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

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ABSTRACT

"Non-biological complex drugs" (NBCDs), such as liposomal formulations, iron-carbohydrate complexes and glatiramoids, gained increased interest from a regulatory perspective in recent years. Similar to biologics, the quality of NBCD products is highly dependent on a robust and well-controlled manufacturing process. This provides challenges for generic drug developers to replicate NBCD products once market exclusivity of the originator product is expired. However, unlike biologics for which a consistent regulatory framework was established with the biosimilars pathway, NBCDs are not recognised as a distinct category of medicines and hence no formal regulatory pathway for their approval is defined. Currently, a "case-by-case" approach is applied for regulating NBCD follow-on products in the EU. Furthermore, NBCDs can follow a non-centralised authorisation procedure, leaving regulatory approvals to national competent authorities. This can lead to heterogeneity in the regulatory approach and outcomes when assessing NBCD follow-on products throughout the EU, which for some product classes has already resulted in some safety and efficacy implications. Here, we explore the regulatory landscape of NBCDs and their follow on products. This study shows that almost all of the 85 NBCD follow-on products available in the EU in 2018 have been approved via various non-centralised procedures. Although most NBCD follow-on products followed an Article 10(1) procedure, we clearly see a recent increase of the use of the hybrid pathway via Article 10(3). This study shows the heterogeneity in the regulatory approach taken for many NBCD follow on products. To what extent this may have consequences for their safety and efficacy evaluations is unknown and needs to be further investigated. The present study should stimulate the rethinking to design prudent regulatory pathways for NBCD follow-on products.

1. Introduction

A class of medicinal products, referred to as "non-biological complex drugs" (NBCDs) has gained increased interest from a regulatory perspective in recent years. Although there is no definition for NBCDs in EU regulation, the NBCD Working Group, a multi-stakeholder partnership promoting a science-based approach for the approval of NBCD products and NBCD follow-on products, has defined NBCDs as "medicinal products, not being a biological medicine, where the active substance is not a homo-molecular structure, cannot be isolated, fully quantified, characterized and/or described by physicochemical analytical means" (Crommelin et al., 2014). Examples of NBCDs are liposomal formulations, iron-carbohydrate complexes and glatiramoids. Similar to biologics, the quality of NBCD products is highly dependent on a robust and well-controlled manufacturing process (Desai, 2012). Their sensitivity to manufacturing changes can be challenging for maintaining batch-to-batch consistency but also lead to problems in the reproducibility when produced by different manufacturers. Such cases have been reported with "follow-on" products for iron sucrose complexes, liposomal doxorubicin and glatiramoids (Toblli et al., 2011; Melamed-Gal et al., 2018; Weinstein et al., 2015). In the iron sucrose follow-on products, it was demonstrated that patient safety was at risk

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when switching patients to an iron sucrose follow-on product, leading to the destabilization of well-controlled haemodialysis patients (Lee et al., 2013; Rottembourg et al., 2011; Stein et al., 2012; Agüera et al., 2015). Furthermore, some NBCD products may have varying immunogenic properties, such as glatiramoids, or can trigger unwanted innate immune responses as was observed with liposomal formulations (Szebeni and Moghimi, 2009; Cohen et al., 2008; Wibroe et al., 2016).

Although NBCDs share many characteristics with biologics, the regulatory approaches significantly differ. For biologics, the biosimilars pathway has been developed in the EU over the last decade (Directive, 2001; Schiestl et al., 2017). For NBCDs, not being recognised as a distinct category of medicines, no dedicated pathway is developed for their approval. Whereas biotechnology-derived medicinal products have to follow a centralised procedure (CP), NBCDs (and their follow-on versions) may be approved through non-centralised procedures. This leaves the regulatory assessment to national competent authorities. These non-centralised procedures may involve 1) the national procedure, for the approval in a single Member State, 2) the mutual recognition procedure (MRP), to extend an already existing marketing authorisation to other Member States, or 3) the decentralised procedure (DCP), to simultaneously apply for marketing authorisations in more than one Member State if no prior marketing authorisation exists. The different EU authorisation procedures are described in detail in various regulatory documents (European Medicines Agency (EMA), 2019a, Heads of Medicines Agency (HMA), 2018, Regulation (EC), 2004, Rocco et al., 2018). Furthermore, it is unclear which abridged application procedures should be followed for follow-on products, e.g. the "generic application" via Article 10(1), requiring only limited quality and bioavailability data, or the "hybrid application" of Article 10(3) requiring additional (pre-) clinical data (Fig. 1) (Directive, 2001). The recently published US Government Accountability Office (GAO) report has shown that the unclarity and inconsistency of the regulatory approach for NBCDs in the US may create setbacks for generic drug developers and therefore could delay or prevent the introduction of much-needed equivalent follow-on products (United States Government Accountability Office, 2018).

