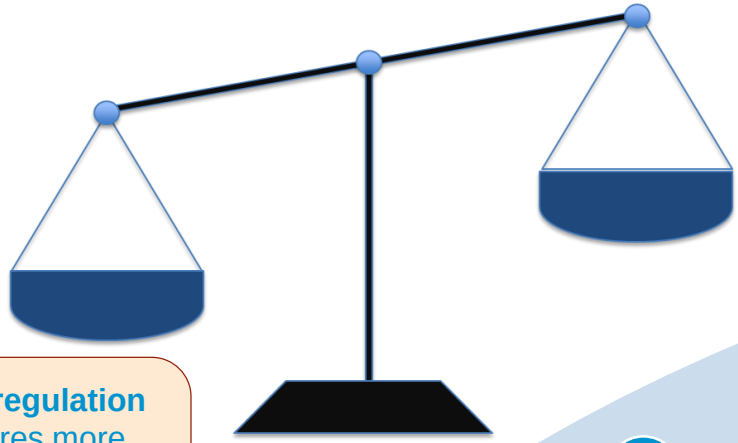
http://www.yeehongedu.cn

From: Judith Macdonald, Pfizer; slides of Regulatory Perspectives on Biosimilars

More data are needed for Biosimilars than for Generic Drugs

	Biosimilars	Generics
Regulatory Pathway	New Drug or biosimilar pathway	Generic
Drug Substance	Highly similar to reference	Identical to reference (Pharmaceutical equivalence)
Structure characterization	Comparable to reference	
Function characterization	Comparable to reference	
Non-Clinical Study	Reduced and comparable to reference	
PK Profile	Comparable PK profile to reference	Equivalence PK profile to reference
PD Profile	Comparable PD profile to reference	
Efficacy	No clinically meaningful differences at least in one indication	
Safety/ Immunogenicity	No clinically meaningful differences at least in one indication	

What foundational features should be considered in building a system to regulate biosimilars?



Under-regulation requires less data than is scientifically necessary

Over-regulation requires more data than is scientifically necessary

Recognise that these are biologicals and an identical copy cannot be produced- NOT GENERICS

Be scientifically grounded, consistent and show similarity to reference product (based on totality of evidence with strong pharmacovigilance)

Stepwise approach to demonstrate biosimilarity (quality, safety, efficacy)

Allow the possibility of extrapolation of indications where justified

Be able to detect products that don't meet the biosimilarity standard

Facilitates patient access & assures patient safety

- **Clear, objective, systematic standards**
- Until you know if your system can reject products of poor quality you don't know it works

From: Judith Macdonald, Pfizer; slides of Regulatory Perspectives on Biosimilars

Regulatory approaches to biosimilars: Regulations

legislation

Biosimilar Developed

File for Market Authorization

guidelines

- Legislative Pathway for the approval of Biosimilars
- Public Health Services Act 351(k) abbreviated licensure pathway
- declaration of biosimilarity or interchangeability possible

- Reviewed and Authorized under the same regulations as New Drugs
- No specific abbreviated legislative pathway
- FDA & R – C08.001
- Guidance for Subsequent Entry Biologics (SEBs) sets out SEB policy
- Regulated as a New Drug after approval – no link to reference

- Regulatory framework grounded by legal basis for the authroization of similar biological medicines
- Requirements set forth in Article 10(4) of Directive 2001/83/EC and annex
- Various guidelines for specific product types as well as overarching guidance

General EU Biosimilar Guidelines

Overarching Guideline (CHMP/437/04)
"Guideline on Similar Biological Medicinal Products"

Revised 2014

Non-clinical/clinical Guidance

Revised 2015

Quality Guideline

Revised 2014

Class-specific EU Guidelines: non-clinical/clinical aspects:

