Regulatory Approval Pathways: Considerations for Complex (Generic) Drug Products in an International Environment

Jon S.B. de Vlieger, PhD

Strategy Director at the Lygature Foundation

Coordinator NBCD Working Group

Jon.deVlieger@lygature.org

Non Biological Complex Drugs working group

Lygature provides independent partnership management

As a not-for-profit organization, Lygature aims to accelerate the development of new medical solutions for patients by driving public-private collaboration between academia, industry and society

Creating a neutral space for innovation & implementation

Driving the partnership forward to deliver (bio)medical solutions

Providing specialized support for partnerships

NBCD Working Group

- The NBCD working group has the mission to ensure that **appropriate *science*-based approval and post-approval standards are created and globally introduced for NBCDs to ensure patient safety and benefit**.
- The Working Group collaborated with many different partners over the years including the Nanotechnology Characterization Lab, Sanofi-Aventis Groupe, Teva Pharmaceutical Industries Ltd., Allergan Plc (Abbvie), Vifor International Inc., University of Lisboa, University of Geneva, University of Basel and many more.
- Hosted by Lygature, a not-for-profit organization based in the Netherlands, the working group consists of experts from industry, academia, and knowledge institutes.
- In addition to in-kind contribution of all partners, funding was provided by Allergan Plc, Teva, Sanofi, and Vifor International Inc.
- www.NBCDs.info

The Mission & Vision of the NBCD Working Group: From awareness in science towards alignment in practice

Workshop

Bioequivalence of Complex Drugs

7 October 2009, Leiden, the Netherlands

TI PHARMA

Regulatory Toxicology and Pharmacology 59 (2011) 176–183

Contents lists available at ScienceDirect

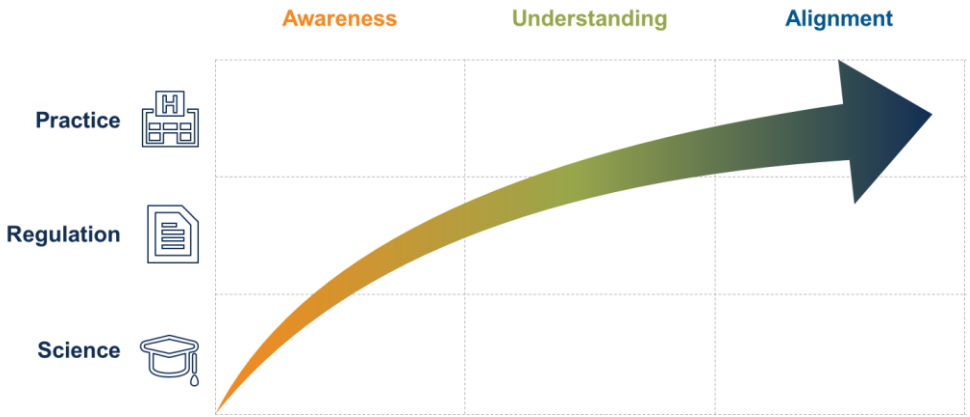
Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The therapeutic equivalence of complex drugs ☆

Huub Schellekens [a,b,*], Ety Klinger [c,1], Stefan Mühlebach [d,2], Jean-Francois Brin [e,3], Gert Storm [f,g], Daan J.A. Crommelin [f,g,h,i]

[a] Department of Pharmaceutical Sciences, Utrecht University, P.O. Box 80.082, 3508 TB Utrecht, The Netherlands
[b] Department of Innovation Studies, Utrecht University, P.O. Box 80.082, 3508 TB Utrecht, The Netherlands
[c] Global Innovative R&D, Teva Pharmaceutical Industries, P.O. Box 8077, Netanya 42504, Israel
[d] Vifor Pharma Ltd., Flughofstrasse 61, P.O. Box CH-8152 Glattbrugg, Switzerland
[e] Pharmaceutical Customer Solutions, 46, Quai de la Rappée 75601, Sanofi-Aventis, Paris Cedex 12, France
[f] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, UIPS, P.O. Box 80.082, TB Utrecht, The Netherlands
[g] Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands
[h] Dutch Top Institute Pharma, Galileiweg 8, 2333 BD Leiden, The Netherlands
[i] P.O. Box 142, 2300 AC Leiden, The Netherlands