Although the European Medicines Agency (EMA) has recently published a number of reflection papers to provide scientific guidance on data requirements for nanomedicine follow-on products (which partly fall under the NBCD definition) (Committee for Medicinal Products for Human Use (CHMP), 2018a, Committee for Medicinal Products for Human Use (CHMP), 2018b, Committee for Medicinal Products for Human Use (CHMP), 2018c, Committee for Medicinal Products for Human Use (CHMP), 2018d), it has been argued that it is still unclear to 'generic developers' which regulatory pathways are appropriate (e.g. generic or hybrid) (Garattini and Padula, 2016; de Vlieger et al., 2016; Hussaarts et al., 2017). Furthermore, the currently applied "case-by-case" approach for regulating NBCD follow-on products may lead to differences in the rigorousness to regulate these products. For example, that may depend on the competent authority that is approached (Garattini and Padula, 2016). This can lead to varying outcomes when assessing NBCD follow-on products throughout the EU, which may have safety and efficacy implications as shown with the iron sucrose complexes.

The EU has established a robust regulatory system for medicinal products. Progressive harmonization across the EU for marketing authorisation and post-marketing surveillance has been achieved throughout the last decades. However, new technological developments may present new challenges that need to be addressed to promote such a robust regulatory system. One example of a potential imperfection in the current system to be remedied is the category of NBCDs. The challenges posed by NBCDs for the regulatory system as identified by the scientific community, can assist to further optimise and harmonize the EU regulatory system, in order to even better guarantee the availability of safe and efficacious medicines to the patient.

Currently little is known about which NBCDs follow-on products are approved in Europe and which regulatory pathways were involved. Therefore, the objective of this study was to look into the regulatory landscape of NBCD follow-on products until November 2018 and to address the question of the level of consistency and heterogeneity in the regulatory approach for individual NBCD products, and NBCD classes.

2. Methods

In order to identify all NBCD follow-on products approved in the EU, we first compiled an exhaustive list of NBCD products from the scientific and grey literature that provides an aggregated overview of drug products that are considered NBCDs. Several lists were identified in the Appendix I of the GAO report, a number of key publications, such as Crommelin and de Vlieger (2015), Astier et al. (2017), Pepic et al. (2014), Ehmann and Pita (2016) and the EMA's regulatory assessment reports for iron-containing intravenous products and propofol (United States Government Accountability Office, 2018; Crommelin and de Vlieger, 2015; Astier et al., 2017) (Pepic et al., 2014, Ehmann and Pita, 2016, European Medicines Agency (EMA), 2018a, European Medicines Agency (EMA), 2018b). Since significant discrepancies exist between

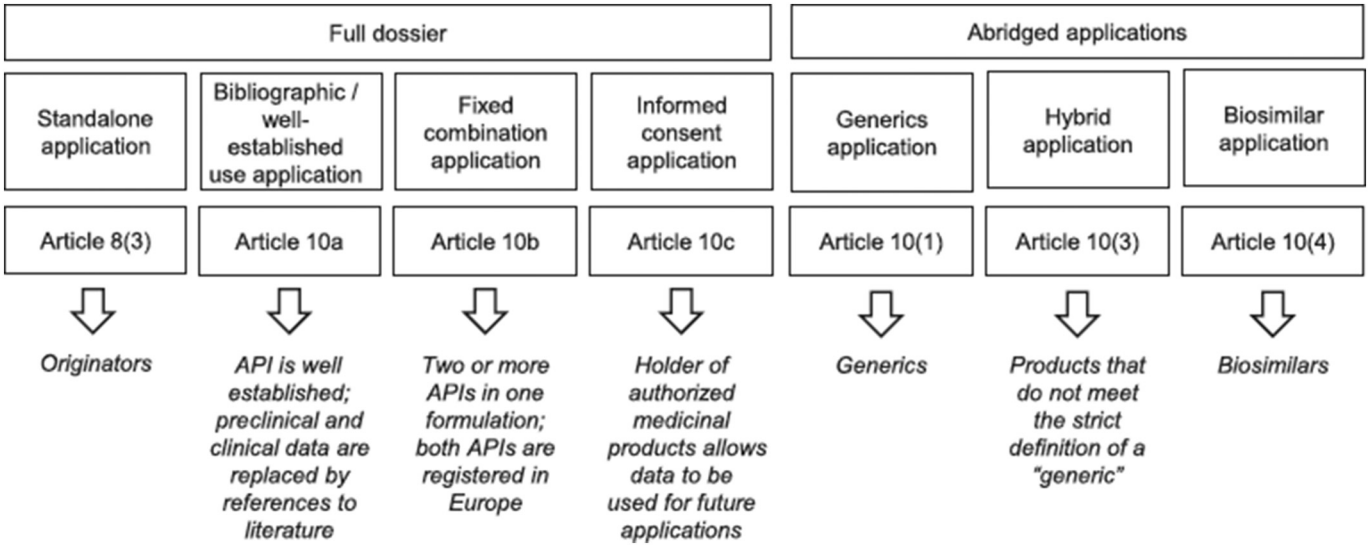

Fig. 1. Schematic representation of the different application procedures available in the EU (adapted from Hussaarts et al., 2017).