Insulin	Somatropin	G-CSF	Epoetin	IFN-α	LMWH	mAbs	IFN-β	Follitropin
2006	2006	2006	2006	2009	2009	2012	2013	2013
Revised 2015	**Revised 2018**	Revision ongoing, draft GL target 2019	**Revised 2018**	Revision ongoing- concept paper target TBD*	**Revised 2016**	Revision being considered date TBD *	Revision planned date TBD*	

http://www.yeehongedu.cn

As of 6th November 2017
Adapted from M.Weise EBG Biosimilars 2016
*EMA guideline revisions delayed due to BREXIT

美　国

- The U.S. biosimilar market started late.
- In 2009, the U.S. Congress passed the biological products price competition and innovation act, which established a specific 351 (k) application path;
- In 2010, the U.S. government formulated a simplified application way for biosimilars to enter the market.
- The first biosimilar was officially approved in 2015. Till December 2019, FDA has approved 26 biosimilars.
- **Interchangeability requirements**
- On May 10, 2019, the FDA issued the guidelines---*Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry*, which provides a clear path for industry to prove that their biosimilars have replaceable relationship with the reference drugs.

FDA Regulatory Guidance Status: Biosimilars

FINAL GUIDANCE

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2015)

Biosimilars: **Questions and Answers** Regarding Implementation of the BPCIA of 2009 (2015)

Formal Meetings *Between FDA and Biosimilar Biological Product Sponsors or Applicants (2015; replaced 2018)*

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016)

Non proprietary naming of biological products (2015)

Labeling for Biosimilar Products (2018)

DRAFT GUIDANCE

Biosimilars: **Additional Questions and Answers** Regarding Implementation of BPCIA of 2009 (2015)

Considerations in Demonstrating **Interchangeability** with a Reference Product (2017)*

Statistical Approaches to Evaluate Analytical Similarity *(2017, withdrawn)**

Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (2018)

PLANNED GUIDANCE

Processes and further considerations related to **post-approval manufacturing changes** for biosimilar biological products (Goal: on or before March 31, 2019)

How to handle in labelling the situation when some indications are under patent and some are not (so called carve-outs and carve-ins) for biosimilars *(tbd)*

Biosimilar Regulatory System Overview

Countries & Regions	Laws and Regulations	Comments
EU	The concept of "biosimilars" was adopted in 2004 and came into force in 2005	The first biological similar drug has been approved in the world, and a relatively complete system of laws, regulations and technical requirements has been established.
US	BPCIA of 2009 2009年《生物制品价格竞争与创新法案》	Up to now, a relatively complete system of laws, regulations and technical requirements has been established; interchangeability / replaceability
Japan	In 2009, guidance documents on R & D, registration, review and approval of biosimilars were issued	The framework basically refers to the regulatory system of biological similar drugs in EU.
Korea	In 2003, KFDA first issued the regulation on review and approval of biological products (MFDs notice)	Vigorously support biopharmaceutical industry in terms of government policies, review and approval, regulatory environment and industrial development.
China	In 2015, the Guidance for Biosimilar's R&D and Evaluation (Tentative) was promulgated	The Drug Registration Administration was revised in 2017 to clarify the definition and classification of biosimilars.

