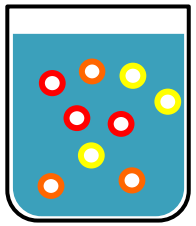
UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE

Regulatory framework on nanotechnology products: how to strike a balance between innovation and public health

Umberto M. Musazzi, PhD

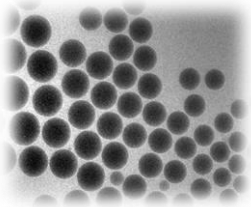
Nanotechnology products… for treating human diseases



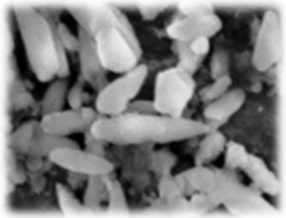
To improve **TECHNOLOGICAL CHARACTERISTICS** of the active ingredient (e.g., high drug solubility and dispersibility of poor soluble drugs)

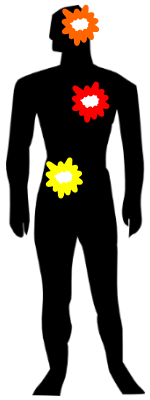
Micelles

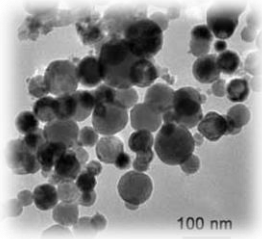
Nanoemulsions



Nanocrystals



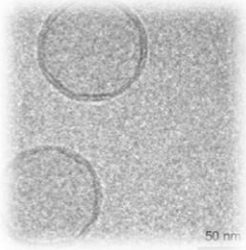




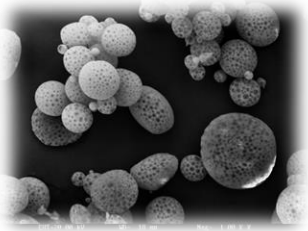
IONs

To modify the drug **PHARMACOKINETICS** and **PHARMACODYNAMICS** in the human body

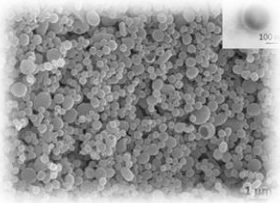
Lipid vesicles



Nanoparticles



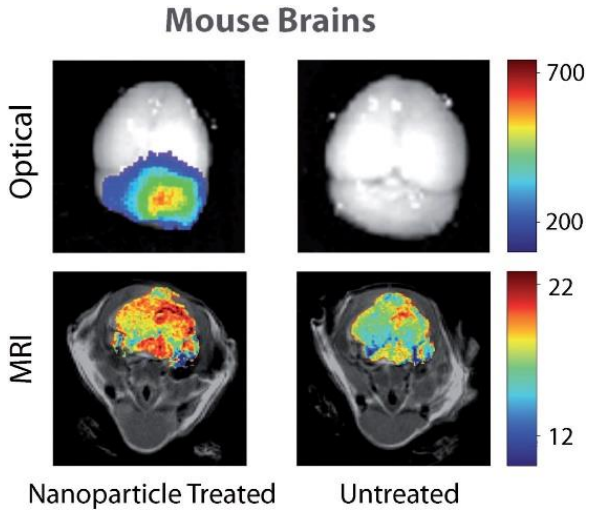
Nanogels



Functionalization of nanosystem surface

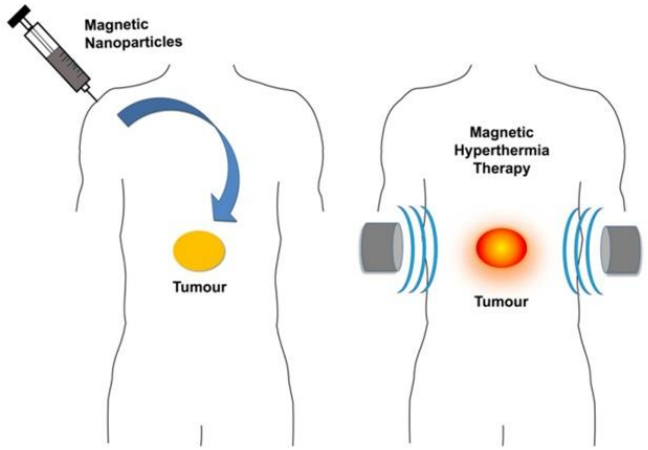
…for treating/diagnose human diseases

DIAGNOSIS



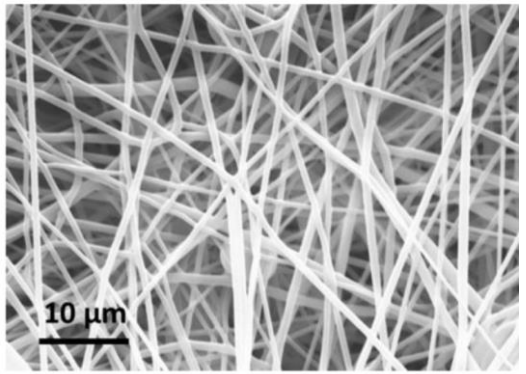
Superparamagnetic nanoparticles for MRI

TREATMENT



Nanoparticle-mediated hyperthermia in cancer therapy

REPLACEMENT OF THE ANATOMY

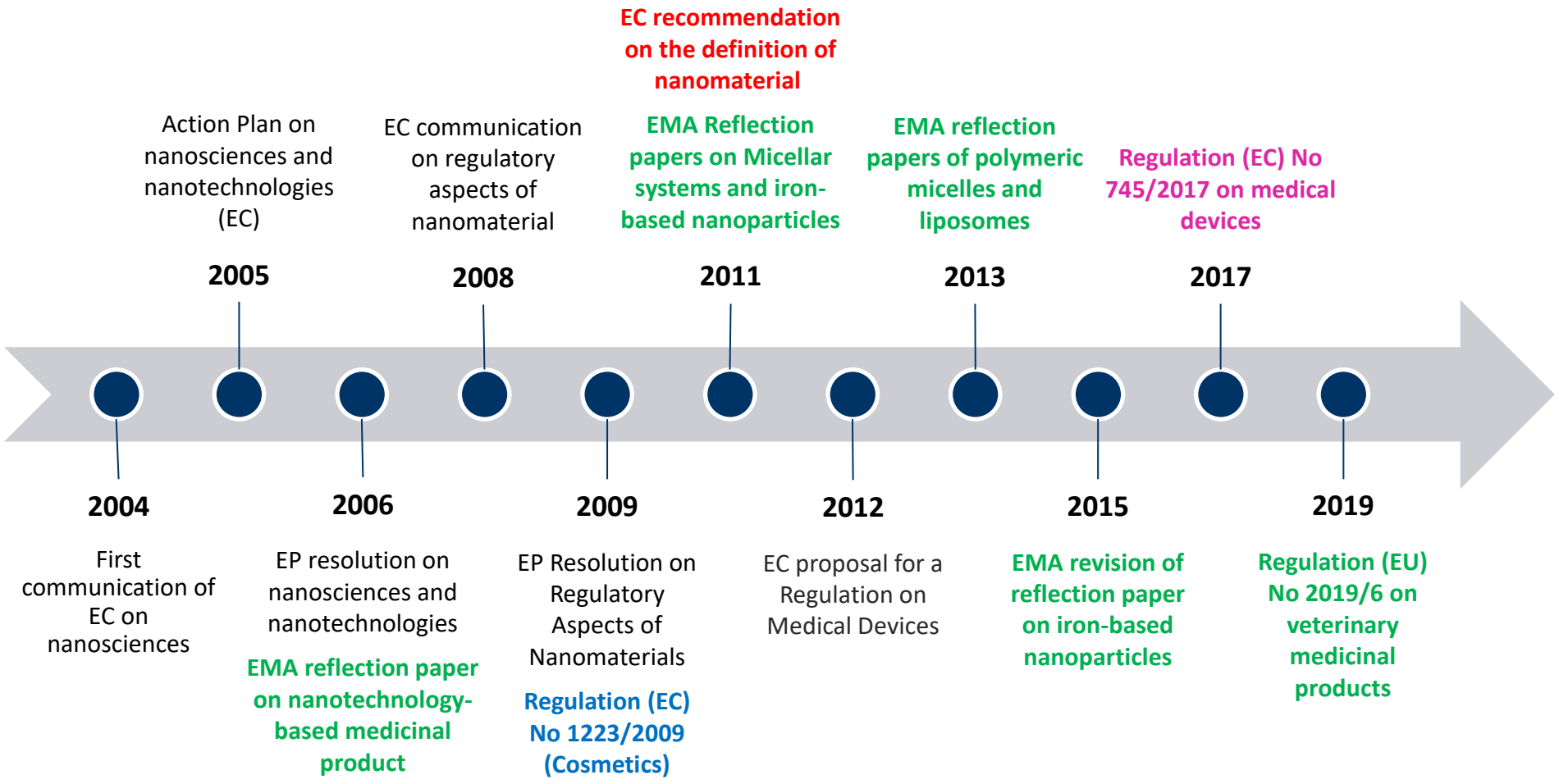


Scaffold made of nanofibers for regenerative therapies

The efficacy/safety balance must be acceptable for human use

Dorati et al., Carbohydrate polymers 2018, 199:150-160
Stephen et al., Mater Today 2011, 14:330-338

The EU regulatory framework of nanotechnology products



The European legislation is still stratified, and several criticisms remain because of the lack of well-established scientific knowledge on nanomaterials. The assessment of safety/efficacy of nanomaterials in medicinal products and medical devices is still based on case-by-case approach.