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

>15 papers

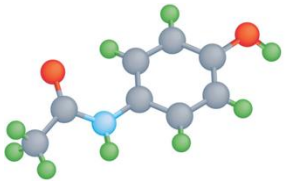
3 blogs

1 book published

Non-biological complex drugs

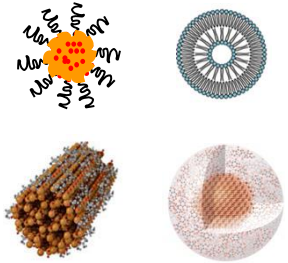
The rise of bio- and nano-technologies has accelerated the development of complex medicines

Conventional drugs



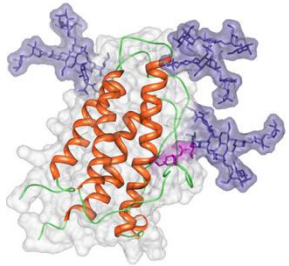
Small molecule drugs
(MW <500d)
e.g. ASA
Fully characterized

(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

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	

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	
Authorization of follow-on versions	**GENERIC APPROACH** *well-established worldwide* Pharmaceutical equivalence + Bio-equivalence = Therapeutic equivalence ➔ Interchangeable	**?**	**BIOSIMILAR APPROACH** *In use and gaining traction* Totality of the evidence How similar? Therapeutic alternative? ➔ Interchangeable? Substitutable?

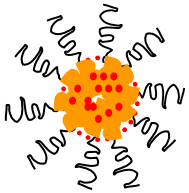
Based on Schellekens et al; Regul Toxicol Pharmacol. 2011 Feb;59(1):176-83.

What is an NBCD? (1)

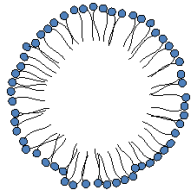
A non-biological complex drug (NBCD)…

- … is a synthetic medicinal product that is **not a biological medicine**
- … with an active substance that is **not homo-molecular** but contains different (closely related, often nano-particulate) structures
- … that **cannot be fully characterized** by physicochemical analytical means.

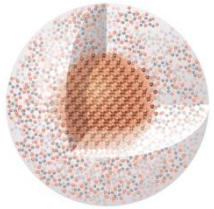
A **well-controlled** robust manufacturing process is fundamental to ensure quality, safety and efficacy.



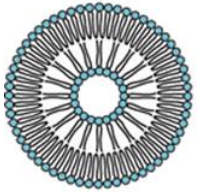
Micelles



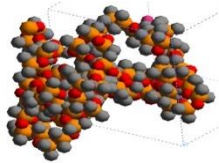
Nanoemulsions



Iron-carbohydrate complexes



Liposomes



Polymers

Full definition NBCD:Crommelin et al. Different pharmaceutical products need similar terminology; AAPS J. 2014

What is an NBCD? (2)

NBCDs are used to treat a **variety of serious medical conditions** including cancer, auto-immune diseases, infectious diseases, anemia, and more.

Doxorubicin liposomes
- Cancer
- Originator: Doxil® (Janssen)

Glatiramer acetate
- Multiple sclerosis
- Originator: Copaxone® (Teva Pharmaceuticals)

Cyclosporine ophthalmic emulsion
- Chronic dry eye disease
- Originator: Restasis® (Allergan)

