Complexity in the making: non-biological complex drugs (NBCDs) and the pharmacopoeias

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Pharmacopoeias, as standard references for pharmaceutical drug specifications and reference standards in the form of monographs, play a pivotal role to assure drug quality and safety. With emphasis on the activities concerning non-biological complex drugs (NBCDs), the mechanisms by which new monographs are introduced into the European and the US pharmacopoeias are presented.

Keywords: Drug quality, ICH, non-biological complex drugs (NBCDs), pharmacopoeia, Ph. Eur., USP

Introduction

Over the last decades we came to realize that high molecular weight drugs of biological origin, such as therapeutic antibodies, are of a highly complex structure, which determines their activity as well as safety in terms of immunogenicity. The manufacturing of such therapeutics requires highly complex and meticulously controlled up- and downstream processes. Still, the final drug product whose properties are determined by the process is characterized by a certain degree of "microheterogeneity", i.e. the presence of several isomers of the active pharmaceutical ingredient (API).

'Follow-on' protein therapeutics will not be manufactured by the same process proprietary to the originator. As the process itself determines the properties, e.g. microheterogeneity, of the final drug product, an originator protein therapeutic and its follow-on product may not be considered to be identical. Hence, the generic principle applied for drugs of low molecular weight, whose properties and composition are well defined and can be reproduced by generic drug producers, cannot be applied to complex drugs such as therapeutic proteins. A regulatory strategy leading to marketing authorization of follow-on biologicals in Europe and by the US Food and Drug Administration (FDA) – the ‘biosimilar’ pathway – has thus been established and refined. This approach includes elements such as clinical testing of the follow-on against the originator product in clinical trials, as well as post-marketing surveillance [1].

Another group of complex drugs of non-biological origin (NBCDs – non-biological complex drugs) share aspects of complex structure, potential immunogenicity and impossibility of full characterization by physicochemical methods alone with biological complex drugs. Examples for these complex drugs include glatiramoids (Copaxone®), liposomal formulations (Doxil®) and nanoparticles such as iron-carbohydrate particles (Venoferr®). These drugs are considered to belong to a new class of 'nanomedicines' [2]. Their size and attributes at the molecular scale confer these systems certain properties to interact with their biological environment.

Nanoscale drug delivery systems have been under investigation for several decades, yet only very few have actually matured to clinical application. While analytical techniques describing the physicochemical properties of these systems are being constantly refined, we had to understand that these systems need a multi-pronged analytical approach to describe their physicochemical properties. However, little is known on the relation between these properties and the clinical outcome, such that these systems always need clinical assessment to ensure efficacy and safety. The situation is rendered even more complex by the appearance of intended copies of NBCDs. Some of those, e.g. iron sucrose products ('iron sucrose similars, ISSs'), and 'generic' Doxil (approved by FDA in 2013 in view of drug shortages in the US) have entered the market under the generics paradigm, partially due to the absence of a more suitable regulatory evaluation process. Therefore, an effort is needed to discover these correlations between nano-properties and biological activity, develop suitable analytical techniques and define specifications, establish clinical protocols and, last but not least, integrate this knowledge in a science-based regulatory approach to nanomedicines [3].

The principle of nanomedicines being complex drugs is well established within the scientific community. Regulatory authorities are also catching up, as shown by recent activities in the field. FDA is currently sponsoring a study comparing two iron carbohydrate products (Nulecit®, Ferrlecit®) for their similarity, involving physicochemical characterization, in vitro and clinical studies [4]. The European Medicines Agency (EMA) has published a reflection paper on the subject of 'data requirements for iron-based nano-colloidal products' in February 2015, which lists a range of characterization methods for these products.

In the context of ensuring the quality and safety of medicines, pharmacopoeias, as standard references for pharmaceutical drug specifications in the form of monographs, play a pivotal role. Derived from the Greek expressions φάρμακον (pharmakon) and παίζει (making), pharmacopoeias appeared as early as 50 AD (De Materia Medica). In Great Britain, the national British Pharmacopoeia (BP) was published for the first time in 1864, the United States Pharmacopeia (USP) already in 1820. In addition to such national pharmacopoeias, international forms do exist as well and may replace national ones. The foundation for the European Pharmacopoeia (Ph. Eur.) was laid in 1964 by a convention of the Council of Europe, and the first volume of the International Pharmacopoeia (Ph. Int.) was published by the World Health Organization (WHO) in 1951.