China

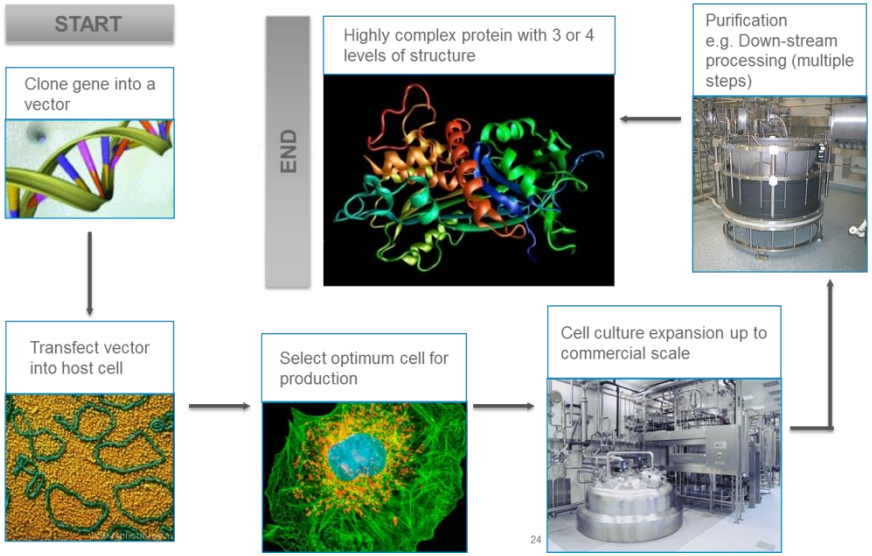
- The relevant review and approval policies in China are gradually in line with the international standards, which also makes this field an competitive place for enterprises with strong R & D strength.
- In March 2015, CFDA issued the Guidance for R&D and Technology of biosimilars (Tentative);
- In 2016, the Drug Registration Administration (Revised Version) further regulated the concept and approval standards of biosimilars.
- At present, there are about 380 biosimilars under research in China, ranking first in the world.
- In 2019, four biosimilars, such as rituximab, bevacizumab, adalimumab and trastuzumab, were approved for marketing, and many companies have entered the third phase of clinical trials

Biosimilar applications in China (June 2018)

Product	Target	Brand Name	Applications
甘精胰岛素（Insulin glargine）	INSR	Lantus®	13
卵泡刺激素（Corifollitropin alfa）	FSHR	ELONVA®	10
阿达木单抗（Adalimumab） *	TNFα	Humira®	30
英夫利西单抗（Infliximab）	TNFα	Remicade®	7
依那西普单抗（Etanercept）	TNFα	Enbrel®	8
贝伐珠单抗（Bevacizumab ）*#	VEGF	Avastin®	36
乌司奴单抗（Ustekinumab）	IL-12；IL-23	Stelara®	2
西妥昔单抗（Cetuximab）	EGFR	Erbitux®	16
托珠单抗（Tocilizumab）	IL-6R	Actemra®	6
利妥昔单抗（Rituximab） *	CD20	Rituxan®	24
伊匹木单抗（Ipilimumab）	CTLA-4	Yervoy®	5
曲妥珠单抗（Trastuzumab） *#	HER2	Herceptin®	14
帕妥珠单抗（Pertuzumab）	HER2	Perjeta®	5
奥玛珠单抗（Omalizumab）	IgE	Xolair®	4
狄迪诺塞麦单抗（Denosumab ）	RANKL	Prolia®	12
Total			192

** NDA application submitted, # Application from Overseas*

General challenge for developing legislation for biosimilars



- In contrast to small molecule chemical pharmaceuticals, the manufacture of biologicals is more complex and highly sensitive.
- Traditional small molecule pharmaceuticals are produced by chemical synthesis, by a relatively simple, standardized process.
- Biologics are produced in living cells by a complex process, which you see depicted here, where small process changes could impact the product.
- Biological products made in these biological systems therefore cannot be identical to the original product as biological systems introduce variability.
- Biosimilar manufacturers reverse engineer the manufacturing process to match the reference product range in quality attributes as closely as possible.

Therefore Biosimilars are neither generic products nor innovator products and so needed a new solution in the law to accommodate them

From: Judith Macdonald, Pfizer; slides of Regulatory Perspectives on Biosimilars

REGULATORY PERSPECTIVES IN CHINA

Key Issues

At the legislative level, to define the definition of biosimilars and to set up independent classifications.

