Regulatory challenges for non-biological complex drug products

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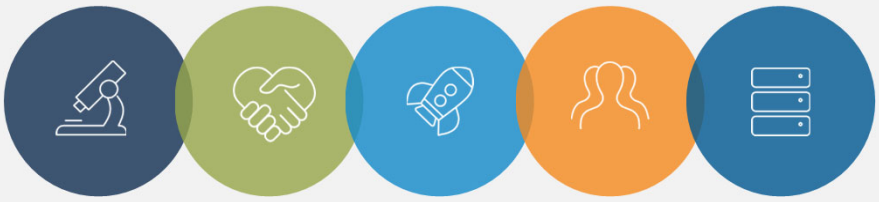
Pioneering medicine. Together

lygature



Lygature is a **not-for-profit** organization. It drives the development of **new medical solutions** for patients by managing **public-private partnerships** involving academia, industry and society.

Every day, Lygature brings together people in many different disciplines and organizations – **to pioneer solutions** in medical technology and pharmacotherapy, and **to serve patients worldwide**.

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The NBCD Working Group: *Towards appropriate, world-wide, science-based approval and post-approval standards for NBCDs*

Map the issues

- Terminology
- CMC/Manufacturing
- Characterization/CQAs
- PK/PD
- In vivo performance
- Substitution / interchangeability

Engage in discussions

- FDA / EMA / other regulators
- Knowledgeable institutes (e.g. WHO)
- Manufacturers
- Conferences

Inform policy

- Science-based
- Global alignment
- Educational
- Interchangeability?
- Substitution?

More info, full list of partners and funders: www.NBCDs.info

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Numerous scientific outputs have been produced by the NBCD Working Group in the last years

- >15 papers
- 3 blogs
- 1 book published

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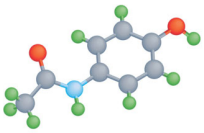
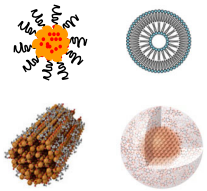
The rise of bio- and nano-technologies has accelerated the development of complex medicines

Conventional drugs



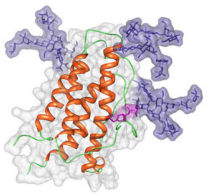
Small molecule drugs
(MW <500d)
e.g. ASA
Fully characterized

(Nano) technology drugs



Complex *(non-biological) drugs*
(MW range 5-900kDa)
e.g. Iron carbohydrates, liposomes
Not fully characterized

Biotechnology drugs



Complex (biological) drugs
(MW range 5-900kDa)
e.g. *mAbs*
Not fully characterized

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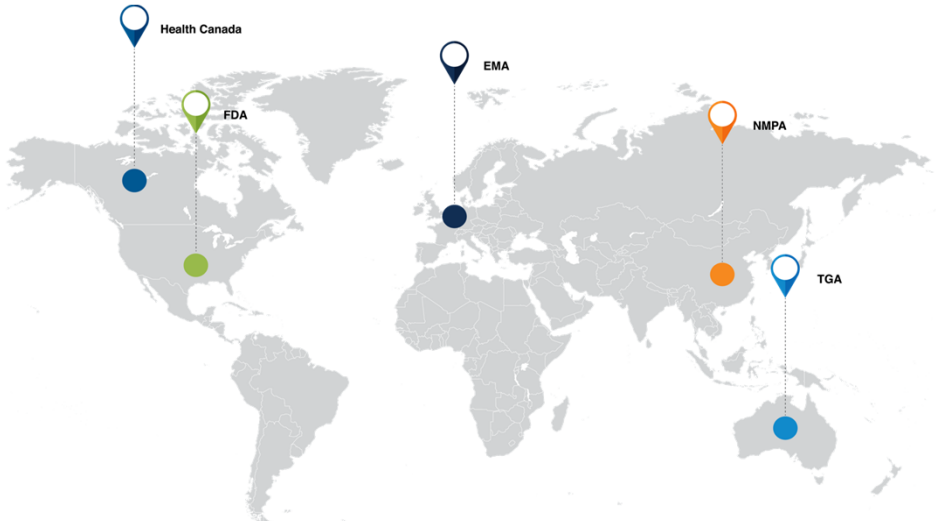
Regulatory guidance for complex drugs are being prepared around the globe