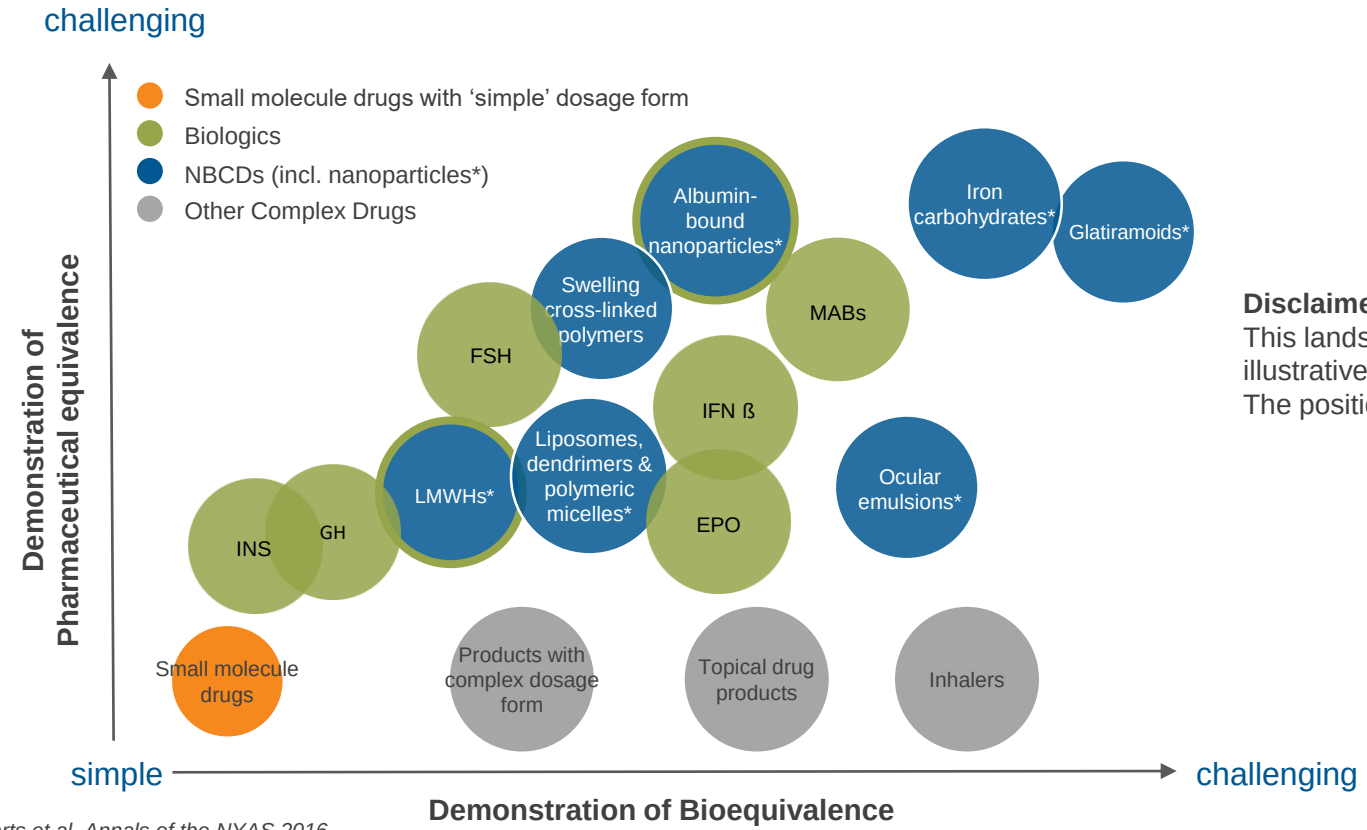
Iron sucrose
- Anemia
- Originator: Venofer® (Vifor Pharma)

Sevelamer carbonate
- Control of phosphorus levels (chronic kidney disease)
- Originator: Renvela® (Sanofi)

Patisiran lipid complex injection
- Polyneuropathy caused by hATTR amyloidosis
- Originator: ONPATTRO® (Alnylam)

Disclaimer: This overview is not exhaustive

The complex drug landscape (an impressionist view)

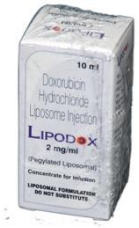


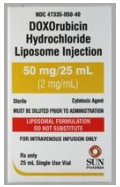
Disclaimer:
This landscape is meant for illustrative purposes only!
The positions are indicative.

Adapted from Hussaarts et al. Annals of the NYAS 2016

Product complexity leads to different regulatory approaches worldwide

Doxil® (USA)
marketed as
Caelyx® (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 Caelyx

