Nanomedicines, Non-Biological Complex Drugs and their similars

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Non Biological Complex Drugs working group

EAASM Webinar November 30, 2021

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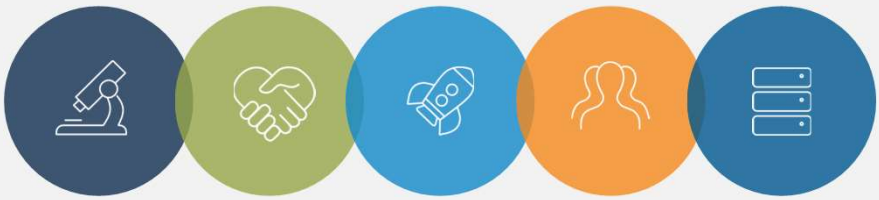
Pioneering medicine. Together

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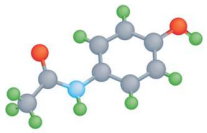
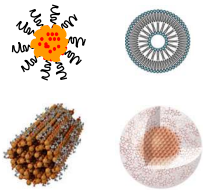
The rise of bio- and nano-technologies has accelerated the development of complex medicines

Conventional drugs



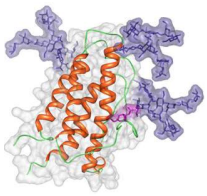
Small molecule drugs
(MW <500d)
e.g. ASA
Fully characterized

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

Map the issues

- Patient safety
- Terminology
- Characterization
- 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?

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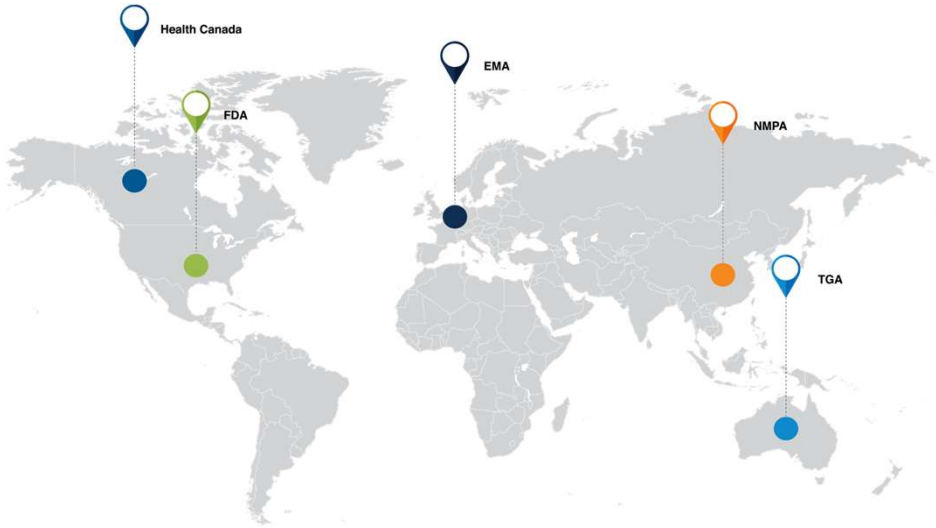
More info, full list of partners and funders: www.NBCDs.info

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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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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EU Regulatory framework for NBCDs and Nanomedicines

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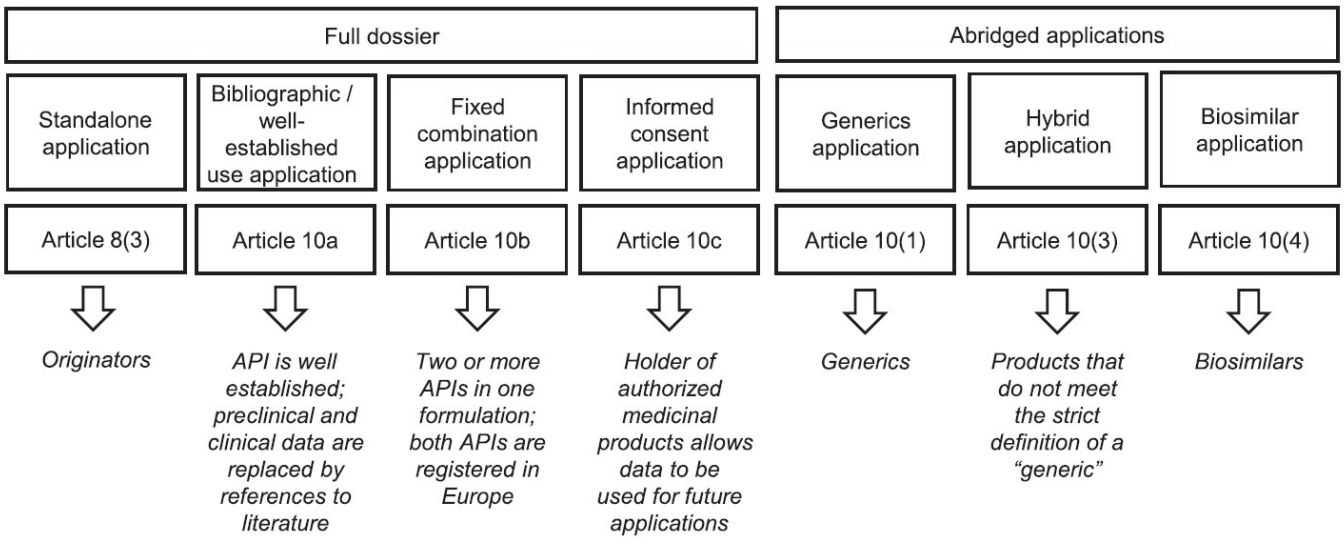
The framework for approval of medicines in Europe



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

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

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

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.