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Having the common goal to ensure access to good quality medicines, the organizational forms of these pharmacopoeias and the procedures followed to introduce new monographs differ largely. This manuscript gives an overview on such issues, and analyses the level of awareness for NBCDs at the European and US pharmacopoeias.

European and US pharmacopoeias and non-biological complex drugs (NBCDs)

1. The European Pharmacopoeia (Ph. Eur.)
The European Directorate for the Quality of Medicines and Healthcare (EDQM) is a directorate of the Council of Europe (CoE), whose function was first defined by the ‘Convention on the elaboration of a European Pharmacopoeia’ [5] signed in 1964. These activities had the goal to define common specifications for medicinal substances and their pharmaceutical preparations, as well as to promote free movement of medicines in the European Union (EU) and the countries of the European Economic Area (EEA). In 1975, a directive by the EC makes compliance with the European Pharmacopoeia Monographs mandatory when requesting marketing authorization for medicines for human use. In 1994, the CoE signed the Ph. Eur. Convention, and the European Network for Official Medicines Control Laboratories (OMCL) was created [6], and its activities organized by EDQM from 1996 onwards. In 2001, EC Directive 2001/83/EC [7] maintains the mandatory character of Ph. Eur. monographs when requesting marketing authorization, superseding all previous directives.

With the task of protecting public health by applying one common compulsory standard in its Member States, the Ph. Eur. is the official pharmacopoeia and legally binding in 37 Member States and the EU. It is complemented by national pharmacopoeias for specific monographs of interest to only one Member State. Ph. Eur. today contains legally binding quality standards for active substances (organic, inorganic), excipients, substances of biological origin and biotechnology, herbal drugs, essential oils and fats, preparations, radiopharmaceuticals, vaccines, sera (human, veterinary), blood derivatives, and homeopathic preparations. These monographs are supplemented by general monographs on dosage forms as well as general texts on quality issues and standard analytical methods. In total, nearly 2,200 monographs currently exist. The first finished product monograph containing a chemically defined active substance (sitagliptin tablets used in type 2 diabetes) was adopted by the Ph. Eur. commission only as recent as March 2015. A second finished product, rosuvastatin tablets, was also added for monograph elaboration to the work programme, taking into account products from multiple manufacturers. In 2016, the EDQM will publish the ninth Edition of the European Pharmacopoeia, which will contain nearly 3,000 monographs and general texts and will become legally binding by 1 January 2017 [8].

The Ph. Eur. Commission (COM) consists of one delegation per each of the 37 members, a delegation from the EU consisting of a representative from Directorate General Health & Consumer Affairs and the EMA, and observers from 22 countries and WHO. Delegates come from health ministries, health authorities, pharmacopoeias, universities, or industry and are appointed by the national authorities on the basis of their expertise. There are cur-

![Image of the Flowchart](image-url)

*a biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control - definition from Directive 2001/85/EC.*
currently 20 permanent Groups of Experts and 52 ad-hoc Working Parties dedicated to revising texts that are to be adopted by the COM which also decides on the composition of these groups.

The procedure by which new texts are introduced into Ph. Eur. is depicted in Figure 1.

On submission of a proposal, typically by a national authority of a Member State, the COM decides to have the new monograph elaborated by a group of experts or working party. A draft elaborated by this group is submitted to Pharmeuropa [9], the free online publication of the EDQM for review and comments by interested parties for the duration of three months. The National Pharmacopoeia Authorities (NPA) of the Member States process the received comments on the draft monograph, which are then compiled and resubmitted to the group of experts or working party. On adaptation of the draft according to the comments received, the monograph is proposed to COM, which adopts it and sets the date of implementation into Ph. Eur., where the monograph is published about six months later.