different stakeholders on how NBCDs are defined, all medicinal products categorised as NBCD in any of the documents from our study sample were included in this study, with one exception. Drug nanocrystals are traditionally not regarded as NBCDs due to limited challenges for demonstrating bioequivalence (Hussaarts et al., 2017). Therefore drug nanocrystals are not included in this study, although they are frequently mentioned in the discussions about nanosimilars. The NBCDs identified in this study were categorised in seven NBCD product classes: (i) liposomal formulations, (ii) iron-carbohydrate complexes, (iii) polymer-based actives, (iv) emulsions, (v) low-molecular weight heparins (LMWHs) and (vi) other. This study includes all NBCD (follow-on) products that are approved anywhere in the EU up to and including marketing authorisations in November 2018.

We then assessed which of these NBCD products are approved in one or more EU Member States and for which of these products, follow-on versions are authorised. We screened the European Public Assessment Reports (EPARs) database, the Heads of Medicines Agency (HMA) Mutual Recognition Information (MRI) product index and all 28[1] national medicines databases to identify any NBCD (follow-on) product approved (European Public Assessment Reports (EPARs) Database, 2018, Heads of Medicines Agency (HMA) Mutual Recognition Information (MRI) Product Index, 2018). The unit of analysis was the authorisation number. The following information for NBCD products was extracted from source documents, such as Public Assessment Reports (PARs), Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PIL), to compile our list: the brand name, Marketing Authorisation Holder (MAH), manufacturer (and country where the product is manufactured), formulation, strength, (first) authorisation date, authorisation procedure (CP, DCP MRP or NP), authorisation number, Reference Member State (RMS) [if applicable], concerned Member State (CMS) [if applicable], abridged application procedure, cf. Fig. 1, [i.e. generic application of Article 10(1), hybrid application of Article 10(3), biosimilar application of Article 10(4), or informed consent Article 10(c)[2]] and reference product [if applicable]. To retrieve any missing information (e.g. where certain source documents were not readily accessible online), we directly contacted national competent authorities.

3. Results

In this study, we identified a total of 85 NBCD follow-on products marketed in the EU. The NBCD follow-on products are approved for 5 different NBCD originator products: Copaxone® (20 & 40 mg/ml), Renvela® (800 mg & 2.4 g), Venofer®, Clexane® and Diprivan® (10 & 20 mg/ml) (Table 1). In total, we found 25 NBCD originator products approved in the EU, with an additional 9 related NBCD products (e.g. different formulation/strength or 'well-established use application', in which the marketing authorisation is based on results from the scientific literature if the medicine has been used for more than 10 years in clinical practice) (European Medicines Agency (EMA), 2019b).

For the 85 NBCD follow-on products identified in this study, only two (~2%) were approved via the centralised procedure, both being enoxaparin sodium follow-on products. The majority of the NBCD follow-on products were approved via the DCP ($n = 45$) and via national procedures ($n = 30$) and, to a minor extent, and in particular for 'older' NBCD follow-on products, via the MRPs ($n = 11$). In contrast, of the 25 NBCD originator products approved in the EU, 11 were authorised through the centralised procedure, nine through national procedures, six through the MRP and two through the DCP.[3]

The NBCDs follow-on products were approved via one of the three different abridged application procedures available in the EU: 48 (56%) via the generic application procedure of Article 10(1) and 32 (38%) via the hybrid application procedure of Article 10(3) (Table 1). However, the five (6%) enoxaparin follow-on versions were all approved via the biosimilar application procedure of Article 10(4). The reason for this is that in contrast to the U.S. where LMWHs are considered complex drugs rather than biologics, LMWHs are considered biologics in the EU, thus requiring the use of the biosimilar application procedure. We also found three informed consent applications of Article 10(c) from innovator companies of glatiramer acetate and sevelamer carbonate, shortly after the approval of the first follow-on versions. Furthermore, a number of well-established use applications (via Article 10(a)) were approved for iron sucrose and iron dextran complex (supplementary material). Table 1 shows that generally the same application procedure for an individual product class was used. For example, the generic application procedure of Article 10(1) was almost exclusively used for the approval of follow-on products for the iron sucrose complexes (Venofer®) and propofol (Diprivan®). In contrast, the hybrid procedure of Article 10(3) was used for the approval of follow-on products for the polymer-based actives glatiramer acetate and sevelamer carbonate. Two deviations with regard to the used application procedures could be identified within product classes. Just recently the MHRA has approved Sucrofer®, a follow-on product for Venofer®, through the hybrid application procedure via Article 10(3). This is contrary to the generic application procedure via Article 10(1) that was used for previously approved follow-on versions for Venofer®. Furthermore, Propofol Lipuro® 5 mg/ml was approved via the hybrid application, as Propofol Lipuro® 5 mg/ml relates to a new dosage form. The results also indicate a trend in the use of application procedures. The hybrid application is more often used in recent application procedures compared to the generic application (Fig. 2). The recent approvals of follow-on versions for sevelamer and glatiramer acetate may dominate this trend, the more recent example of Sucrofer® suggests that there might be a change in the regulatory approach for certain NBCDs.