How do NBCDs compare to other drugs?

	SMALL MOLECULE DRUGS	NBCDs	BIOLOGICS
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.

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

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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

ELSEVIER
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]
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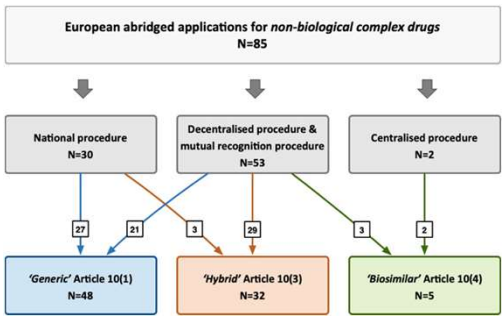

- 85 NBCD follow-on products marketed in the EU (also same product, different brandname in different countries)
- 5 different originator product
- DCP (n=45), national procedure (n=30), MRP (n=11), CP (n=2).
- >80% of DCP/MRP procedures by only 3 countries (i.e. DK, DE, NL)

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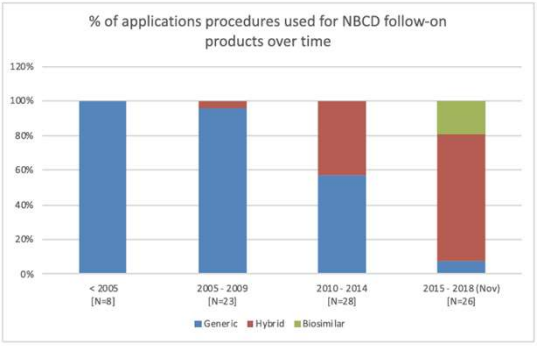

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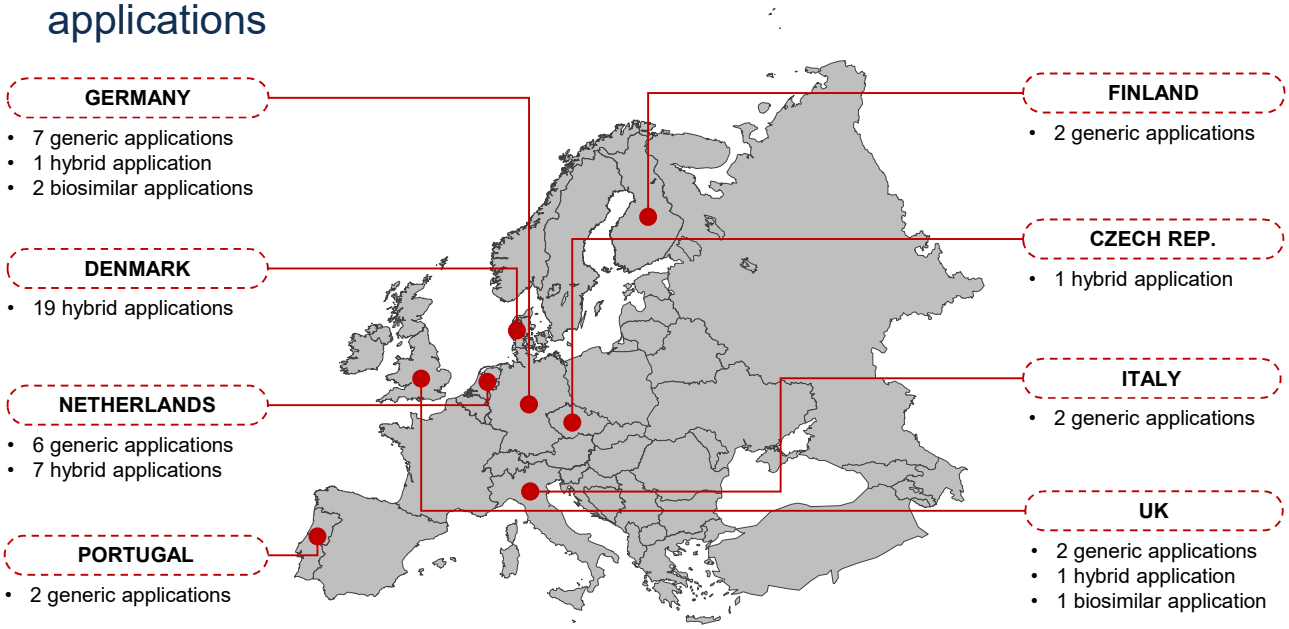
Eight different reference member states for the 53 DCP/MRP applications



Klein et al.: The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. Eur J Pharm Sci. 2019 May 15;133:228-235.

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Why a mandatory centralised procedure is the way forward

There is a **lot of variation** in the regulatory approaches for NBCDs, including Nanomedicines and their follow-on products in the EU**, predominantly relying on non-centralised procedures.**

NBCDs including Nanomedicines will benefit from **a mandatory centralised procedure**, as this will **guarantee consistency in the scientific evaluation of follow-on products (mandatory hybrid for follow-ons):**

- Combined competence of the large network of EMA experts is *directly* available, as is the case for biosimilars.
- Guaranteed application of up-to-date scientific knowledge and evaluation tools
- Centralised safety monitoring (and a single brandname in Europe)
- Predictability for NBCD developers may increase access to high quality, similar follow-on versions

De Vlieger et al.: Is the EU ready for non-biological complex drug products?
Article in Generics and Biosimilars Initiative Journal · September 2016 DOI: 10.5639/gabij.2016.0503.026

Klein et al.: The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations. Eur J Pharm Sci. 2019 May 15;133:228-235.

Non Biological Complex Drugs working group

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