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

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

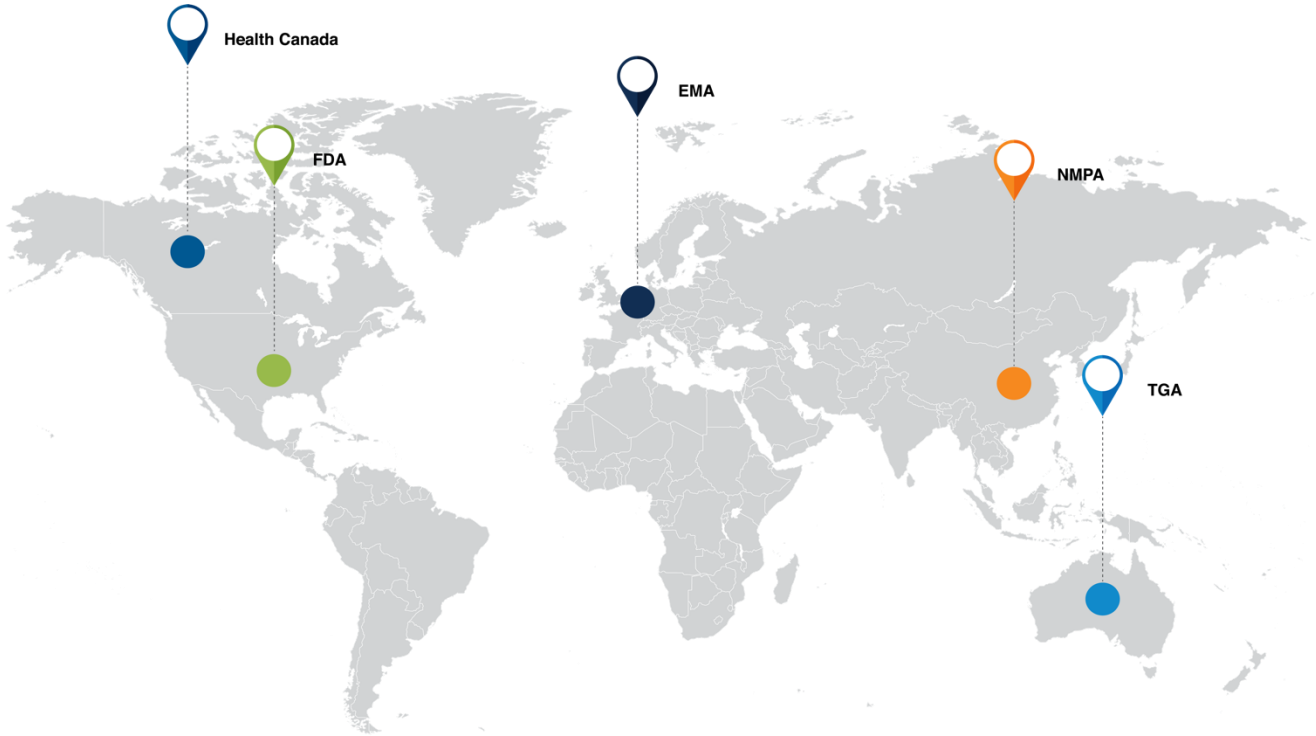
"the CHMP was of the opinion that the studies did not provide enough evidence to show that **Doxorubicin SUN** was similar to the reference medicine [Caelyx]"

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"

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

Guidelines are developed to assist developers

Quality assessment

WG of non-biological complexes

Revision iron sucrose injection monograph

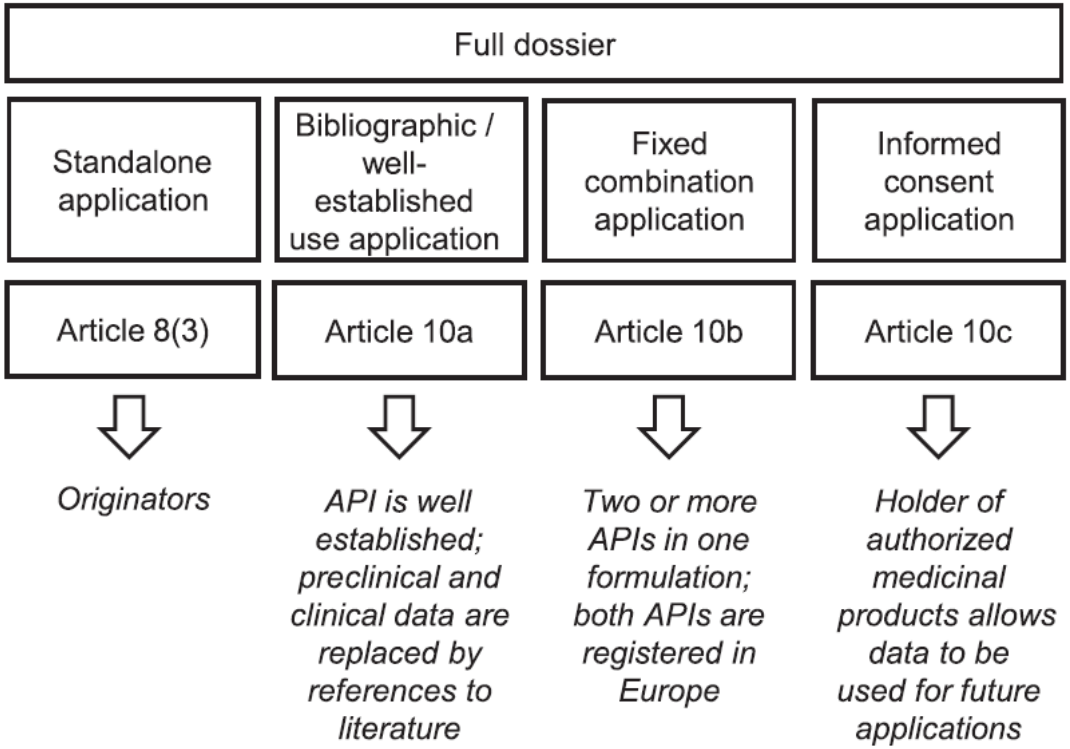
Modernization of existing monographs, development of new ones for NBCDs

Reflection papers, industry guidance, educational session (authorities)

Frameworks for evaluation of Complex Drugs

- EMA
- FDA
- Harmonization?