At EDQM, the Non-Biological Complexes (NBC) Working Party was created in 2011 following an initiative of SwissMedic, the Swiss agency responsible for the authorization and supervision of therapeutic products (medicinal products and medical devices). The COM decided to add to its work programme the elaboration of a monograph on Iron Sucrose Concentrated Solution as a first example for NBCDs. Iron sucrose (IS) and its follow-on products, so-called iron sucrose similars (ISSs) products consist of a poly-nuclear iron core of iron(III)-oxyhydroxide, which is stabilized by a complex coating of sucrose. IS products have been used in parenteral replacement therapy of anaemia, e.g. in chronic kidney disease (CKD) patients on dialysis to stimulate the generation of erythrocytes. ISSs in Europe received marketing authorization of USP, who will also perform laboratory testing. A draft monograph is then submitted to the Council of Experts and one of its Expert Committees for scientific opinion and merits of the proposed monograph. The Council of Experts then decides to publish the draft monograph for a three-month public review at Pharmaceutical Forum (PF), the online peer-reviewed journal of USP [11].

Successively, the comments received are reviewed by the Expert Committee and integrated into the monograph draft. A USP liaison (scientific officer) compiles and analyses these comments and the draft, and submits either for further revision or for publication in USP-NF. The draft thereby becomes an official monograph, the specifications stated in the standard must be abided to when marketing the product within the US.

Besides the development and publication of monographs for prescription and over-the-counter (OTC) drugs (a relatively new activity at USP), the preparation of Reference Standards is a major activity and source of income for USP. The more than 3,500 USP Reference Standards are used in the examination of the identity, strength, quality and purity of drugs, biologicals and excipients, thus contributing to the quality of drug manufacturing. The USP Council of Experts is closely interacting with experts from industry and regulatory agencies. Until 2015, USP has made available a compendium of public standards (Medicines Compendium, MC) for approved medicines on a global basis. The MC monographs were freely available online, providing performance tests for critical quality attributes and acceptance criteria, a source-independent Reference Procedure and one or more Acceptable Procedures. The website was discontinued and shall be replaced in the future by a ‘collaborative programme’ [12].

Concerning activities in the area of NBCDs, and in addition to a published monograph on Iron Sucrose Injection as mentioned and a national formulary. In 1850, colleges were invited to contribute to the revision of the USP, and in 1888, the first National Formulary (NF) was introduced by the American Pharmacists Association (APhA). USP was incorporated in 1900 in its present form as a not-for-profit organization; it is thus not a governmental organization like the Ph. Eur. The USP and NF standards for strength, quality, purity, packaging and labelling are recognized as official and enforced by FDA from 1938 onwards. In 1977, the scopes of USP and NF are defined such that standards for drug substances and dosage forms are specified in USP, whereas excipient standards are included in NF. From 1980 onwards, both USP and NF are published under one cover. The USP-NF is also translated into Chinese and Russian. While being a national organization, USP has developed an international presence with offices and laboratory facilities in Hyderabad (India), Shanghai (China) and São Paulo (Brazil). Along with these facilities, USP also runs an office in Basel (Switzerland).
properties to Copaxone®. While good safety and tolerability in the manufacturing process, Teva had produced a glatiramoid (TV-5010) that was similar in terms of amino acid ratio and physical properties ('the process is the product'). In fact, by slight alteration of the fundamental reaction scheme, the drug's physicochemical properties including composition, structural signatures for polymerization and depolymerization and results in a relevant biological assay. On 15 April 2015, FDA approved Glatopa® as a first generic glatiramoid, Momenta/Sanofi's Glatopa®, can be demonstrated by showing equivalence in the inherent complex-ity of glatiramoids requires a very well controlled manufacturing process. As is the case for biological complex drugs, the inherent complexity of glatiramoids, as well as whether profiles of Copaxone® to purported 'generic' glatiramoids, e.g. Glatimer® (India), Probioglat® (Mexico) and Escadra® (Argentina) revealed essential differences between the originator and the follow-on drugs [14,15]. It was therefore suggested by Teva that follow-on glatiramoids should not receive marketing authorization by the generic drug pathway. However, as stated in a Dental Letter [16] to a Citizen's Petition Letter by Teva, FDA insisted that sameness between Copaxone® and a follow-on glatiramoid, Momenta/Sanofi’s Glatopa®, can be demonstrated by showing equivalence in the fundamental reaction scheme, the drug's physicochemical properties including composition, structural signatures for polymerization and depolymerization and results in a relevant biological assay. On 15 April 2015, FDA approved Glatopa® as a first generic glatiramoid for the treatment of relapsing MS. Based on these discussions, FDA may issue the draft of a guidance document on glatiramoids in the future.