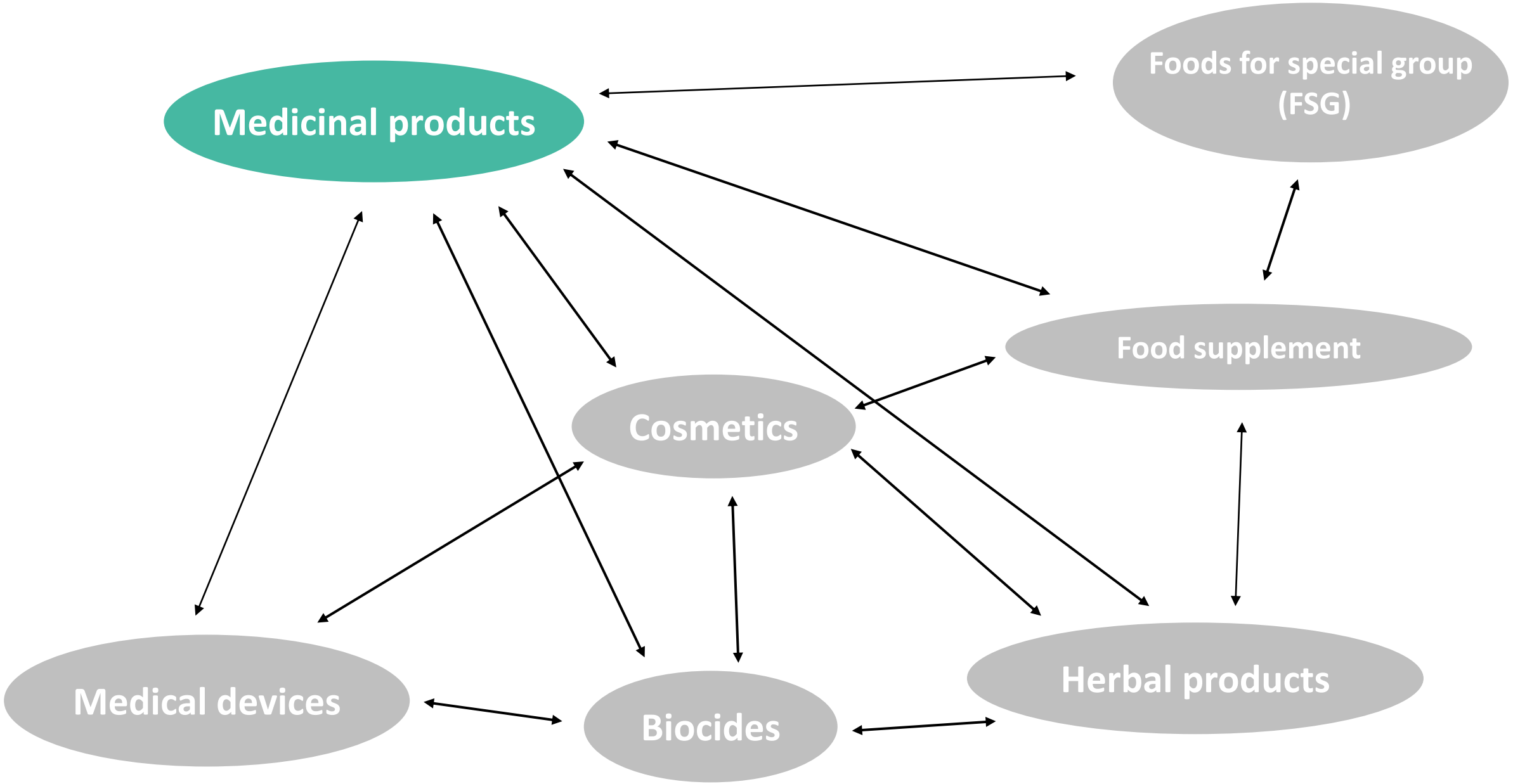
Musazzi et al. Drug. Discov. Today (2017); doi:10.1016/j.drudis.2017.01.016

Definition of nanomaterial

A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range **1 nm - 100 nm**. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

→ A material should be considered as falling under the definition where the specific surface area by volume of the material is greater than 60 m^2/cm^3.

European Commission recommendation of 18 October 2011 on the definition of nanomaterial


Medicinal products
Foods for special group (FSG)
Food supplement
Cosmetics
Medical devices
Biocides
Herbal products

Nanotechnology vs nanomedicine

Nanotechnology is the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around **0.2 nm (2 Å) up to around 100 nm**.

However, EMA also include all the 'structures' with size less than **1000 nm** that are designed to have properties that are peculiar of nanotechnological materials.

Nanomedicine is the **application** of nanotechnology **in view of making a medical diagnosis or treating or preventing diseases**. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale.

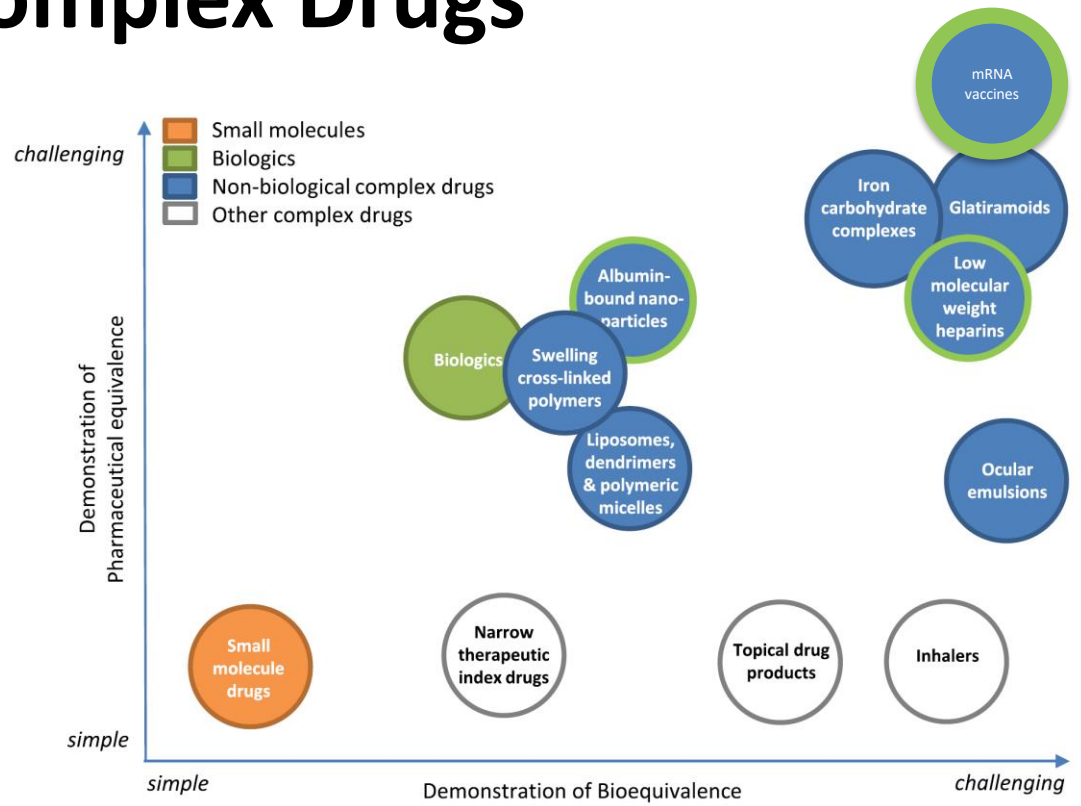
EMEA/CHMP/79769/2006
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&

Non-Biological Complex Drugs

Nanomedicine products →

Categories of drugs considered to be complex by the FDA, as listed in the GAO report [6]

#	Category	Examples
1	Complex active ingredient	Peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients, naturally sourced ingredients
2	Complex formulations	Liposomes and colloids
3	Complex routes of delivery	Locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels
4	Complex dosage forms	Transdermals, metered dose inhalers and extended-release injectables
5	Complex drug–device combinations	Autoinjectors, metered-dose inhalers
6	Other	Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement



Modified by Hussaarts et al., Ann. N.Y. Acad. Sci. 1407 (2017) 39–49

Drug	Biological source	Complex manufacturing	Regulatory approach to copies	Classification of copies	interchangeable
Small molecule	No	No	Generic	Generic	Yes
NBCD	**No**	**Yes**	**USA: generic + additional data EU: hybrid or generic**	**USA: generic EU: variable**	**USA: yes EU: variable**
Biological	Yes	Yes	Biosimilar	Biosimilar	No

Rocco, Musazzi et al., Drug Discov. Today (2019) 24:250-255

Nanomedicine products

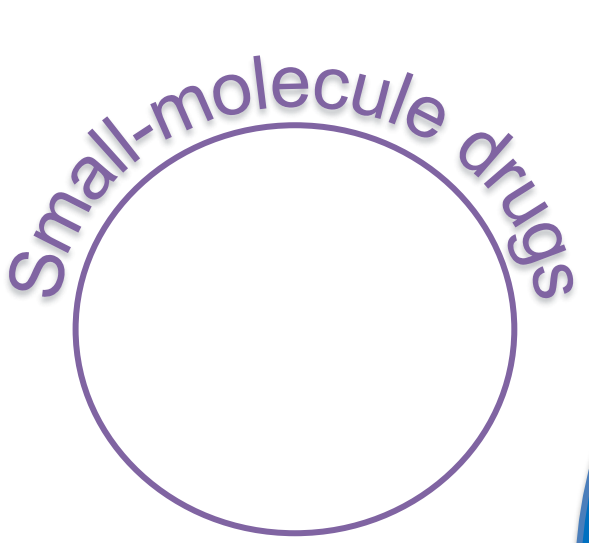
- **Which marketing authorization (MA) procedure should they have to follow?**