Differences were also observed with regard to the selected authorisation procedures over time and RMS between and within product classes. The DCP, which is available in the EU since 2005, is almost exclusively used in newer authorisation applications whereas older applications (prior to the establishment of the DCP) were predominantly relying on the MRP or national procedure. The change towards the use of the DCP application can for example be seen for the approvals of the propofol follow-on products over time (Table 1). Another finding is that enoxaparin follow-on versions were initially approved via the biosimilar application using a centralised procedure (Inhixa® and Thorinane®), but three more follow-on versions were subsequently approved via the biosimilar application using a DCP. We also found that within some product classes, for example the enoxaparins and propofol, different RMS were approached for the approval of follow-on versions for the same reference product. Overall, the majority of the 56 follow-on application procedures involving a DCP or MRP were received by Denmark 19 (34%), the Netherlands 13 (23%) and Germany 13 (23%).

4. Discussion

In this paper we reviewed the approvals of NBCDs follow-on products in the EU and the different regulatory approaches applied. We identified a total of 85 NBCD follow-on products approved in the EU, of which half since 2013. Although the majority of NBCD follow-on

[1] With the exception of Cyprus because the national drug database of Cyprus was not accessible.

[2] We included the informed consent application via Article 10(c) as this application was sometimes used by innovator companies to bring their product to the market under a different brand name (sometimes referred to as 'branded generics').

[3] The numbers deviate from the total as in two instances a combination of MRP and NP was used and in one occasion DCP and MRP depending on the Member State where the NBCD is approved,

Table 1
An overview of NBCD follow-on products approved in the EU via the three abbreviated applications: generic, hybrid and biosimilar pathway, as well as new applications by originator companies via informed consent, sorted by authorisation date since the first approval in 1999 until November 2018.