The framework for approval of (complex) 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.

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

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

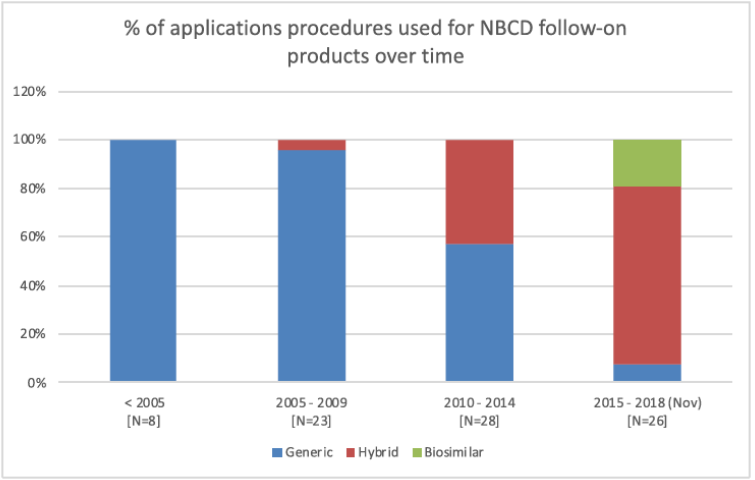
Today, the European regulatory landscape for approval of NBCD follow-on products is heterogenous

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

More consistency in the EU regulatory approach is proposed

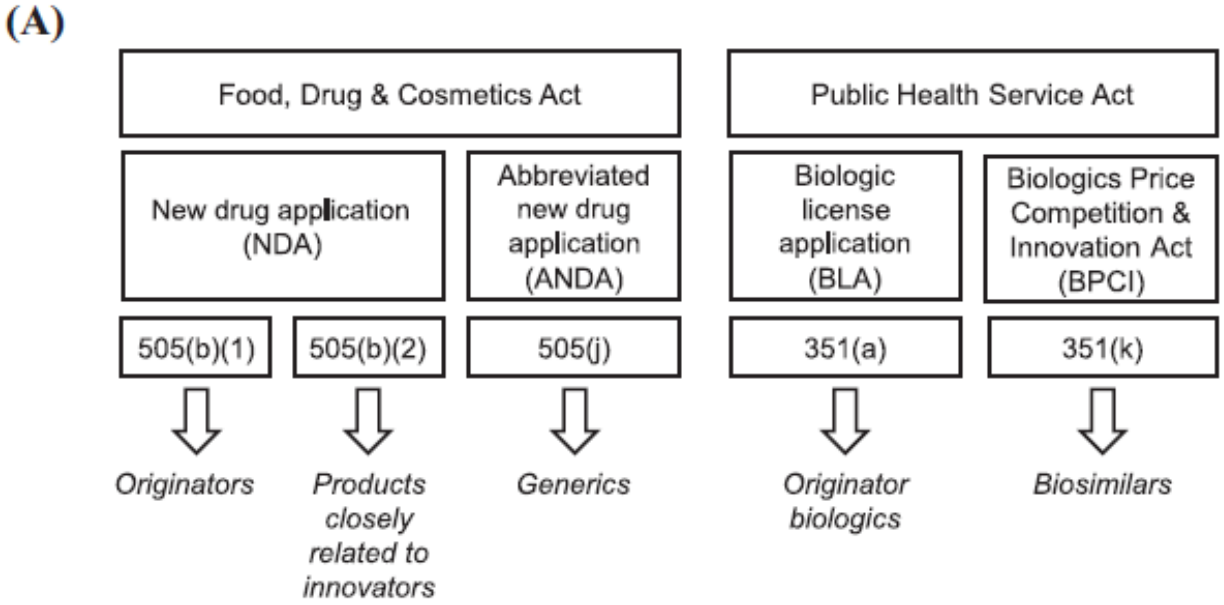
European Journal of Pharmaceutical Sciences
Volume 133, 15 May 2019, Pages 228-235