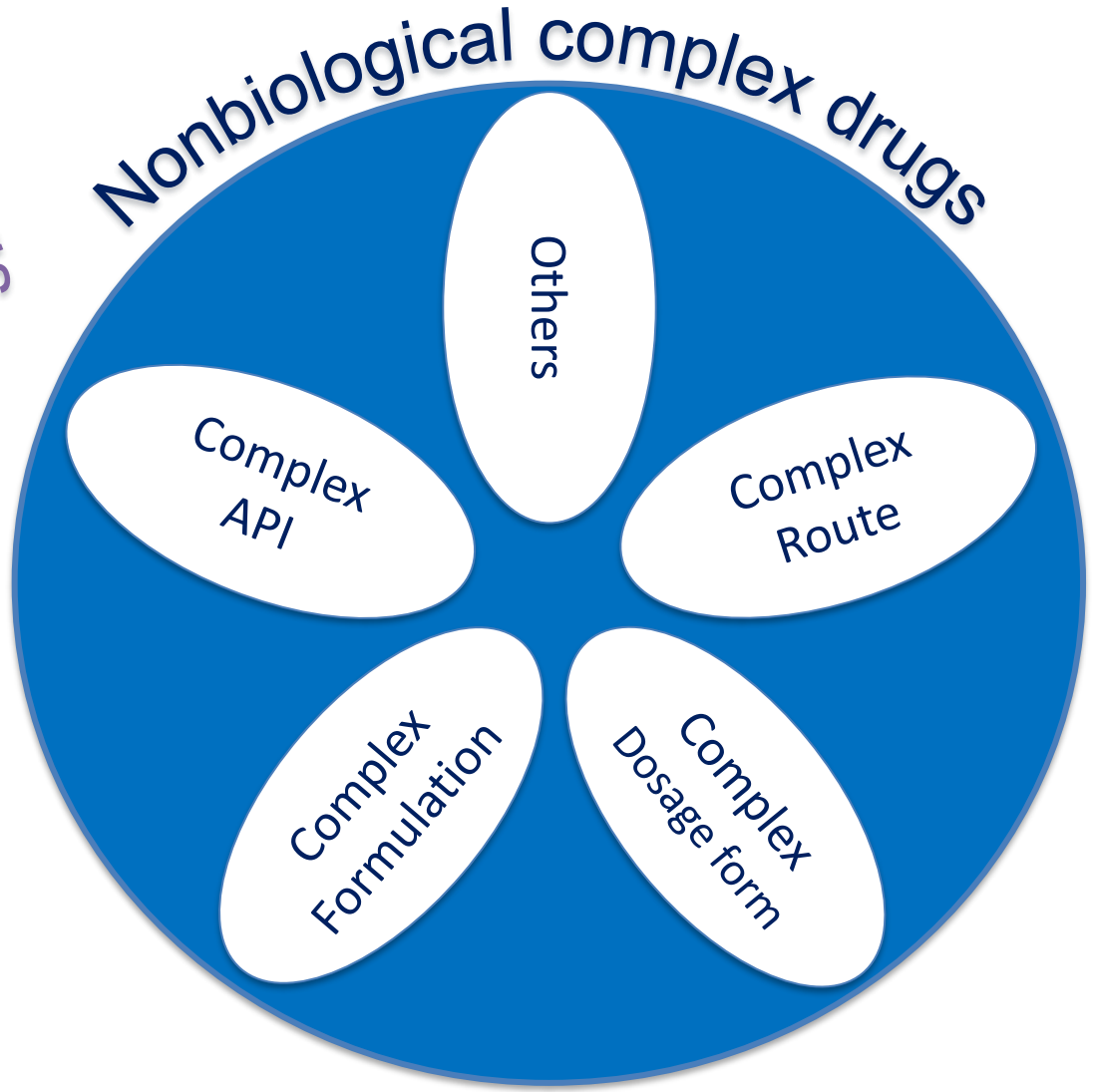
- What data should be submitted to EMA/NCAs? (first-in-human/follow-on products)

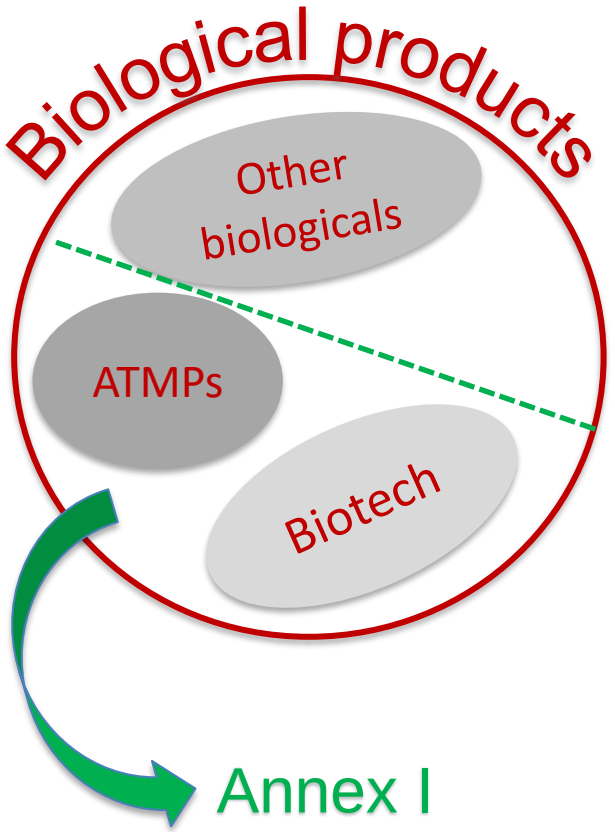
MA applications in EU

Centralised	Valid throughout the Community; granted by the EMA; mandatory for biotechnology products
Mutual recognition	In cases the medicinal product has already received a MA at the time of application.
Decentralised	In cases the medicinal product has not received a MA at the time of application
National	Valid in the authorising Member State