Canada
Public consultation of draft guidance by Health Canada

United States
Published guidance for complex medicine developers by FDA

European Union
Published guidance for complex medicine developers by EMA

China
Public consultation of draft guidance by NMPA

Australia
Public consultation of draft guidance by TGA

Disclaimer: This overview is not exhaustive

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EU regulatory framework for NBCDs, nanomedicines and their follow-on products

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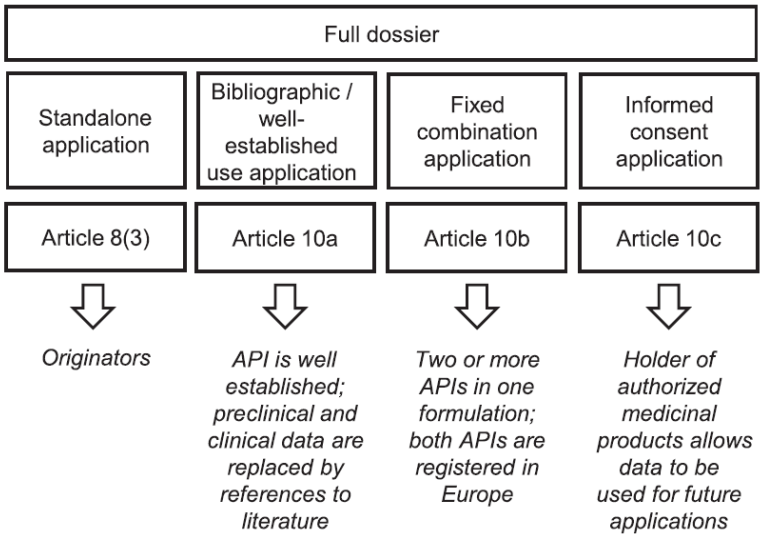
The framework for approval of medicines in Europe



From: Hussaarts et al.; Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann N Y Acad Sci. 2017 Nov;1407(1):39-49.

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National, decentralised or centralised procedures?

Each EU Member State has its own national authorisation procedures

If a company wishes to request marketing authorisation in several EU Member States for a medicine that is outside the scope of the centralised procedure, it may use one of the following routes:

- mutual-recognition procedure, whereby a marketing authorisation granted in one Member State can be recognised in other EU countries;
- decentralised procedure, whereby a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU Member States.

https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

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Biotech products and ATMPs have to follow the centralised procedure to obtain marketing authorization (EMA)

The centralised procedure is **compulsory** for:

- human medicines containing a new active substance to treat:
  - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
  - cancer;
  - diabetes;
  - neurodegenerative diseases;
  - auto-immune and other immune dysfunctions;
  - viral diseases.
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- orphan medicines (medicines for rare diseases);
- veterinary medicines for use as growth or yield enhancers.

https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

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Biotech products and ATMPs have to follow the centralized procedure to obtain marketing authorization (EMA)

It is **optional** for other medicines:

- containing new active substances for indications other than those stated above;
- that are a significant therapeutic, scientific or technical innovation;
- whose authorisation would be in the interest of public or animal health at EU level.

https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

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What is the benefit of the centralised procedure for EU citizens?

Medicines are authorised in all EU countries at the same time

Centralised safety monitoring

ABC XΨΩ Product information available in all EU languages at the same time

https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

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How do NBCDs compare to other drugs?

	SMALL MOLECULE DRUGS	NBCDs	BIOLOGICS
Molecular weight	Low (<500)	High (range 5-900 kDa)	
Structure	Simple, well-defined	Complex, heterogeneous, defined by manufacturing process	
Modifications	Well-defined	Many options	
Manufacturing	Chemical synthesis	Synthetic technologies *(incl. nanotech)*	Produced in living cells or organisms
Stability	Stable	Generally unstable, sensitive to external conditions	
Immunogenicity	Mostly non-immunogenic	Immunogenicity varies	Mostly immunogenic
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	

Adapted from GaBI Online – Generics and Biosimilars Initiative www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs, based on Declerck and Schellekens.

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13 6 December, 2022

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How do NBCDs compare to other drugs?

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How do NBCDs compare to other drugs?

