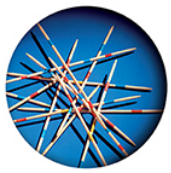
To:
Scientific Operations Management Section
Scientific Evaluation Branch
Therapeutic Goods Administration
PO Box 100, WODEN ACT 2606

Non Biological Complex Drugs working group



March 20, 2019
Utrecht, the Netherlands

Dear Sir, Madam,

We are responding to the invitation to comment on the consultation paper relating to "Reforms to the generic medicine market authorisation process", version 1.0 (February 2019).

We represent the Non-Biological Complex Drugs Working Group hosted at Lygature, a non-profit organization in The Netherlands. Our network consists of (pre)clinical experts from academia, industry, regulatory bodies and knowledge institutes, who offer expertise in the development and evaluation of 'non-biological complex drugs' (NBCDs).

NBCDs are fully synthetic materials: they are medicinal products but not biological medicines, where the active substance is not a homo-molecular structure but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. Like biologics, the composition, quality, and in vivo performance of NBCDs are highly dependent on the manufacturing processes of the active ingredient, as well as (in most cases) the formulation [Crommelin et al. 2014; Crommelin, D.J.A. & J.S.B. de Vlieger 2015].

Those NBCDs include a significant proportion of nanomedicines. Our mission is to ensure that appropriate and harmonized science-based approval and post-approval standards for NBCDs are introduced globally, for patient safety and benefit.

Over recent years, the NBCD Working Group has been facilitating and organizing science-based discussions between all stakeholders on the challenges involved during evaluation and approval of NBCDs and related generic/similar follow-on products. Terms in regulatory science have to be precise, as 'complex generics' implies full therapeutic equivalence, which is unattainable in the case of NBCDs. We consider the biosimilar-inspired term similar more appropriate taking into consideration their complex nature [Ehmann *et al.* 2013; Marden *et al*. 2018]. We believe that currently unresolved scientific and regulatory challenges hamper much-needed progress in this important field. We stimulate science-based discussions and have regularly published on the outcomes and advances associated with these discussions.

The regulatory challenges for approving complex similars are currently a hot topic in the global regulatory community [United States Government Accountability Office 2017; Ehmann *et al.* 2013; De Vlieger *et al.* 2016]. The NBCD Working Group has actively interacted with the regulators on this topic and coordinated and engaged in various regulatory stakeholder meetings to discuss globally harmonized approaches for regulating complex similar, such as the American Association of Pharmaceutical Scientists, FIP Pharmaceutical Sciences World Congress, International Symposium on Scientific and Regulatory Advances in Complex Drugs [SRACD 2016; Crommelin *et al.* 2015], New York Academy of Sciences [Hussaarts *et al.* 2017], European Foundation for Clinical Nanomedicine (CLINAM) etc.. In the past we also provided input to US FDA guidance documents on complex generics [Comment on FDA Notice (Docket ID: FDA-2017-N-6644); Comment on FDA Notice (Docket ID: FDA-2017-N-3615); Comment on FDA Notice (Docket ID: 2017-D-0759)].

The TGA accurately highlights the changing landscape of generic medicines, referring among others to liposomal formulations and polymers. TGA is pointing out the challenges of developing complex similars and to establishing bioequivalence to the existing medicine. We support TGAs statement to develop guidance similar to the guidance materials recently established by the EMA and FDA. We applaud TGA for highlighting the importance of global alignment on this matter to improve the generic medicine authorisation process of complex similars. We agree that such efforts to align regulatory processes for complex similars can decrease the costs of development and unnecessary repetition of clinical trials and lead to improved access for the global community.

With this letter we wish to provide some comments to the request for input and highlight a number of important topics that we believe need to be considered in order to ensure the quality, availability and uptake of equally safe and effective complex similars. Ensuring that generic/similar versions of NBCDs are therapeutically equivalent to the originator product presents a major challenge. This is because it is not possible to characterize fully the physico-chemical properties of NBCDs, and there is frequently a lack of detailed understanding of the impact on product performance made by small differences in manufacturing process. The complex drug product landscape published in the NYAS report (Figure 1) illustrates whether pharmaceutical equivalence (PE) and/or bioequivalence (BE) are/is the major cause of complexity in establishing therapeutic equivalence for the indicated product families [Hussaarts et al. 2017]. As the intrinsic differences between the product families pose different challenges when determining equivalence, one may consider simply labelling all these products as ‘complex’, but it is important to understand that there is no ‘one size fits all’ approach for the different product ‘families’. The main challenge for a number of complex similars is to establish bioequivalence. For NBCD families, the additional difficulties involved in establishing PE add further complexity.