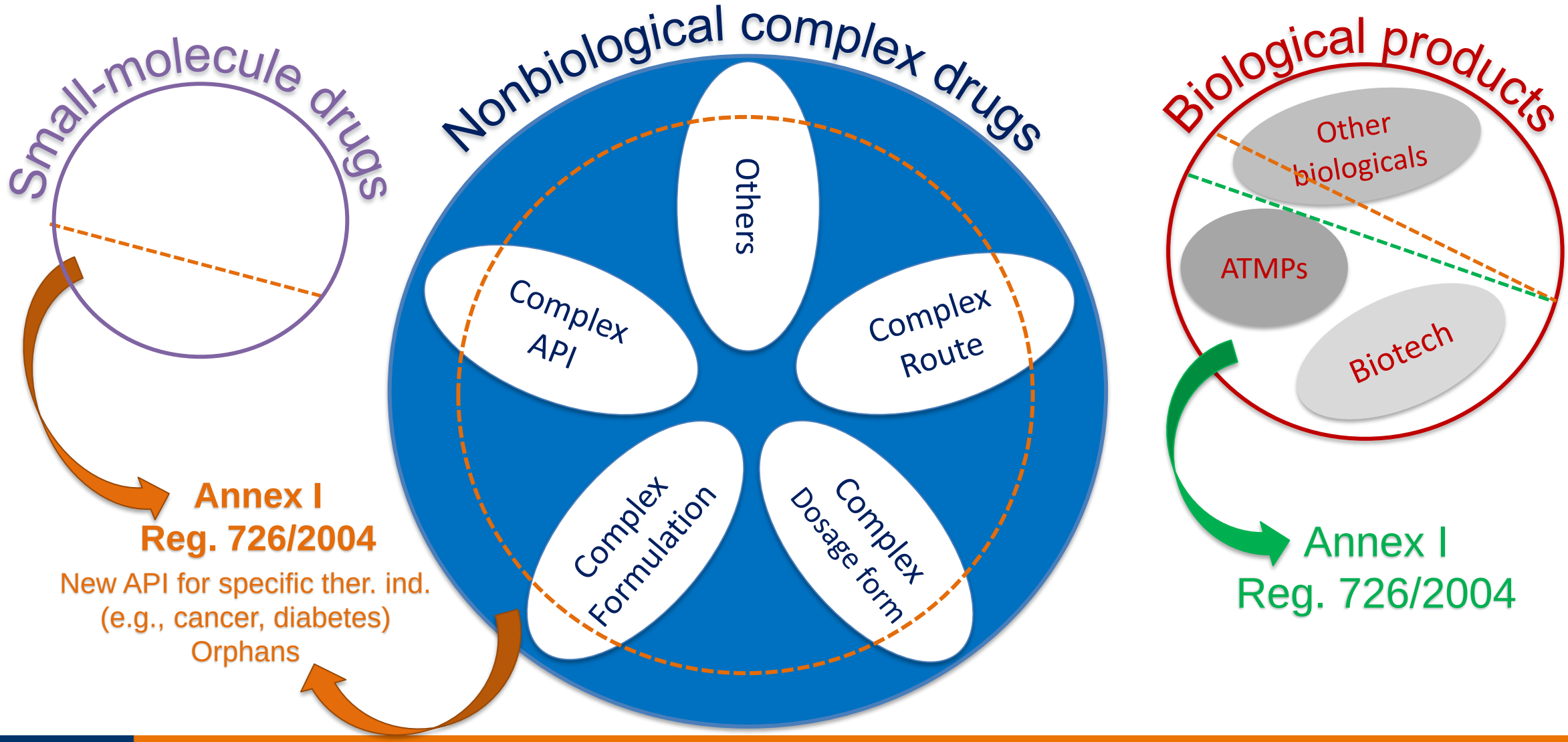
Mandatory Centralised Procedure



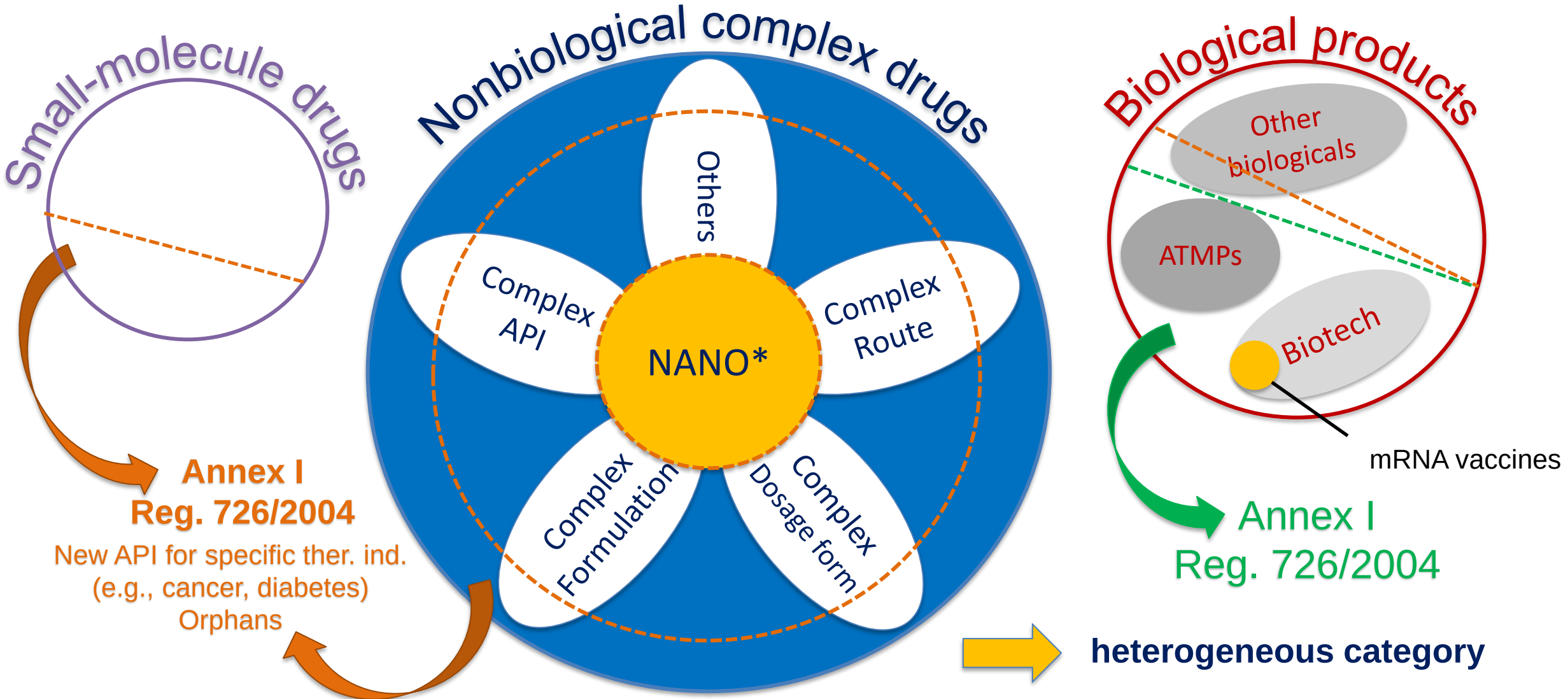




Mandatory Centralised Procedure



Mandatory Centralised Procedure (humans)



Annex I
Reg. 726/2004

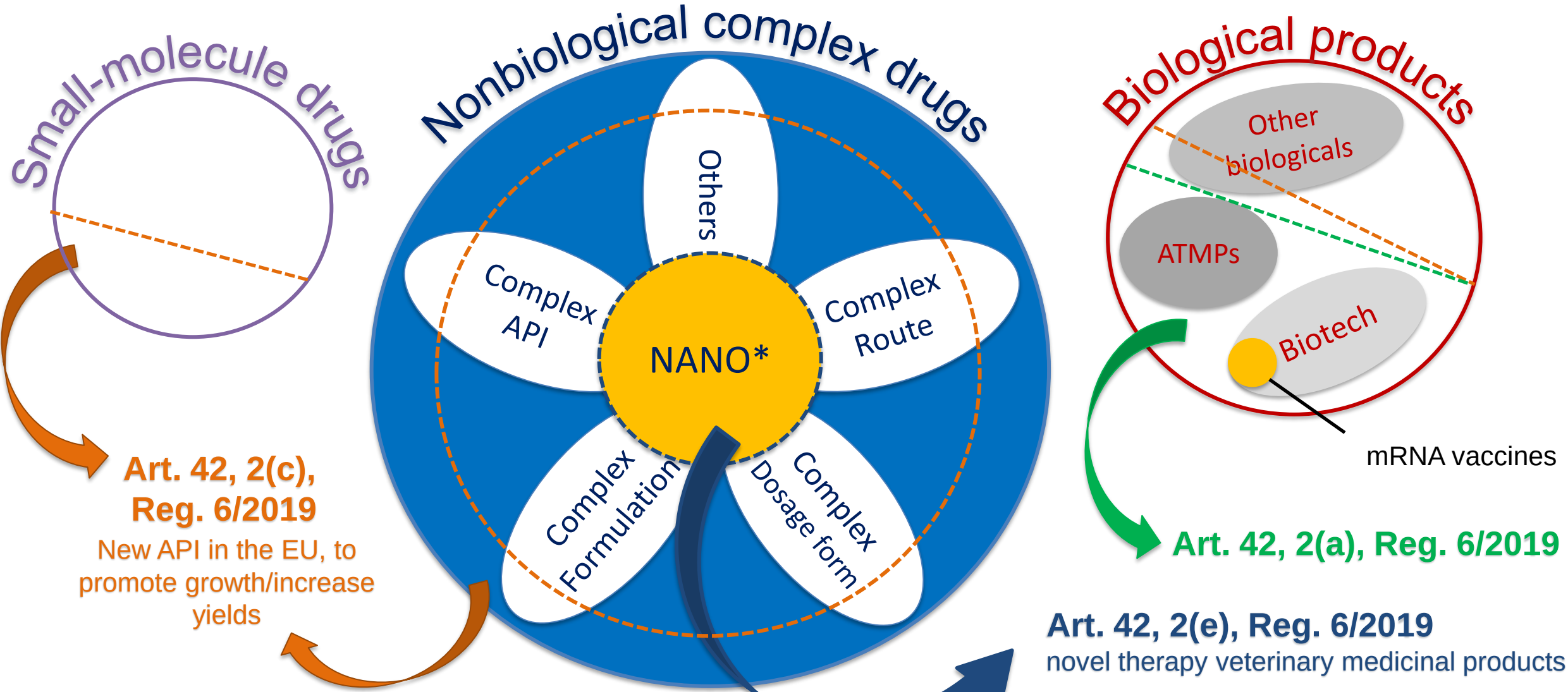
New API for specific ther. ind.
(e.g., cancer, diabetes)
Orphans

Annex I
Reg. 726/2004

heterogeneous category

*nanomedicine products, nanodrugs, drug products that contain nanomaterials

Mandatory Centralised Procedure (veterinary)



Art. 42, 2(c), Reg. 6/2019
New API in the EU, to promote growth/increase yields

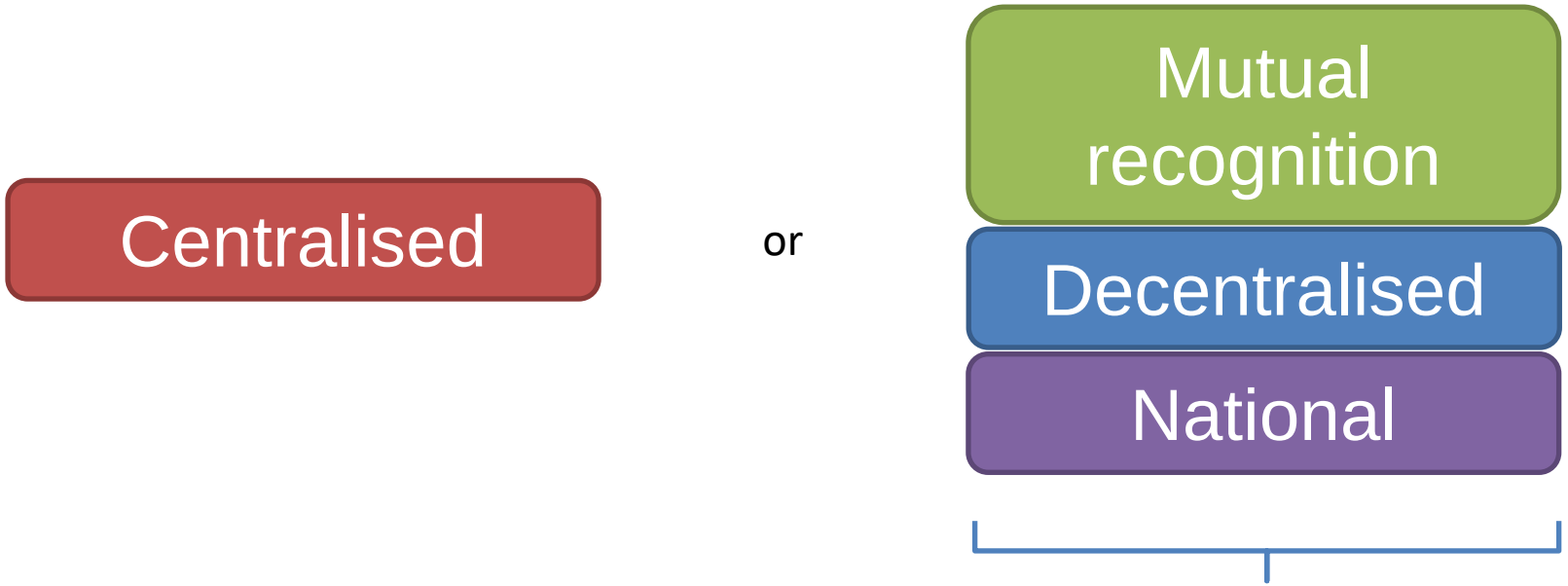
Art. 42, 2(a), Reg. 6/2019

Art. 42, 2(e), Reg. 6/2019
novel therapy veterinary medicinal products

*nanomedicine products, nanodrugs, drug products that contain nanomaterials

Marketing authorization

It is <u>not mandatory</u> for nanomedicine products to follow centralised procedure