Reference product (MAH)	Follow-on product (MAH)[a]	Authorisation date	Authorisation procedure	RMS (if applicable)	Application procedure
Venofer® 20 mg/ml (Vifor) Iron sucrose complex					
	Ferrovin (Refarm)	27-01-2005	NP (GR, MT)	n/a	Article 10(1)
	Óxido Férrico Sacarosado Generis (Generis Farmacêutica)	28-05-2007	NP (PT)	n/a	Article 10(1)
	Hemafer-S (Uni-Pharma)	16-07-2008	NP (GR)	n/a	Article 10(1)
	Faremio (Demo)	26-08-2008	NP (GR)	n/a	Article 10(1)
	Dextrifer-S (Intermed)	28-08-2008	NP (GR)	n/a	Article 10(1)
	Intrafer (Vianex)	01-09-2008	NP (GR)	n/a	Article 10(1)
	Fer Sandoz (Sandoz)	05-09-2008	NP (FR)	n/a	Article 10(1)
	Óxido Férrico Sacarosado Accord (Accord Healthcare)	09-10-2008	NP (PT)	n/a	Article 10(1)
	Fer Mylan (Mylan)	27-10-2008	NP (FR)	n/a	Article 10(1)[b]
	Alvofer (Cooper Pharmaceuticals)	13-11-2008	NP (GR)	n/a	Article 10(1)
	Ferrinemia (Help Pharmaceuticals)	21-11-2008	NP (GR, MT)	n/a	Article 10(1)
	Ironcrose (Target Pharma)	21-11-2008	NP (GR)	n/a	Article 10(1)
	Venotrix (Alternova)	12-02-2009	NP (FI)	n/a	Article 10(1)
	IJzerhydroxide sacharose complex (Teva)	18-02-2009	NP (NL)	n/a	Article 10(1)
	Nefro-Fer (Medice Arzneimittel Pütter)	15-03-2009	DCP	DE	Article 10(1)
	Veniron (Viofar)	17-06-2010	NP (GR)	n/a	Article 10(1)
	Nephroferol (Verisfield)	10-01-2011	NP (GR)	n/a	Article 10(1)
	Reoxyl (Medicus)	04-01-2012	NP (GR)	n/a	Article 10(1)
	Järnsackaros Rechon (Rechon Life Science)	14-03-2012	NP (SE)	n/a	Article 10(1)
	Ferracin (Acino)	26-07-2012	NP (NL)	n/a	Article 10(1)
	Fer Panpharma (Panmedica)	10-02-2014	NP (FR)	n/a	Article 10(1)
	Sucrofer (Claris Lifesciences)	01-06-2018	DCP	UK	Article 10(3)
Copaxone® 20 mg/ml (Teva) Glatiramer acetate					
	Brabio (Synthon)	10-05-2016	DCP	NL	Article 10(3)
	Sclerthon (Synthon)	10-05-2016	DCP	NL	Article 10(3)
	Glatiramer acetate Mylan (Mylan)	10-05-2016	DCP	NL	Article 10(3)
	Glatiramer acetate Teva (Teva)	18-09-2018	DCP	DE	Article 10(c)
Copaxone® 40 mg/ml (Teva) Glatiramer acetate					
	Glatiramer acetate Alvogen (Alvogen)	02-11-2017	DCP	NL	Article 10(3)
	Glatiramer acetate Mylan (Mylan)	02-11-2017	DCP	NL	Article 10(3)
	Marcyto (Synthon)	02-11-2017	DCP	NL	Article 10(3)
	Sclerthon (Synthon)	02-11-2017	DCP	NL	Article 10(3)
	Glatiramer acetate Teva (Teva)	18-09-2018	DCP	DE	Article 10(c)
Renvela® 800 mg (Genzyme) Sevelamer carbonate					
	Sevelamer carbonate AL (Aliud Pharma)	12-03-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Teva (Teva)	23-04-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Synthon (Synthon)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Housthon (Amneal Pharma Europe)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Aurobindo (Aurobindo Pharma)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Sandoz (Sandoz)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Genthon (Genthon)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Mylan (Mylan)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Sandoz (Sandoz)	22-05-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Heaton (Heaton)	22-05-2014	DCP	CZ	Article 10(3)
	Sevemed (Medice Arzneimittel Pütter)	18-06-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Stada (Centrafarm B.V.)	18-08-2014	DCP	DK	Article 10(3)
	Sevelamer carbonate Zentiva (Genzyme)	14-01-2015	CP	n/a	Article 10(c)
	Sevelamer carbonate Ratiopharm (Ratiopharm)	16-03-2015	DCP	DK	Article 10(3)
	Sevelamer carbonate Arrow (Arrow Generiques)	16-11-2017	NP (FR)	n/a	Article 10(3)[b]
Renvela® 2.4 g (Genzyme) Sevelamer carbonate					
	Sevelamer carbonate Zentiva (Genzyme)	14-01-2015	CP	n/a	Article 10(c)
	Sevelamer carbonate Sandoz (Sandoz)	15-09-2015	DCP	DK	Article 10(3)
	Sevelamer carbonate Genthon (Genthon)	30-09-2016	DCP	DK	Article 10(3)
	Fosquel (Avansor Pharma)	30-09-2016	DCP	DK	Article 10(3)
	Sevelamer carbonate Stada (Stada Arzneimittel)	17-10-2016	DCP	DK	Article 10(3)
	Sevelamer carbonate Aurobindo (Aurobindo Pharma B.V.)	16-02-2017	NP (NL)	n/a	Article 10(3)
	Sevemed (Medice Arzneimittel Pütter)	05-04-2017	DCP	DK	Article 10(3)
	Sevelamer carbonate Mylan (Mylan)	08-05-2017	DCP	DK	Article 10(3)
	Sevelamer carbonate Arrow (Arrow Generiques)	13-06-2017	NP (FR)	n/a	Article 10(3)[b]
	Sevelamer carbonate Aurobindo (Aurobindo Pharma)	05-07-2017	DCP	DK	Article 10(3)
Diprivan® 10 mg/ml (Aspen) Propofol					
	Propofol (Genthon)	10-08-1999	MRP	UK	Article 10(1)
	Propofol Lipuro (B. Braun)	11-12-1999	MRP/NP	DE	Article 10(1)
	Propofol Genthon (Genthon)	06-03-2000	NP (NL)	n/a	Article 10(1)
	Propofol MCT/LCT Fresenius (Fresenius Kabi)	18-01-2005	MRP	DE	Article 10(1)
	Propofol Claris (Claris Lifesciences)	27-03-2006	MRP	NL	Article 10(1)
	Propofol Panpharma (Claris Lifesciences)	18-06-2008	NP (FR)	n/a	Article 10(1)
	Propofol Lipuro[c] (B. Braun)	14-07-2008	DCP	DE	Article 10(3)
	Propofol Primex[d] (Primex Pharmaceuticals)	17-04-2009	MRP	FI	Article 10(1)
	Propofol Norameda (UAB Norameda)	28-04-2011	DCP	DE	Article 10(1)