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Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	
	GENERIC APPROACH *well-established worldwide*	**?**	**BIOSIMILAR APPROACH** *In use and gaining traction*
Authorization of follow-on versions	Pharmaceutical equivalence + Bio-equivalence = Therapeutic equivalence ➔ Interchangeable	Generic pathway? Hybrid pathway? Biosimilar pathway?	Totality of the evidence How similar? Therapeutic alternative? ➔ Interchangeable? Substitutable?

Based on Schellekens et al; Regul Toxicol Pharmacol. 2011 Feb;59(1):176-83.

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15 6 December, 2022

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How are NBCD follow-on versions approved in the EU?

	SMALL MOLECULE DRUGS	NBCDs and nanomedicines	BIOLOGICS
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	
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Objective:

- To look into the EU regulatory landscape of NBCD / NBCD follow-on products (until November 2018)
- To assess the level of consistency and heterogeneity in the regulatory approach for individual NBCD products

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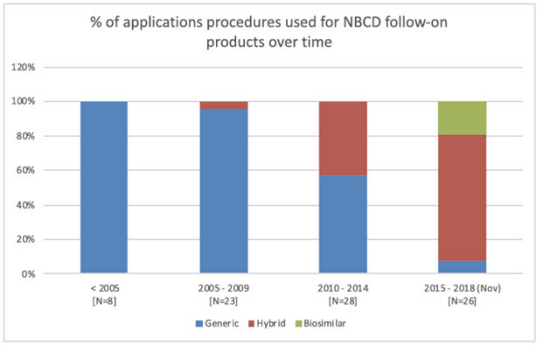
Today, the European regulatory landscape for approval of NBCD follow-on products is heterogenous

European Journal of Pharmaceutical Sciences
Volume 133, 15 May 2019, Pages 228-235

The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations

K. Klein [a, b, c], P. Stolk [a, b, c], M.L. De Bruin [a, d], H.G.M. Leufkens [a, b], D.J.A. Crommelin [e], J.S.B. De Vlieger [b]

Show more



- Time trend analysis in the EU shows an increase of the use of the hybrid application procedure via Article 10(3) for approvals of NBCD follow-on products
- Recent approval of Sucrofer® (a follow-on product for Venofer®) through the hybrid application procedure via Article 10(3), in contrast to previous use of the generic application procedure via Article 10(1), shows a change in the regulatory approach for certain NBCDs in the EU

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More consistency in the EU regulatory approach is proposed

European Journal of Pharmaceutical Sciences
Volume 133, 15 May 2019, Pages 228-235

….. NBCDs are currently not recognised as a separate product class, and no distinct regulatory pathway exists for the approval of NBCD follow-on products. This study shows the **variation in the regulatory approaches** for NBCDs and their follow-on products in the EU**, predominantly relying on non-centralised procedures.**

…….. A more consistent approach for regulating NBCDs in the EU could already be achieved by **building on the EMA guidance documents on nanomedicines** and provide an outline on appropriate regulatory pathways for specific NBCD product classes (e.g. generic or hybrid application).

…… Furthermore, like biotechnology-derived products or advanced therapy medicinal products (ATMPs), **NBCDs could also benefit from a mandatory centralised procedure**, as this will **guarantee consistency in the scientific evaluation of follow-on products.**

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Global alignment on regulatory guidance for (non-biological) complex drug products ?

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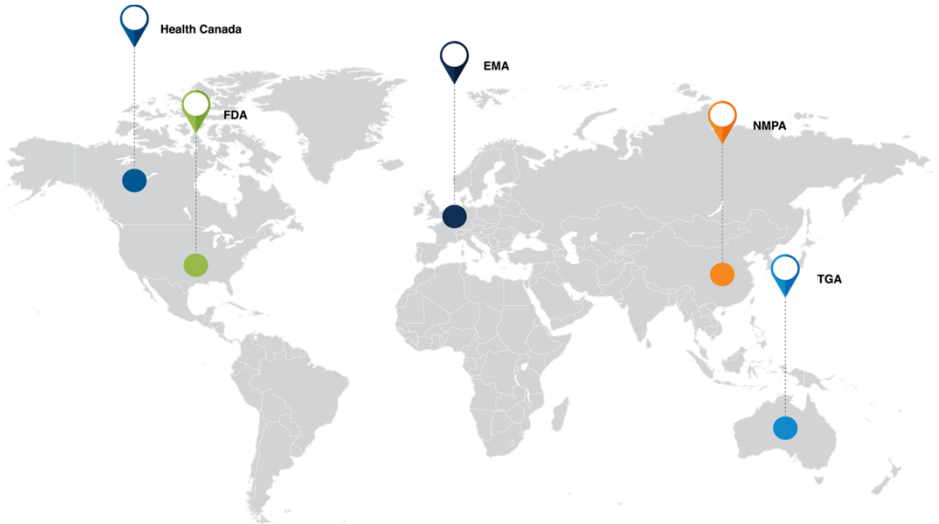
Regulatory guidance for complex drugs are being prepared around the globe