….. 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.**

FDA approval pathways for (nano)medicines



Hussaarts et al., Ann. N.Y. Acad. Sci. (2017), Complex drug equivalence: advances and challenges, doi: 10.1111/nyas.13347

FDA Draft Guidance, issued December 2017

Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

DRAFT GUIDANCE

FDA U.S. FOOD & DRUG ADMINISTRATION

NBCD WG main comments:

- It reads as a white paper
- Deals with NDAs and ANDAs
- Premise renders the document invalid for many products
- Product specific guidance more useful
- CQAs key topic

Multi-stakeholder discussions lead to clarity and understanding:

aaps Workshops

AAPS GUIDANCE FORUM

SEPTEMBER 11-12, 2018 • SILVER SPRING, MD

The AAPS Journal (2019) 21: 56
DOI: 10.1208/s12248-019-0329-7

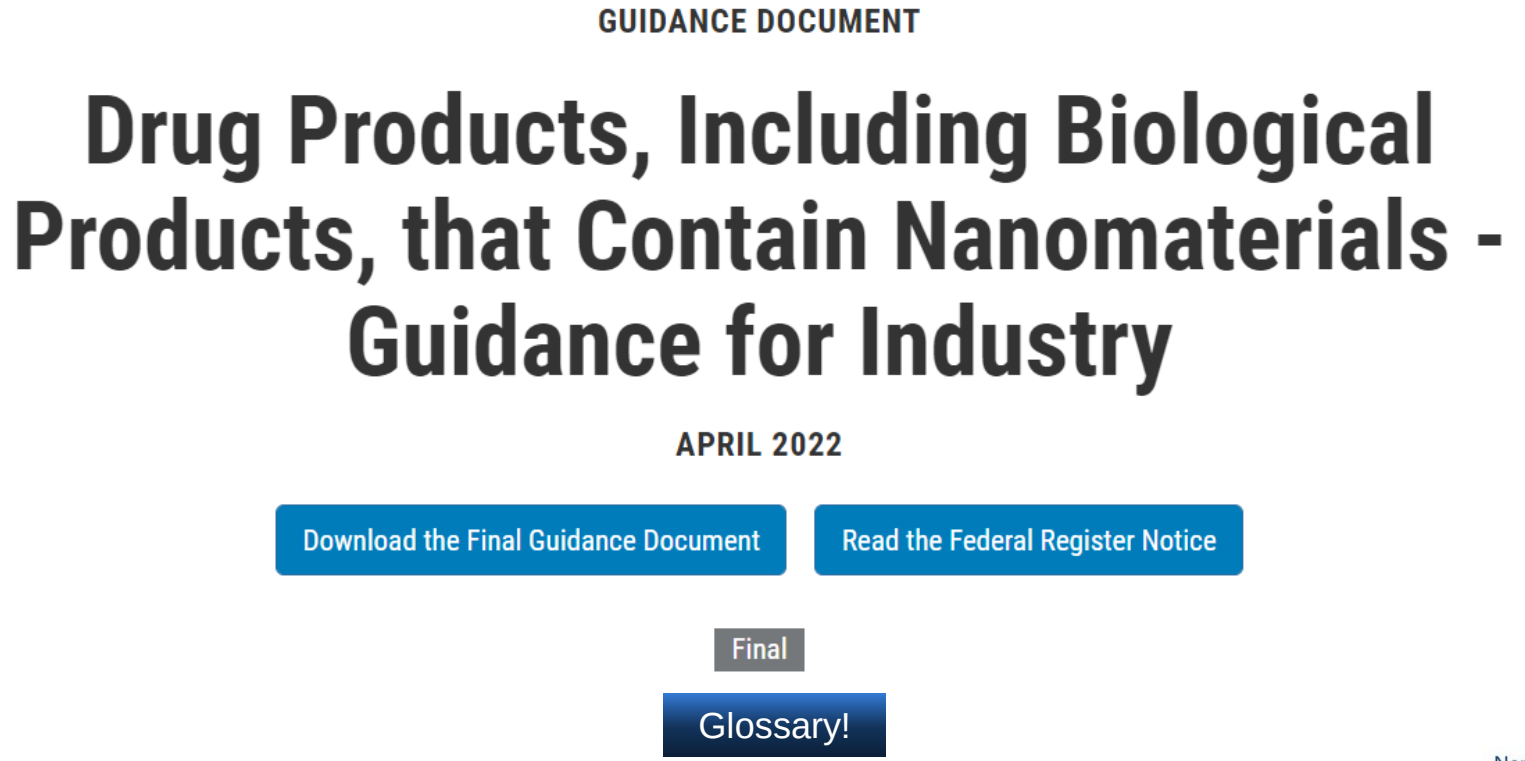
Check for updates

Meeting Report

Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: "Drug Products, Including Biological Products, that Contain Nanomaterials"