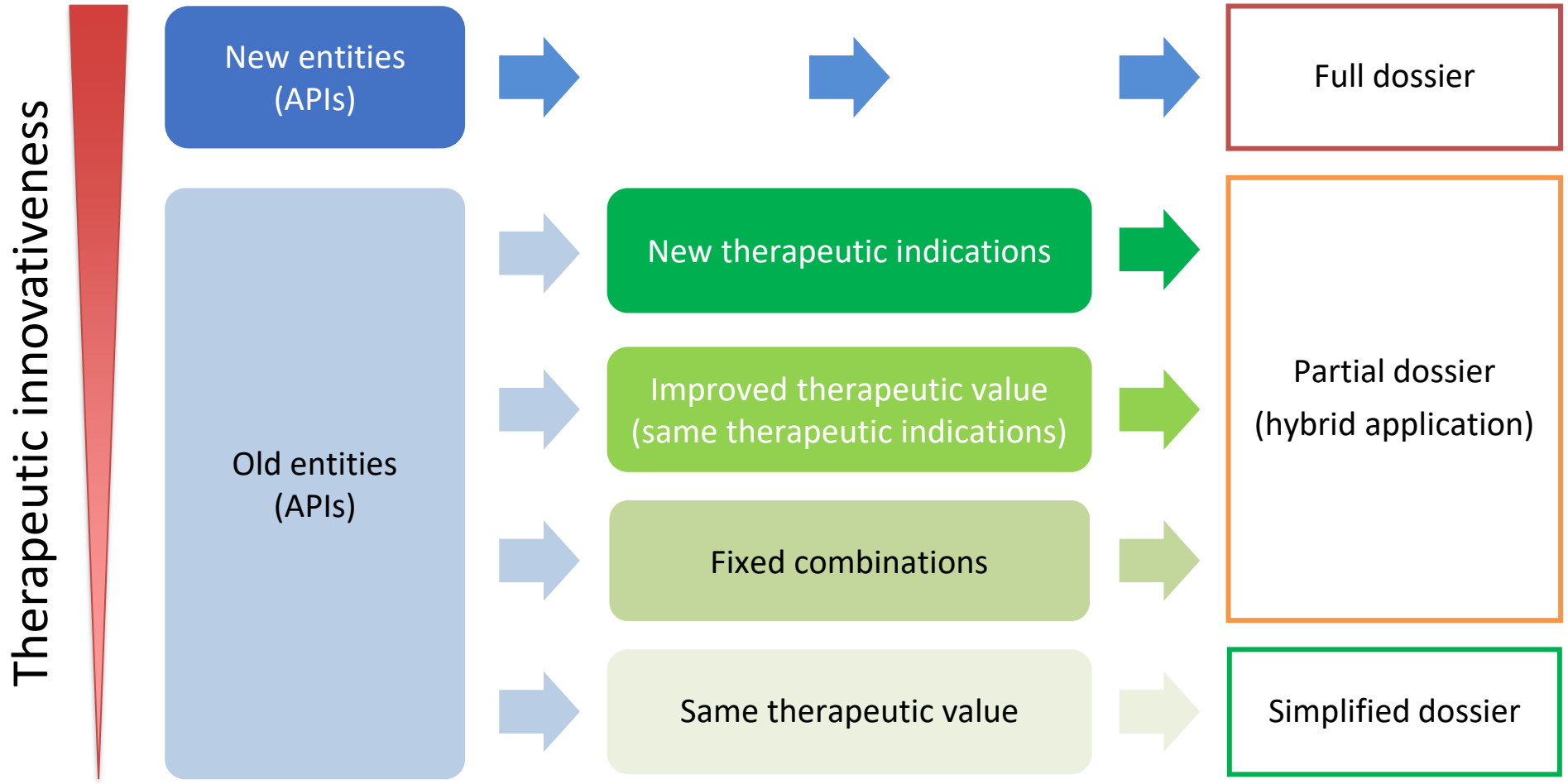
..without harmonized guidelines, risk of different data requirements; different time-to-market in EU Member States

Nanomedicine products

- Which marketing authorization (MA) procedure should they have to follow?

- **What data should be submitted to EMA/NCAs? (first-in-human/follow-on products)**

Nanomedicine products…



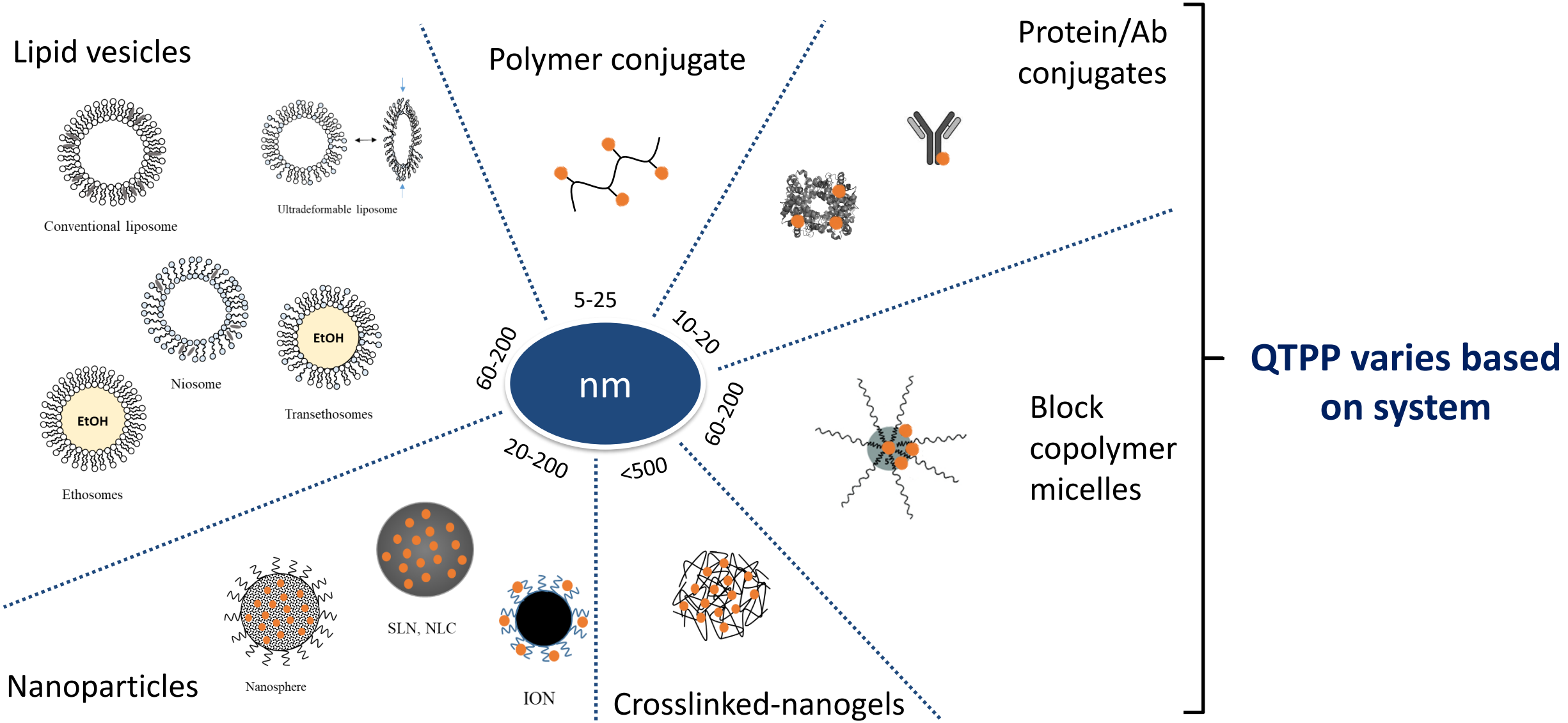
Common Technical Document (CTD)

- It is a framework for presenting data, not a guidance for data generation.
- It is intended to apply to all categories of medicinal products although some adaptation may be necessary for specific applications/products types.
- It will be applicable for all types of procedures (centralised, mutual recognition, national).