(*continued on next page*)

Table 1 (*continued*)

Reference product (MAH)	Follow-on product (MAH)[a]	Authorisation date	Authorisation procedure	RMS (if applicable)	Application procedure
Propofol BioQ Pharma (BioQ Pharma)		06-07-2012	DCP	NL	Article 10(1)
Propofol Sandoz (Sandoz)		06-07-2012	DCP	NL	Article 10(1)
Ripol (Corden Pharma)		21-02-2013	DCP	IT	Article 10(1)
Propofol MCT/LCT Fresenius pre-filled syringe (Fresenius Kabi)		12-03-2013	DCP	DE	Article 10(1)
Propofol Demo (Demo)		03-05-2017	DCP	PT	Article 10(1)
Diprivan® 20 mg/ml (Aspen) Propofol					
Propofol Genthon (Genthon)		06-03-2000	NP (NL)	n/a	Article 10(1)
Propofol (Genthon)		08-08-2000	MRP	UK	Article 10(1)
Propofol 2% (Fresenius Kabi)		21-05-2001	MRP/NP	DE	Article 10(1)
Propofol Lipuro (B. Braun)		02-12-2001	MRP/NP	DE	Article 10(1)
Propofol Mylan (Mylan)		05-05-2003	NP (FR)	n/a	Article 10(1)
Propofol MCT/LCT Fresenius (Fresenius Kabi)		18-01-2005	MRP	DE	Article 10(1)
Propofol Claris (Claris Lifesciences)		02-11-2006	MRP	NL	Article 10(1)
Propofol Primex[d] (Primex Pharmaceuticals)		17-04-2009	MRP	FI	Article 10(1)
Propofol Norameda (UAB Norameda)		28-04-2011	DCP	DE	Article 10(1)
Propofol BioQ Pharma (BioQ Pharma)		06-07-2012	DCP	NL	Article 10(1)
Propofol Sandoz (Sandoz)		06-07-2012	DCP	NL	Article 10(1)
Ripol (Corden Pharma)		21-02-2013	DCP	IT	Article 10(1)
Propofol MCT/LCT Fresenius pre-filled syringe (Fresenius Kabi)		12-03-2013	DCP	DE	Article 10(1)
Propofol Demo (Demo)		03-05-2017	DCP	PT	Article 10(1)
Clexane® 2000–15,000 IU (Sanofi-Aventis) Enoxaparin sodium					
Inhixa		15-09-2016	CP	n/a	Article 10(4)
Thorinane		15-09-2016	CP	n/a	Article 10(4)
Enoxaparin Becat		24-03-2017	DCP	DE	Article 10(4)
Enoxaparin Crusia		24-03-2017	DCP	DE	Article 10(4)
Ghemaxan		05-04-2018	DCP	UK	Article 10(4)

CP = Centralised Procedure; DCP = Decentralised Procedure; MRP = Mutual Recognition Procedure; NP = National Procedure; MAH = Marketing Authorisation Holder; RMS = Reference Member State; CZ = Czech; DE = Germany; DK = Denmark; ES = Spain; FI = Finland; FR = France; GR = Greece; IT = Italy; MT = Malta; NL = Netherlands; PT = Portugal; SE = Sweden; UK = United Kingdom.

[a] This refers to the MAH listed for the RMS as in some cases different MAHs exist in different Member States.

[b] The authors could not retrieve any (publicly) available information on the application procedure.

[c] Refers to a new dosage form (5 mg/ml) approved via a hybrid application procedure.

[d] This generic application was transferred via an informed consent application procedure from Bayer to Primex.