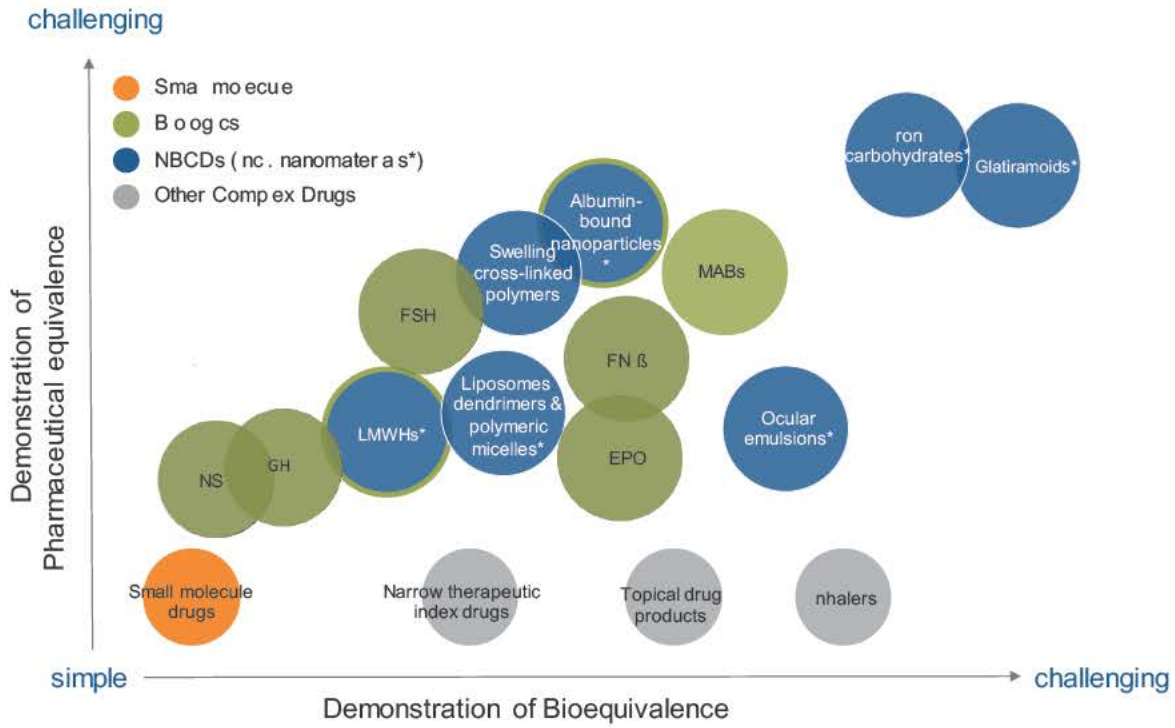


Figure 1; adapted from Hussaarts *et al.*

By far most important, in our view, is to address the challenges in determining the Critical Quality Attributes (CQAs) of complex products. At present, the CQAs for many (non-biological) complex drugs are unknown, and future identification of the CQAs may significantly catalyse the development of high quality, therapeutically similar versions. As such, priority should be given to validate scientific tools allowing for independent assessment of the relevant quality attributes. Subsequently, equivalence guidance including reference to established CQAs are needed to help generic developers to prepare marketing authorisation applications for complex similars. In line with our mission, we stimulate the dissemination of relevant data related to attempts of determining CQAs of products. Productive discussions can only take place when the relevant data is available for experts to review. Furthermore, understanding the in-vitro in-vivo correlations (IVIVCs) of product characteristics is crucial for the rational development of therapeutic similar products.

Another important consideration for complex similars that we believe should require more regulatory focus is pharmacovigilance. The pharmacovigilance system in the EU and US for example does not always discriminate between brand and generic product in particular for synthetically produced drugs. In fact, some of the adverse side effects of generic products are attributed to its brand name product [Grampp, G. & T. Felix. 2015.; Klein *et al.* 2016]. This renders the pharmacovigilance data useless for validation of the assumptions made when establishing the CQAs and IVIVCs of such products. Consideration should also be given to potential implications for clinical practice with regard to substitution and interchangeability of complex similars. A robust pharmacovigilance system for adequate safety monitoring may be needed to identify any product-specific safe issues in clinical practice. Clinical guidelines and education on complex similars for healthcare professionals can contribute to ensuring the safe use in routine clinical practice.

Finally, we agree with the TGA that global alignment on data requirements for complex generic drugs (e.g. based on CQAs) together with work sharing arrangement between regulators may significantly reduce marketing authorisation timelines. Global efforts and learnings from the biosimilar approach should be used to come to globally accepted approaches for regulating complex similars [Crommelin et al. 2015]. We encourage TGA to actively join international regulatory discussions about complex similars to allow reaching globally harmonized approaches for bringing complex similars to patients around the world.

We welcome any opportunity to discuss with TGA how to strengthen the science base for approval and post approval standards for NBCDs (including nanomedicines).

Sincerely, on behalf of the Steering Committee of the NBCD Working Group,

the NBCD Working Group
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References:

Comment on FDA Notice (Docket ID: FDA-2017-N-6644); *Fiscal Year 2018 Generic Drug Regulatory Science Initiatives; Public Workshop; Request for Comments*; Available from: https://www.regulations.gov/document?D=FDA-2017-N-6644-0007

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