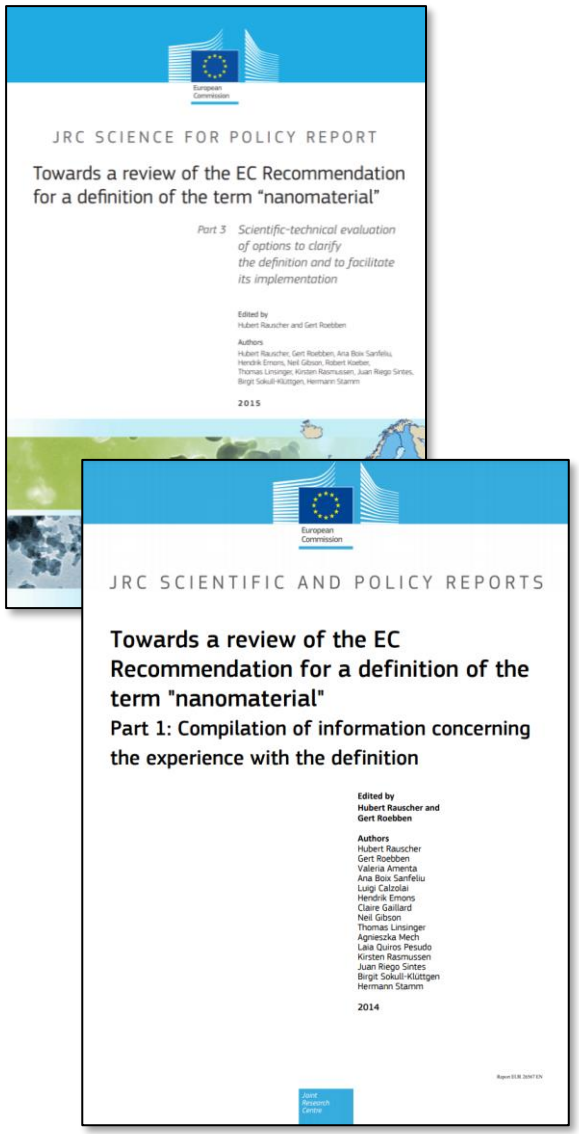
Full dossier

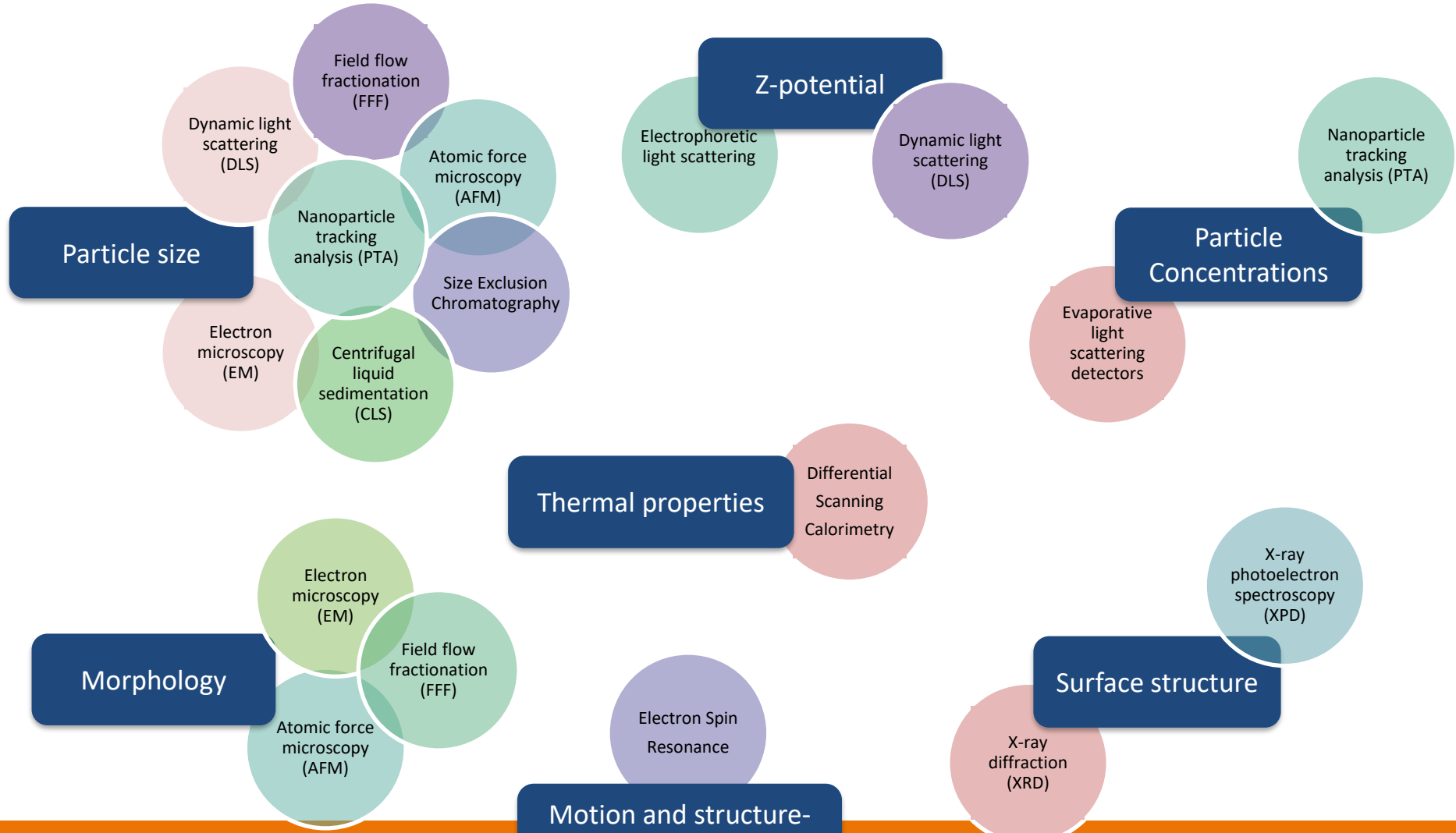
Module 1	Administrative information
Module 2	Summaries
Module 3	Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances (quality)
Module 4	Non-clinical study reports (safety)
Module 5	Clinical study reports (efficacy)

Quality of nanomedicine products: the nanosystem



Quality of nanomedicine products: the characterisation





Quality of nanomedicine products: manufacturing process

Small **differences relating to raw materials or differences in manufacturing processes** of the nanomedicine product may have a strong impact on its quality profile*;*

Enforced quality assessment and management (quality by design approach)

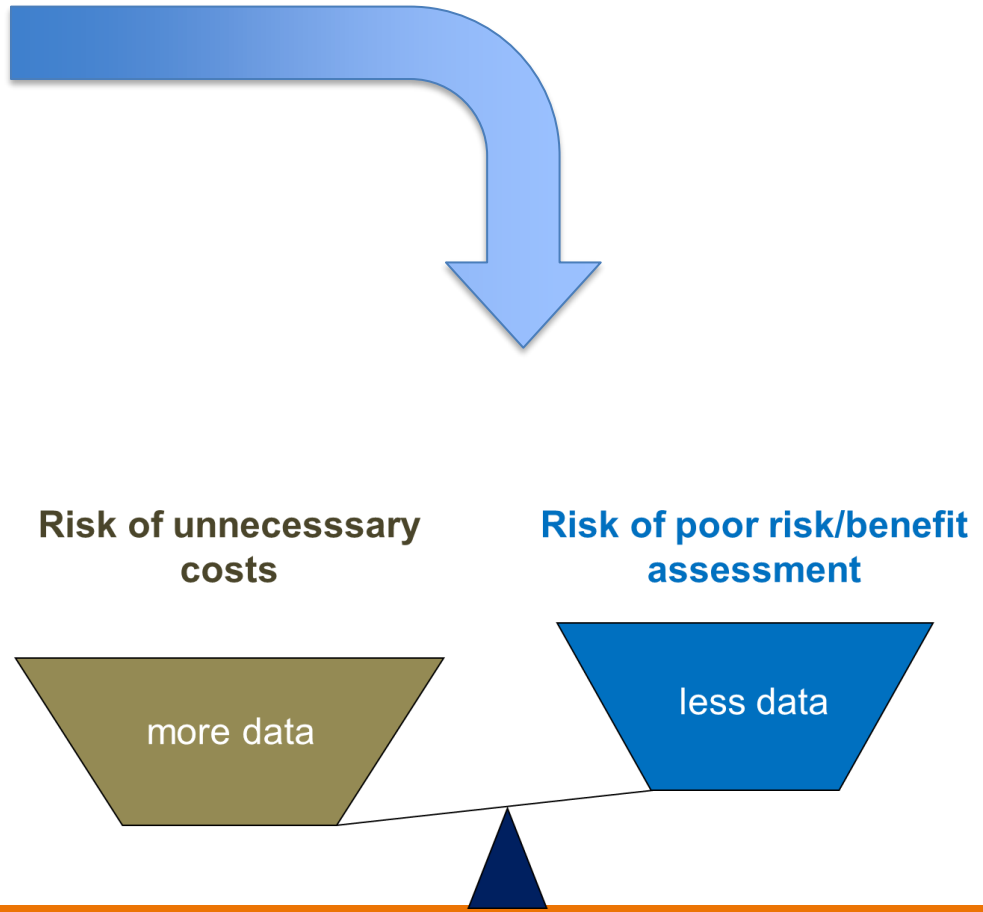
Copies/Follow on products

Patent/SPC/data protection expiration of a medicinal product

Copies/Follow on products

Small molecule	Non biologic complex drugs	Biological products
Generics	NBCD copies	Biosimilars

No improvement in the therapeutic value



Rocco P, et al. Drug Discov Today. 2019 Jan;24(1):250-255

Copies/Follow-on: type of application

Full Dossier

- New active substances [art. 8].

Partial Dossier

- **Hybrid [art. 10(3)]:**
  - medicinal product (MP) does not fall within the definition of a generic or
  - bioequivalence cannot be demonstrated through bioavailability studies or
  - in case of changes in the active substance, therapeutic indications, strength, pharmaceutical form or route of administration;

- Biosimilar [art. 10(4)]:
  - biological MP similar to a reference biological MP does not meet the conditions in the definition of generic, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product;

- Fixed combination medicinal products [art. 10b].

Simplified Dossier

- **Generic medicinal products [art. 10(1)];**
- Co-marketing [art. 10c];
- Well-established medicinal use (ten years) [art. 10a];
- Traditional herbal medicinal products [art. 13a];
- Homeopathic medicinal products [art. 13].

Copies/Follow-on: type of application

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In EU, several copies of nanomedicine products have been authorized as generics

Copies/Follow-on: Equivalence or Sameness?