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Two failed attempts to approve follow-on version of liposomal doxorubicin in the EU are an example of the regulatory challenges

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2016

Withdrawal of the marketing authorisation application

"the CHMP was of the opinion that the studies did not provide enough evidence to show that **Doxorubicin SUN** was similar to the reference medicine [Caelyx]"

31 January 2019

Medicine was refused authorization for use in the EU

"the CHMP was of the opinion that there was insufficient evidence to show that **Doxolipad** was bioequivalent to Caelyx"

Product complexity leads to different regulatory approaches worldwide

Doxil® (USA) marketed as **Cealyx**® (EU) by Janssen

Lipodox (Sun Pharma)

FDA (2012): temporarily imported without approval due to shortage of Doxil

DOXOrubicin Sun (Sun Pharma)

- FDA (2013): approved as a generic for Doxil
- EMA (2016): rejected as a generic for Cealyx

Copaxone®
Teva Pharmaceuticals

Glatopa (Momenta)

FDA: approved in 2015 through Generics application based on sameness defined by FDA, without clinical studies

Glatiramer Acetate (Synthon)

EMA: Approved in 2016 through hybrid application, including one Phase III study

Are we closer to alignment worldwide?

In September 2021 EMA and FDA have launched a pilot:

FDA U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2021

PILOT PROGRAM: EMA-FDA PARALLEL SCIENTIFIC ADVICE FOR HYBRID/COMPLEX GENERIC PRODUCTS - GENERAL PRINCIPLES

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services have established a pilot program to provide parallel scientific advice (PSA) to applicants of marketing authorization applications (MAAs) for hybrid products (EMA) and abbreviated new drug applications (ANDAs) for complex generic drug products, hereafter referred to as "complex products" (FDA).[1] The goal of the PSA program

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What type of results can we expect?

11. After a PSA procedure, each agency will retain its individual regulatory decision-making authority regarding drug development issues and marketing applications. The advice of each agency may still differ after the joint discussion. Each agency will provide the sponsor its independent advice on the questions posed during the PSA process, according to usual procedures and timelines. Sponsors should neither expect to receive similar recommendations from the two agencies regarding drug development issues nor expect to receive similar agency decisions regarding marketing applications that have undergone PSA. However, both agencies will strive to provide PSA responses that are convergent.

Will it be used by generic companies? Will agencies share information on statistics of use?

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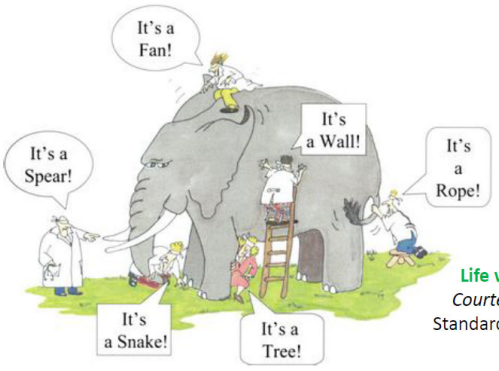
What is next? How can we prevent divergence of our regulatory approaches worldwide?

Regulatory Challenge

Non-standardization of nomenclature, test method and characterization



Life without standards

Courtesy: Hany Demian, Standard Executive at FDA

www.fda.gov

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What do we need to advance the field?

→ Alignment of science-based regulatory views worldwide

- Better analytical tools for in vitro and in vivo analysis
- Engage all stakeholders in discussions
- Better ways to measure efficacy and safety in the clinic
- Scientific findings published by manufacturers (innovator and follow-on)
- Identification of clinically relevant parameters (the critical quality attributes)

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