Jon S. B. de Vlieger,[1,9] Daan J. A. Crommelin,[2] Katherine Tyner,[3] Daryl C. Drummond,[4] Wenlei Jiang,[5] Scott E. McNeil,[6] Sesha Neervannan,[7] Rachael M. Crist,[6] and Vinod P. Shah[8]

Multi-stakeholder discussions lead to clarity and understanding:



FDA draft guidance on Therapeutic Equivalence 2022:

GUIDANCE DOCUMENT

Evaluation of Therapeutic Equivalence

JULY 2022

Download the Draft Guidance Document

Read the Federal Register Notice

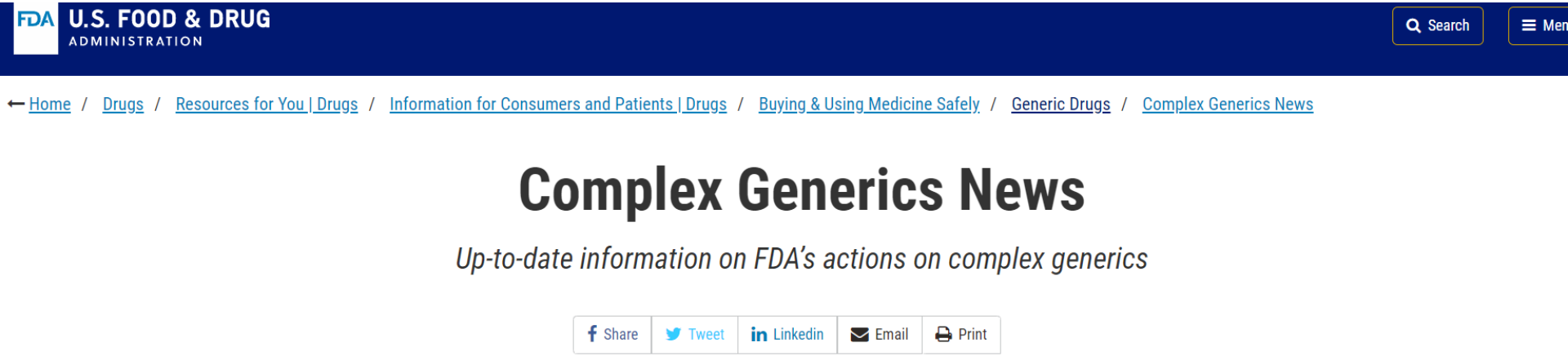
Draft

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

Share | Tweet | Linkedin | Email | Print

Complex generics are now high on FDA's agenda



Complex (generic) drug products are defined as a product with:

- **a complex active ingredient(s)** *(e.g., peptides, polymeric compounds, complex mixtures of APIs, and naturally sourced ingredients)*;
- **a complex formulation** *(e.g., liposomes and colloids);*
- **a complex route of delivery** *(e.g., locally acting drugs, such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels);*
- **a complex dosage form** *(e.g., transdermals, metered dose inhalers, and extended release injectables).*

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

A pragmatic regulatory approach for complex generics through the U.S. FDA 505(j) or 505(b)(2) approval pathways