The lesson of biosimilars

- A company may choose to develop a new biological medicinal product claimed to be "**similar**" to a reference medicinal product, which has been granted a MA in the Community on the basis of a complete dossier (art. 8, Dir. 2001/83/EC)
- **Comparability studies** are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product

EMEA/CHMP/437/04
EMEA Biosimilars in the European Union Regulatory perspectives. Available at http://www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_IVa_Biosimilars.pdf

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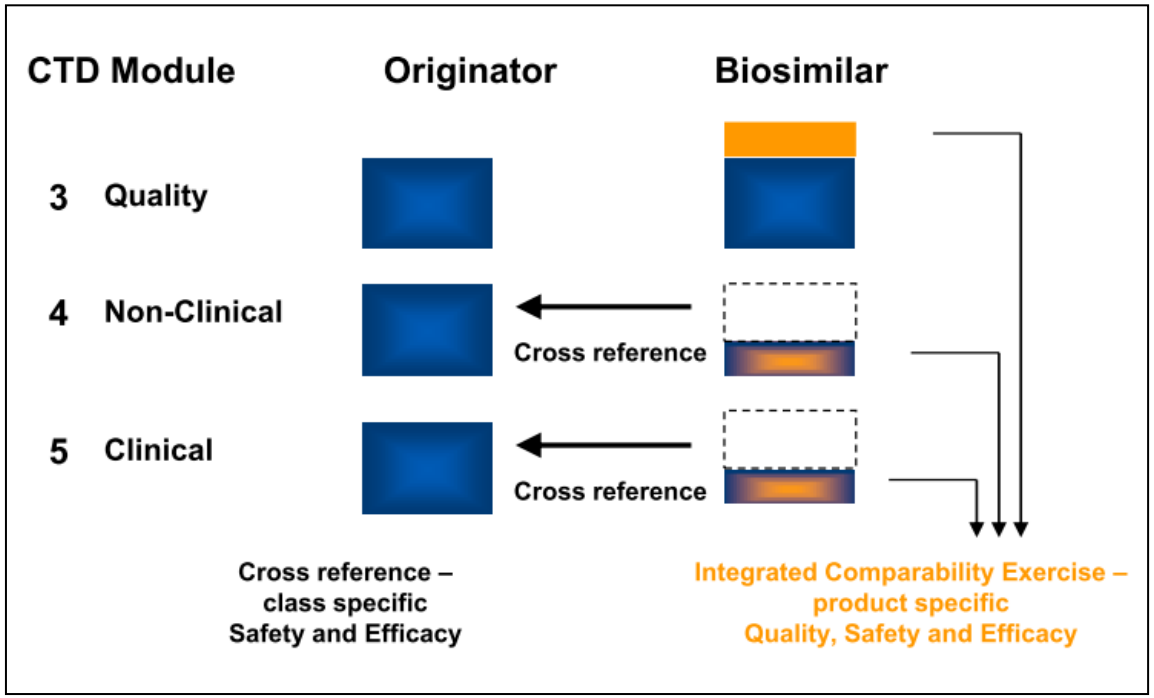
Current requirements for Biosimilars' dossier



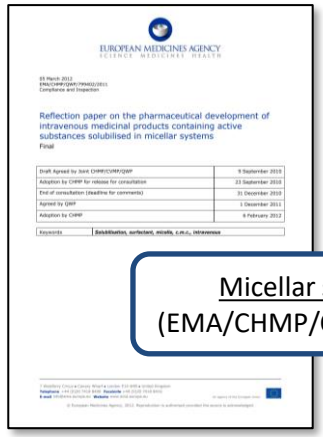
EMEA/CHMP/437/04
EMEA Biosimilars in the European Union Regulatory perspectives. Available at http://www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_IVa_Biosimilars.pdf

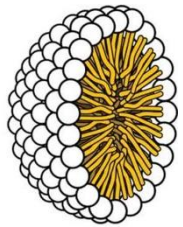
Copies/Follow-on: CTD

CTD	*Generics*	*Biosimilars; "**Nanosimilars**"*
Module 1	*Full*	*Full*
Module 2	*Full*	*Full*
Module 3	*Full*	*Full + comparability studies*
Module 4	-	*Comparability studies*
Module 5	*Bioequivalence studies*	*Comparability studies*

Partial dossier

EMA guidelines on nanomedicine products

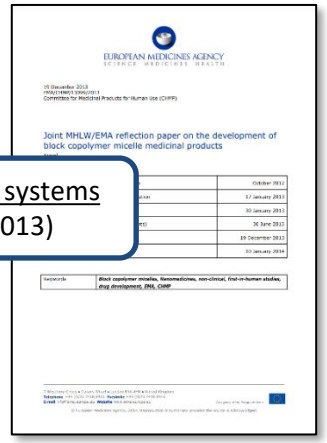




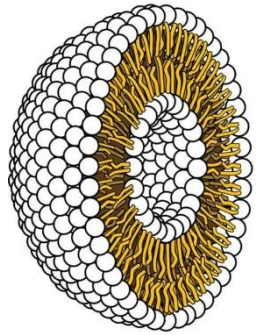
Micellar systems

Micellar systems for i.v.
(EMA/CHMP/QWP/799402/2011)

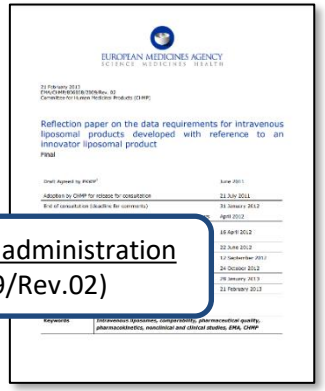
Block co-polymer micellar systems
(EMA/CHMP/13099/2013)



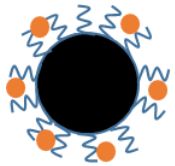
Lipid vesicles

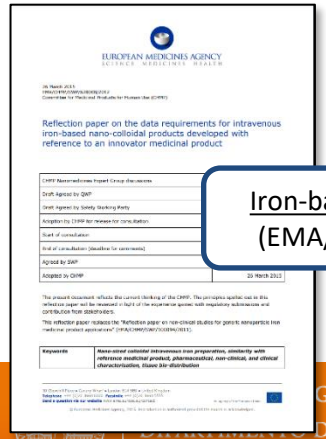


Liposomal products for i.v. administration
(CHMP/806058/2009/Rev.02)



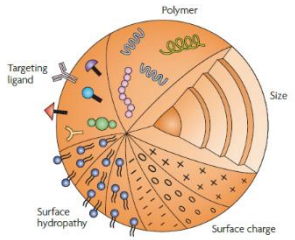
Iron-core nanoparticles



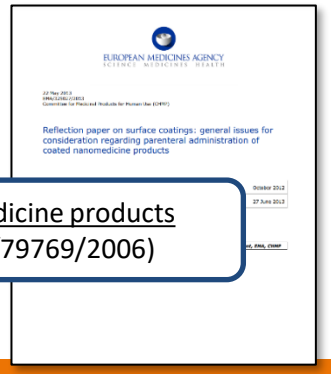


Iron-based nano-colloidal products
(EMA/CHMP/SWP/620008/2012)

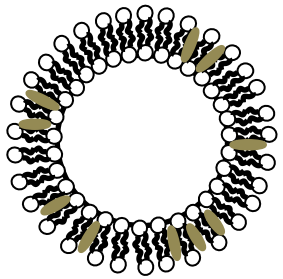
Coating of nanosystem surface



Coated nanomedicine products
(EMEA/CHMP/79769/2006)



Guidelines for liposomal “nanosimilars”



- **Doxil®**, a doxorubicin loaded PEGylated liposome was first approved in 1995 in USA, when nanomedicines regulations were not yet in place;
- It is the most famous liposomal medicinal product and one of the most characterized in vitro and in vivo nanosystems;
- There is an extensive literature and a deep scientific knowledge on liposomes;
- ***Expiration of Doxil®*** patent was in 2010;

EMA scientific guideline: Data requirements for intravenous *liposomal products* developed in reference to an innovator liposomal product (CHMP/806058/2009/Rev.02), *February 2013*

FDA guidance: Guidance for industry on Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labelling (FDA-2016-D-2817), October *2015*

Additional data that are required concerning…

…the QUALITY of drug product:

- **Complete characterization of all liposome components, including the quality and the purity of lipids;**
- **Morphological properties** of liposomal systems;
- **Drug fraction encapsulated and its distribution** in liposome;
- Determination of **lipid bilayer phase transition** behaviour;
- **pH** of internal compartments (only for pH-gradient loaded liposome);
- Full characterization of **ligand** if liposome is functionalized (PEGgylated);

Functionally-related excipients

Guideline on coated nanomedicine products (*)

- Identification of the key steps of manufacturing process;

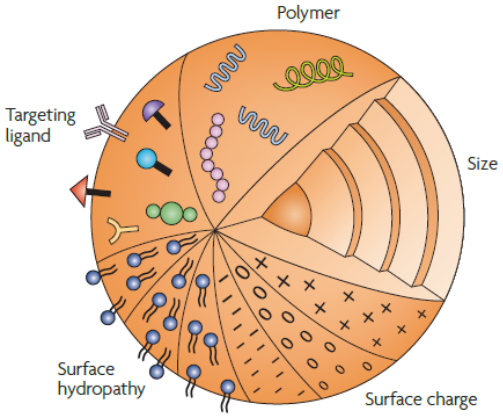
Manufacturing process

- **Stability in physiological fluids** (e.g., plasma);
- Stress tests for determining **physical and chemical degradation profiles** (only for copies);
- **Stability of drug, lipids, and other critical excipients** in the finished product;
- Stability of liposomal systems during **storage and in-use conditions**;
- Robustness of **reconstitution process**.

(*) Guideline on coated nanomedicine products

…the QUALITY of drug product:

- **characterization of coating materials**;
- complete validation of **coating steps**;
- **additional information** (e.g., conformational state, protein consistency) for **complex ligands** (e.g., protein or antibody) intended to active targeting;
- **coating stability** during storage and in use;
- premature detachment and release of coated ligands and/or their degradation pattern
- **in vitro stability** of the coating in respect of proposed use.



Additional data that are required concerning…

..the SAFETY:

- **Comparative studies of pharmacokinetics, toxicology and pharmacodynamics** (only for copies);
- **Interaction between liposome and cellular lines** that are pharmacologically and toxicologically relevant;
- In vitro or in vivo immune reactogenicity assays;
- CARPA tests;
- Organ function tests.