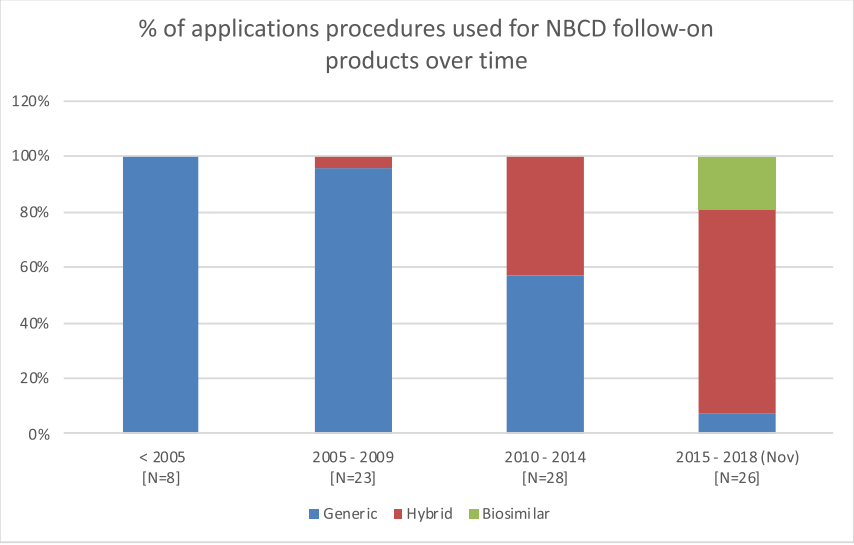

Fig. 2. Time trend analysis for the application procedures involved in the approval of NBCD follow-on products since the first approval in 1999 until November 2018.
N = Total number of applications in the indicated time period; Generic = Generic application procedure via Article 10(1); Hybrid = Hybrid application procedure via Article 10(3); Biosimilar = Biosimilar application procedure via Article 10(4).

products in the EU have been approved via the generic application procedure of Article 10(1), we identified an increase of the use of the hybrid application procedure of Article 10(3) in recent approvals (Fig. 2). This trend must be viewed with caution, as the recent hybrid applications are mainly related to glatiramer acetate and sevelamer carbonate and can often be traced back to the same manufacturer. However, this trend towards the hybrid application could indicate that for certain NBCD product classes, regulatory authorities in EU Member States try to address the uncertainty of the performance of these follow-on candidate products in practice by requesting additional (pre-)clinical data using the hybrid application procedure. The recent approval of the iron sucrose follow-on product Sucrofer® via the hybrid application procedure in June 2018 (in contrast to earlier approvals via the generic pathway), is a particularly interesting example that illustrates an apparent change in the regulatory approach for approving (NBCD) follow-on products.

This study also showed that almost all NBCD follow-on products have been approved via non-centralised procedures. The only two approved NBCD follow-on products via the centralised procedure were found in the enoxaparin product class and were approved via the

biosimilar application of Article 10(4). However, three subsequent enoxaparin follow-on products for which the same biosimilar application was applied, were approved via the DCP. The reason for this is unknown. It could be related to the revision of the EMA guidelines for enoxaparin shortly after the approval of the first two biosimilars, no longer requiring the execution of clinical trials to demonstrate similarity (Imberti et al., 2017). This also illustrates that generic developers seem to prefer a non-centralised procedure to a centralised procedure.

Since NBCD (follow-on) products don't have to follow a mandatory centralised procedure, the designation of different EU regulatory authorities as RMS could result in heterogenous regulatory approaches and different outcomes for approving NBCD follow-on products (Garattini and Padula, 2016, de Vlieger et al., 2016). This could be particularly challenging in cases where marketing authorisation is pursued via the hybrid approach of Article 10(3) or biosimilars approach of Article 10(4), as these application procedures may involve additional evidence requirements that could be differently defined by Member States. To what extent this may have consequences for their safety and efficacy evaluations is unknown and needs to be further investigated. However, the experience with iron sucrose follow-on products and the recently observed compositional differences within the glatiramoid product class highlight the public health relevance and importance to further evaluate the present regulatory system in the EU for NBCDs (Melamed-Gal et al., 2018, Stein et al., 2012).

As Table 1 shows, the number of approvals of NBCD follow-on products has been increasing in recent years. With many innovator NBCD products at the verge of market exclusivity expiration such as liposomal formulations, a wave of new follow-on products is expected in the coming years (Ehmann et al., 2013). Furthermore, innovations in the field of targeted delivery and targeted formulations, e.g. with more advanced site- and rate-specific release properties, are rapidly expanding the field of NBCD products. These increasingly complex novel therapeutic interventions coming to the market in the decades to come, may pose even more challenges for the regulatory system (Noorlander et al., 2015, Caster et al., 2017). At present, fast-developing synthetic technologies are already catching up with biotechnology, which is exemplified with the newly approved synthetic follow-on version for the recombinant (biological) teriparatide Forsteo®. Since it is not considered a biologic, Teva's synthetic teriparatide was, in contrast to earlier approved biosimilars Movymia® and Terrosa®, not approved via the biosimilar application of Article 10(4), but via the hybrid application of Article 10(3), allowing for generic-type substitution (Bundesinstitut für Arzneimittel und Medizinprodukte, 2018, Lau and Dunn, 2018).