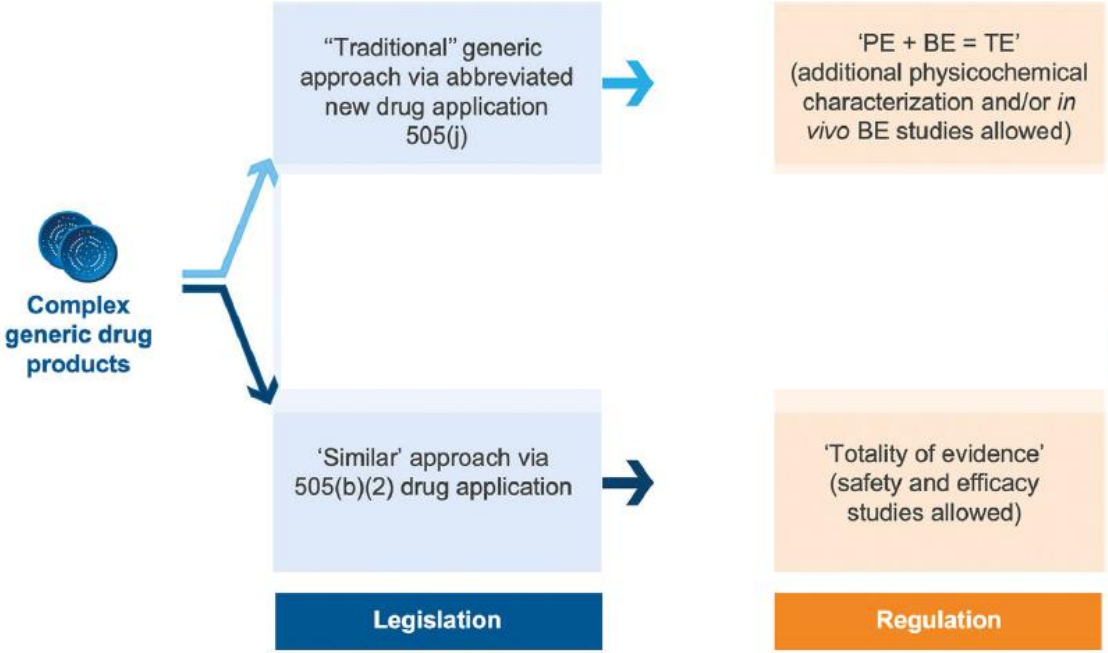


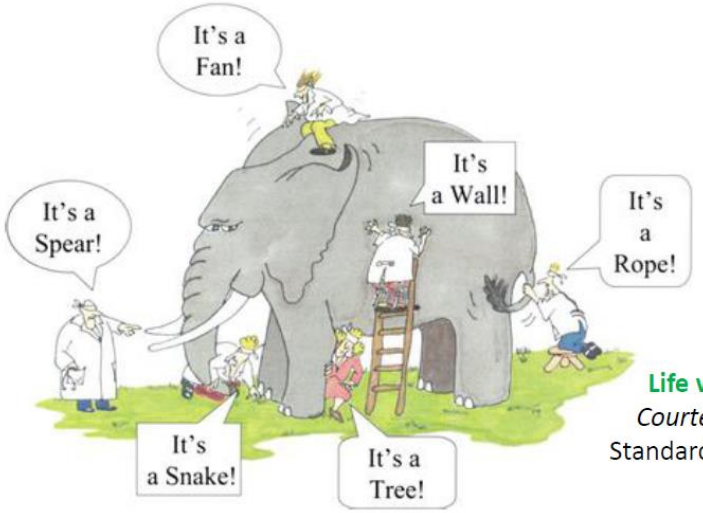
Figure 2. Two regulatory pathways 505(j) and 505(b)(2) within the FDA's regulatory framework that can be used for complex generic drug products depending on the types of characteristics and challenges of the product.

Ref: Klein et al., Ann. N.Y. Acad. Sci. 1502 (2021) 5–13

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

14

There is no harmonization in terminology worldwide

Hybrid medicines are medicines whose authorisation depends partly on the results of tests on the reference medicine and **partly on new data** from clinical trials.

This happens when a manufacturer develops a generic medicine that is based on a reference medicine, but has a **different strength**, a **different route of administration** or a slightly **different indication** from the reference medicine.

https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines

Are we closer to alignment worldwide?

In September 2021 EMA and FDA have launched a pilot:

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

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.

Is it considered useful by generic companies? Will agencies share information on statistics of use?

Reflecting on 10 years of NBCD activities

→ Increase of worldwide discussions around complexity of products

→ Guidance documents developed worldwide

→ EMA & FDA parallel scientific advice mechanism in place

→ Complexity of product AND complexity of assessment acknowledged in newly proposed EU pharma legislation:

"Training opportunities will be provided so that all Member States build expertise in new areas of science and technology, so they can actively contribute to the work of the regulatory network in assessing and monitoring medicinal products, including cutting edge innovative and ***complex medicinal products****."* from: Proposed Regulation.

Proposed: *Complex Hybrids ➔ Centralized through EMA*

Simple Generics ➔ national agencies

Questions?

NBCD Working Group c/o

Foundation Lygature

Beatrixgebouw

Jaarbeursplein 6

3521 AL UTRECHT

The Netherlands

www.NBCDs.info

E-mail: jon.devlieger@lygature.org