Registration and Review Procedures

Communication mechanism

Data Exclusivity and Market Protection for biological innovators

Whether the first approved biosimilars be protected by market or not

Testing

Post marketing supervision

Selection principles of reference drugs

Naming Principals

Extrapolation of indications

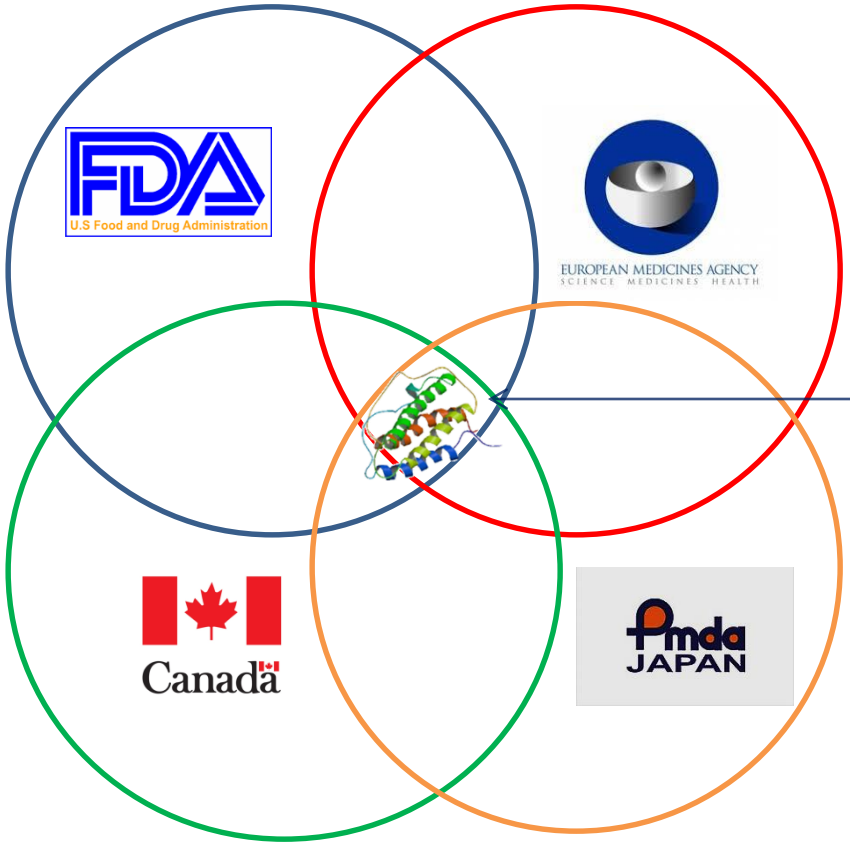
Labeling

Switching and interchangeability

Non-comparable biological products

Technical guideline framework

Requirements for Reference Products in ICH area



All of them require the reference products should be approved in their regions.

FDA, EMA and ICH will accept reference products from other countries or regions, with bridging data or reasons

Selection Principals of Reference Drugs

---based on the Phased research results

☐ Considerations on selection principals of reference drugs

- The reference drugs should be the new biological products approved by China regulatory agency according to the safety and efficacy data.
- Availability, quality assurance and needs for the global co-development.

☐ Recommendations: for the reference drugs approved by China regulatory agency , the sources could include:

- It can be purchased in China market, or
- It can be purchased from the main ICH regions + the same manufacturing site as the reference drug approved by China regulatory agency, or
- It can be purchased from the main ICH regions + the different manufacturing site from the reference drug approved by China regulatory agency + bridging study data (key factors in bridging study: CMC and/or PK/PD).

Naming Principals

———based on the Phased research results

- **Considerations on naming**

- The lifecycle pharmacovigilance management
- Convenient for prescription management
- Convenient for Indications Management
- Product Brand Building based on quality

Mepsevii™
(vestronidase alfa-vjbk)
injection

- **Recommendations**

- Principals: **INN+suffix**, used for prescription and pharmacovigilance ***(TBD)***
- 'INN+brand name' is not adopted, because the revision of multiple laws and regulations might be involved with increased difficulty and unpredictable time needs
- To keep the brand name for biosimilars to encourage brand building of the products

Extrapolation of Indications

———based on the Phased research results

- **Considerations on extrapolation of indications**

- Scientific considerations of the Prerequisites for extrapolation of indications
- As an exclusive policy for biosimilars to encourage R&D of biosimilar

- **Recommendations**

- Prerequisites for indication extrapolation: CMC (Quality) of biosimilar and its reference drug are highly similar, and: no clinically meaningful difference in the indication studies between biosimilar and reference drug, similar PK and similar immunogenicity in different populations, the same mechanism of action in each condition of use, similar expected toxicities in different populations.
- The extrapolated indications should be the approved indications of the reference drugs in China
- Indication extrapolation is case by case, based on the similarities of CMC (Quality) to evaluate the acceptability of differences among the above elements.