We found that many of these NBCD follow-on products are marketed under different brand names throughout the EU. Furthermore, some NBCD follow-on products from different MAHs, are actually manufactured by the same manufacturer. For example, almost all of the 20 sevelamer carbonate follow-on versions identified can be traced back to the generic manufacturer Synthon. This means that although these NBCD follow-on products have distinct brand names, usually associated with different MAHs, from a drug safety and efficacy perspective, they could actually be regarded as the same product. Interestingly, this is also observed for enoxaparin and its approved biosimilars. Since enoxaparins are regarded as biologics in the EU, they have to comply to the legislative framework for biologics with regard to brand name traceability (Directive, 2010; Klein et al., 2016). The use of a variety of different brand names (e.g. for marketing purposes in different EU Member States) could potentially delay the identification and the processing of new important safety and efficacy information from routine clinical practice. Moreover, NBCDs for which follow-on versions are approved may not be distinguishable in post-marketing surveillance, which could hamper the timely detection of product-specific safety issues. Therefore, it needs to be explored if NBCDs may benefit from extending the legislative framework for brand name and batch number traceability for biologics to NBCDs (Directive, 2010). Another example here is the case when synthetic generic versions are approved for biological originator products, such as teriparatide. The synthetic version of teriparatide is not a biologic and therefore, from a legislative perspective, does not require brand name traceability, complicating timely detection of product specific safety issues (EuropaBio, 2019). We therefore recommend further investigating the need and implications for post-marketing safety surveillance of NBCDs.

The scientific community has signalled that - compared to small-molecule generics - NBCDs and NBCD follow-on products, require particular regulatory scrutiny (Schellekens et al., 2011, Schellekens et al., 2014). However, 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. This is in contrast to the regulation of biologics, for which a harmonized regulatory approach was established with the biosimilar pathway throughout the last fifteen years. Since NBCDs share many characterises with biologics, the question this paper wants to raise is how the experience from these complex medicines can be used to further improve and harmonize the EU regulatory system for ensuring timely access to safe and efficacious medicines for patients.

Although the EMA guidance documents on nanomedicines may provide some assistance for the approval of certain NBCD follow-on products, it has been argued that guidelines alone are insufficiently reducing the uncertainty for both regulators and generic companies, for example due to changing regulatory standards (Garattini and Padula, 2016, de Vlieger et al., 2016, United States Government Accountability Office, 2018, Ragelle et al., 2017). In the current EU setting, the regulatory framework for approving NBCD follow-on products is based on a case-by-case approach (Ehmann and Pita, 2016). This approach allows regulators in the EU to request additional data in case of remaining uncertainty. This case-by-case approach reduces the epistemic uncertainty of the regulatory system, but at the same time increases the decision uncertainty for generic drug developers. Interestingly, the FDA applies a rule-based approach to regulating medicines, which in the case of the NBCDs, could potentially provide more certainty to generic drug developers about particular regulatory requirements. For example, whereas glatiramer acetate follow-on products were approved by the FDA on the legal basis of a generic application and without requiring additional clinical trial data, in the EU detailed comparative characterisation and clinical studies were requested due to the recognised complexity. An excellent analysis of the discrepancies in the evaluation of these products was recently described by Rocco et al. (Rocco et al., 2018).

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. Another benefit of the centralised procedure is the guarantee of centralised safety monitoring and the obligation for the use of a single brand name throughout EU. This will facilitate a better traceability and adequate identification of product specific safety issues for NBCDs (European Parliament, 2019). Nonetheless, more research is needed to understand the impact of the scientific and regulatory challenges of the NBCDs on clinical practice (Hussaarts et al., 2017). Important initiatives such as the FDA Generic Drug User Fee Amendments (GDUFA) research program could ultimately lead to the science-base that is needed to establish an appropriate regulatory framework for NBCDs and NBCD follow-on products (U.S. Food and Drug Administration Center for Drug Evaluation and Research Nanotechnology Programs, 2018, U.S. Food and Drug Administration FY2016 Regulatory Science Report, 2018).

5. Conclusion

The dynamics of the fast-developing field of NBCD products pose significant challenges on how to regulate these products in an aligned and proportionate fashion. The absence of a consistent regulatory approach for NBCDs and in particular for NBCD follow-on products, has resulted in a diversified regulatory landscape throughout the EU. This study shows that almost all of the 85 NBCD follow-on products available in the EU in 2018 have been approved via various non-centralised procedure. Although most NBCD follow-on products followed an Article 10(1) procedure, we clearly see an increase of the use of the hybrid pathway via Article 10(3). This study also raises the question on how to proceed giving the expected surge of follow-on NBCDs in the next decade. The observed heterogeneity carries the risk of lack of predictability for NBCD developers and many other uncertainties for stakeholders. For sure there are lessons learned from the experiences with the biosimilar pathway for biologics over the last decade. But NBCDs cannot be classified in the same way as we do with biologicals. The EMA's class-specific guidance documents for nanosimilars could form another source for establishing consistency in the regulation of NBCD follow-on products. But all this will probably not be enough to ensure innovation in the NBCD space and protecting public health. More rethinking in order to design prudent regulatory pathways for NBCD follow-on products is needed. This paper aims to contribute to that process.

Declaration of Interest

All authors declare no support from any organisation for the submitted work.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejps.2019.03.029.

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