Free/loaded drug fractions

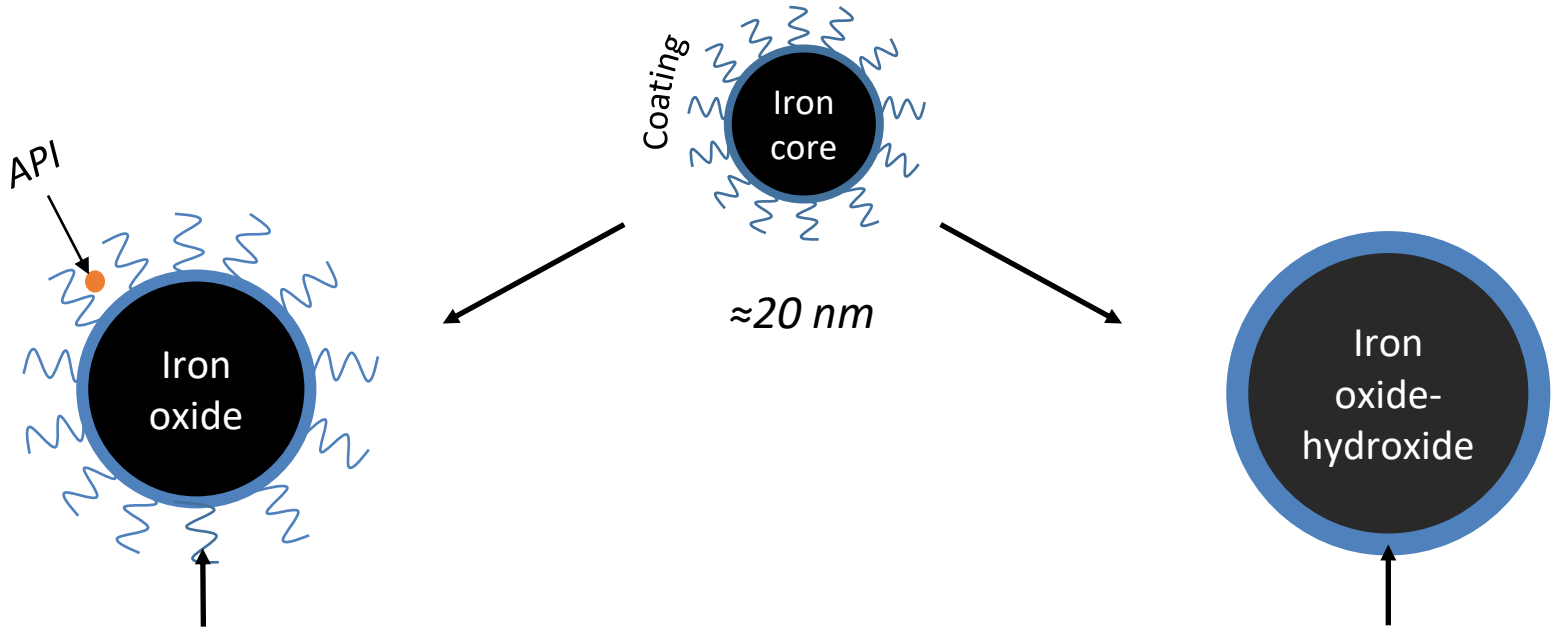
…the EFFICACY:

- **Comparative pharmacokinetics studies for assessing the equivalence of copy and originator products** (e.g., systemic exposure of total, unencapsulated and encapsulated drug, similar distribution and elimination profiles).

… plus, if nanosystems is “coated”:

- impact of **surface coverage heterogeneity** and coating physicochemical stability on safety/efficacy profiles;
- impact of **coating materials/surface coverage** on pharmacokinetics and biodistribution of drug product.

Iron-based nano-colloidal products



Superparamagnetic IONs have been studied as MRI contrast agents, hyperthermia treatments, drug nano-delivery systems

Medicinal products authorized for treating severe anaemia (since 1950)

Intravenous iron-containing medicinal products

Types	**Ferric carboxymaltose; Iron dextran (high, low MW); Ferumoxytol**	**Iron sucrose**	**Iron(III)-citrate + iron(III)-sorbitol + iron dextrin; Sodium ferric gluconate + iron sucrose**
Authorized medicinal products	Ferinject®; InFeD®; Cosmofer®; Imferon®; Dexferrum®; Feraheme®	Venofer®; Fesin®	Jectofer®; Ferrlecit®
Molecular weight*	>100,000 Da	30,000-100,000 Da	<50,000 Da
In vitro percentage iron donation to transferrin (%)	2.4-3.4	4.5	5.8
LD_{50} (mice)	1,013 mg iron/kg (iron dextran)	359 mg iron/kg (Venofer®)	155 mg iron/kg (Ferrilecit®)

* expressed with respect to dextran standards

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2013
EMA/579491/2013

New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines

On 27 June 2013 the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) completed its review of intravenous iron-containing medicines used to treat iron deficiency and anaemia (low red blood cell counts) associated with low iron levels. The CHMP concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to

Different similar nano-colloidal products have different pharmacokinetics, efficacy and safety profile. The switch should be carefully evaluated.

Geisser et al. Pharmaceutics, 2011, 3, 12-33

Guidelines for iron-based “nanosimilars”

- **EMA’s present scientific guidelines**

  Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications (EMA/CHMP/SWP/100094/2011; 2011);

  Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (EMA/CHMP/SWP/620008/2012; 2015).

- **FDA’s present scientific guidelines**

  Draft Guidance on Iron Sucrose;

  Draft Guidance on Iron Dextran.

Additional data that are required concerning…

…the QUALITY of drug product:

- Complete characterization of **physicochemical properties of raw materials** (e.g., **carbohydrate** characterization, polymorphism of iron core);
- **Morphological properties** of iron core and iron-carbohydrate complexes;
- **Ratio between bound carbohydrate to iron**;
- Impact of physicochemical properties of carbohydrate matrix on the **nanoparticle stability** during storage;
- Impact of physicochemical properties of carbohydrate matrix **in vivo pharmacokinetics and toxicokinetics**;
- **Amount of labile iron** released from the product when administered;
- Impurities [e.g., ratio of iron-(II) and iron(III)];
- **Degradation profiles**;
- Measurement of amount of iron-(III) released by the systems;
- Stress tests for determining physical and chemical degradation profiles (for copies).

Functionally-related excipients

EMA/CHMP/SWP/100094/2011
EMA/CHMP/SWP/620008/2012

Additional data that are required concerning…

…the SAFETY:

- **Biodistribution studies on compartments involved in pharmacological action** (e.g., plasma, RES, spleen) **and in therapeutic** (e.g., bone marrow) **and toxic target tissues** (e.g., kidney, liver, lungs, heart).

…the EFFICACY:

- **Bioequivalence studies** to compare originator and copies;
- When considering a **clinical trial** to address differences, the clinical trial would ideally be at least **3 months in duration** and performed in a group of patients with a **similar aetiology for their anaemia** (e.g., patients with chronic renal failure). **End points** to be considered include: ferritin, transferrin saturation, Haemoglobin, Total iron dose and Total EPO dose administered over study.

Specific provisions for clinical trials

Iron sucrose similar (ISS)

Physicochemical properties

Parameter	Venofer®	ISS 1	ISS 2
Osmolarity	1260 mOSM/l	991 mOSM/l	1315 mOSM/l
pH	10.9	10.7	10.8
Molecular weight*	Mw = 45,700 Da Mn = 34,000 Da P = 1.3	Mw = 45,000 Da Mn = 34,000 Da P = 1.3	Mw = 31,000 Da Mn = 25,000 Da P = 1.3
Kinetics of degradation	9.0 min	31.5 min	17.2 min

* expressed with respect to dextran standards

Serum iron in rats (mean ± SD)

Time	Venofer®	ISS 1	ISS 2	Control
24 h	359.8±51.1**	510.3±95.2*	482.1±42.9*	305.6±33.9
7 days	370.0±23.6**	434.8±46.4*	418.3±31.1*	320.3±28.3
28 day	364.0±18.1**	414.5±11.1*	403.8±21.1*	299.5±9.2

* *P < 0.01 versus reference and control*

** *P < 0.01 versus control*

Toblli et al. Arzneimittelforschung, 2009, 59:176-190

Open issues?

Pharmaceutical development of new nanomedicine products

Post-marketing variations

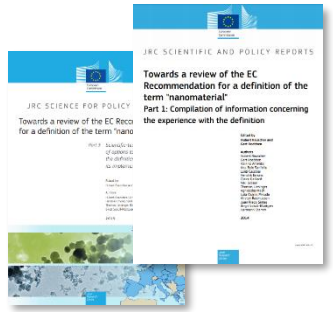
Development of a therapeutically equivalent copy of a nanomedicine products

MARKETING AUTHORISATION

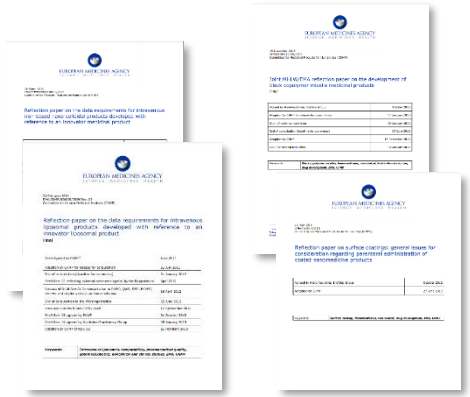
Is a specific regulatory pathways for nanomedicine products needed?

CHARACTERIZATION

Physicochemical characterization of nanomaterials



Class-specific guidelines



PERFORMANCE

Development and validation of in vitro biorelevant methods (/establish IVIVCs) that can be used as surrogate of clinical studies for assessing the similarity between nanosystems.

Musazzi et al., Drug Discov. Today (2017) 22: 870-882
Selmin et al., Drug Discov. Today (2020) 25:321-329

Thank you for the kind attention