Labeling

---based on the Phased research results

☐ Considerations on labeling

- To objectively present the research data of the reference drug and biosimilar to ensure safety in drug use
- Declaration that shows biosimilarity.
- Phased Improvement of the label contents

☐ Recommendations

- **In consideration that China biosimilar regulatory system is still developing, we recommend to learn from Canadian experiences at the starting stage** [*To declare in the label that the product is the biosimilar of the reference drug, summarize the safety and efficacy data of the approved reference drug(only data corresponding to the indications approved by the biosimilar].*
- **With the improvement of the biosimilar regulatory system in China, to gradually simplify the label contents, and to adopt the EU experiences.** *[identical to the label of reference drug, declare in the label that the product is a biosimilar to the reference drug, but clinical trial data of biosimilar is not included].*

Switching and Interchangeability

---based on the Phased research results

☐ Considerations on Switching and interchangeability

- The development of biosimilars is at the starting stage in China, interchangeability requires the additional technical requirements, which is not mature in China now and interchangeability may not be considered in the registration and review process.
- In addition to policy incentives, it is more feasible for doctors to lead the use of biosimilars.

☐ Recommendations

- Because the concepts and evaluation/technical standards for 'interchangeability of biosimilars' have not been set up in China, and it's difficult for the macromolecular structure of biosimilars to be identical to the reference drug, interchangeability may not be considered in the registration and review process at present stage.
- Doctors prescribe biosimilars according to the patients' situation and the characteristics of the biosimilar. Biosimilars should be prescribed by clinicians according to the conditions of patients and the products.

Biosimilar Technical Guideline System

---based on the Phased research results

☐ **Considerations on technical guideline system:**

- Technical guideline system is a technical support to effectively guide the biosimilar R&D.
- Technical guideline system is not done at one kick, and the framework of the guideline system and the urgent technical guidelines should be prioritized.
- The logic, the principles and the methods for establishing the technical guidelines should be in line with international standards.

☐ **Recommendations**

- To establish the general principles for biosimilar technical requirements, and according to international standards to revise the 2015 version of Technical Guidelines for Biosimilar R&D and Evaluation (Tentative)
- To preferentially establish the urgently-needed technical guidelines , such as guidelines on CMC similarities , non-clinical similarities, clinical study similarities, selection of reference drugs, naming, labels, immunogenicity assessment, statistical analysis of similarities, etc.
- To establish the guidelines for specific product to guide the specific biosimilar R&D.
- Before China has a comprehensive biosimilar technical guideline system, the ICH guidelines and agencies with advanced experiences could be adopted.

Legislation (laws) and guidance, (guidelines)

Legislation

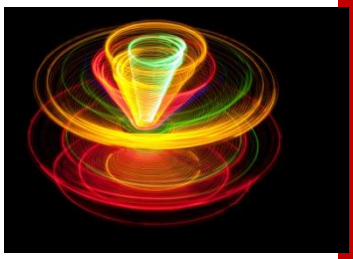
- Is usually written in a very specific way for the country or region

- Needs to be a high level framework,
- Not expected to need to be updated regularly, is long-term in nature

Guidance

- Must stay within the framework of the law
- But fills in the gaps showing how to apply
- May be revised more easily than laws but aiming to be fit for purpose for around 5 years
- Scientifically based but also needs to be written to allow:

1. Room for growth	2. Flexibility/ divergence	3. Allow time for debate - new science



  - (includes phrases like “as required”, “if necessary”, “case by case”)

What lessons can we learn on these 3 aspects of guidance?

From: Judith Macdonald, Pfizer; slides of Regulatory Perspectves on Biosimilars


THANKS!