USP is now in the process of establishing an expert panel to discuss the draft of a monograph on glatiramer acetate. The panel will most likely include experts from academia, regulatory authorities and manufacturers. Major issues to be addressed may include the definition of critical quality attributes for glatiramoids, as well as whether bioassays should be included in the monograph to show activity and safety.

International harmonization: ICH and PDG
The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was launched in 1990 at Brussels headquarters of EFPIA (European Federation of Pharmaceutical Industries and Associations) in the presence of representatives from regulatory agencies of Europe, Japan and the US, and from industry. The mission of ICH is to achieve greater harmonization in regulatory requirements for pharmaceutical product registration [18]. Such harmonization would result in the avoidance of the repetition of studies in the research and development of new human medicines. During the last 25 years, ICH has established harmonized technical requirements for the quality, safety and efficacy of new medicines in EU, Japan and the US.

ICH is governed by its Steering Committee (SC), which is composed of representatives from the European Commission, EFPIA, the Japanese Ministry of Health, Labour and Welfare,
changeability is compiled only with respect to the harmonized
Such monograph for a drug harmonized by attribute, inter-
of the monograph are harmonized (harmonization by attribute).
may not be possible. In such case, only harmonizable elements
macroepiaes in the three regions, serving also the mission of
general chapters and excipients monographs of the major phar-
year. Main activities of PDG are retrospective harmonization of
The Pharmacopoeial Discussion Group (PDG) [28] was formed
in 1989 with representatives of EDQM, MHLW representing the
Japan and the US. The five-step harmonization process is initi-
ated by endorsement of a concept paper and business plan by
The SC has appointed Working Groups to review the differences
in requirements between EU, Japan and the US and develop
the scientific consensus required to reconcile those differences.
The four types of ICH working groups include Expert Working
Groups (EWG) charged with developing a harmonized guide-
line, Implementation Working Group that develops Q & As to
facilitate implementation of existing guidelines, Informal Work-
ing Groups having the objective of developing/finalizing a
Concept Paper, as well as developing a business plan for harmo-
nization activities, and Discussion Groups dedicated to discuss
specific scientific considerations or views. ICH convenes twice
a year with the location of meetings rotating among Europe,
Japan and the US. The five-step harmonization process is initi-
ated by endorsement of a concept paper and business plan by
the SC [19].

Several ICH guidelines are suggested for stability testing of
nanomedicines [20], e.g. guideline for stability testing of non-
targeted nanomedicines (Q1A (R2)) [21], new dosage forms
(Q1C) [22] and biotechnology-based drug products (Q5C)
[23] for targeted nanomedicines including a biological targeting
moiety such as an antibody. Stability studies of liposomal
formulations following ICH guidelines have been reported in
literature [24]. A range of methods for testing nanotoxicology
has recently been reviewed [25]. It has been suggested that the
ICH-S6 guideline [26] may be applied for non-targeted nanopar-
ticles, whereas the ICH-S8 guideline [27] may be applied for the
assessment of toxicity of targeted nanoparticles conjugated to
biological targeting moieties.

The Q6A guideline has the purpose to help select common test
procedures and acceptance criteria for new drug substances of
chemical origin and new drug products not previously regis-
tered in the EU, Japan and the US. The guideline does not apply
to the clinical test phase, but only to the marketing approval
process of new drug products and combinations thereof. The
guideline specifically mentions drugs such as low molecular
weight peptides and (semi)synthetic antibiotics. Not covered,
however, are radiopharmaceuticals and oligonucleotide-based
drugs.

Summary
Increasing awareness of the intricacies of NBCDs in the science
and regulatory communities was bound to have an effect on
drafting of pharmacopoeial content in the form of monographs
and general guidelines. Already existing content should be
reviewed and revised according to the changing understanding
of these complex drugs. International harmonization of pharma-
copoeial contents to maintain drug quality, efficacy and safety
in the three major areas will be possible through the networks
(ICH, PDG) in place today.

Competing interests: The author declares that he is a member of
the steering committee of the NBCD Working Group, hosted at the
non-profit organization Lygature – formerly known as Top Institute

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