

Non-Biological Complex Drugs

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# Is the EU ready for non-biological complex drug products?

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Comment on the [Regulatory](#) paper by Dr Falk Ehmann and Dr Ruben Pita: The EU is ready for non-biological complex medicinal products, published in *GaBI Journal*, 2016;5(1):30-5.

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It is with great interest that we read the publication entitled: 'The EU is ready for non-biological complex medicinal products' by Dr Falk Ehmann and Dr Ruben Pita published in *GaBI Journal* 2016 [1]. In this *GaBI Journal* paper the authors of the European Medicines Agency (EMA) express their personal view on the policies that the European Union (EU) and EMA have been developing with regard to the regulation of non-biological complex drug (NBCD) products in the EU and on a global scale. The full definition of NBCD products, among which a substantial number of nanomedicines are found, is stated in their paper. As the publication refers to several papers co-authored by us, please allow us to make some comments on the message presented by Drs Ehmann and Pita.

It is a laudable and appreciated initiative of the authors to provide their personal view on the regulatory aspects of NBCD products. The text clearly describes the current framework in which the EU and EMA operate, as well as the global initiatives to harmonize the regulation of NBCD products. However, we would like to ask that the authors consider some points to further the discussion regarding the suitability/degree of adaptation of this regulatory framework in practice and make some recommendations. Our comment is based on the fact that the debate on scientific evidence and understanding of these drugs of high complexity and their related *in vivo* profiles are still ongoing, which render the selection of appropriate evaluation tools difficult. In our comment we follow the same section headings as used by Ehmann and Pita.

## Re: Marketing authorization procedures and the legal basis of submission

In several European countries, nanomedicines (follow-on versions of nanomedicines and falling under the NBCD definition) have received marketing authorization following national procedures allowing for different appreciation of the complexity leading to different outcomes. Over time, the outcome of clinical studies from independent sources published in reputable journals became available [2-4]. They clearly showed differences in clinical performance between the innovator and follow-on products. Although these findings may have contributed to the generation of EMA referral and reflection papers [5, 6], it did not lead to clear actions of the competent authorities, e.g. to inform the medical community about therapeutic inequivalence. This aspect is of highest importance as such follow-on medicinal products are put on the market mainly to obtain established therapeutics in a 'generic version' allowing drug accessibility at a lower price. Given the assumed comparability of quality, safety and efficacy, substitution or interchange may be possible without notification of healthcare professionals or the patient. For NBCDs and their 'similar', this does not only interfere with traceability of the dispensed drug product but also has therapeutic consequences for the patient as clinical evidence has shown.

In our view, the approval process of follow-on versions of NBCD products should follow (being mandatory and not optional) the centralized procedure where the combined competence of the large network of EMA experts is *directly* available,

as is the case for biosimilars. This approach guarantees the application of up-to-date scientific knowledge and evaluation tools. Moreover, drafting EMA reflection papers for the approval of NBCD product families such as liposomes, glatiramoids, iron-colloids and others stimulates discussion and hopefully leads to the introduction of validated preclinical models and/or a request for the performance of clinical studies, if deemed necessary in NBCD guidance protocols. Last but not least, the outcome of independent research showing lack of equivalence of NBCD follow-on versions requires actions from the side of the competent authorities. For example, EMA may follow the example set by the US Food and Drug Administration (FDA) by performing Generic Drug User Fee Amendment (GDUFA) type programmes, including supporting scientific investigations on NBCD related topics [7].

## Re: Harmonization of requirements across regions

Ehmann and Pita mention current initiatives to harmonize EMA and FDA technical requirements for follow-on medicinal products. For outsiders it is difficult to judge the extent of progress as little information is brought into the public domain. Both EMA and FDA claim that regulatory decisions regarding equivalence should have a strong science base. However, Lipodox, the follow-on version of Doxil (doxorubicin-liposomes) which received marketing approval in the US failed to do so in Europe. Another example is the follow-on versions of low-molecular weight heparins. They are not considered biologicals in the US, but are in Europe, where they are seen as biosimilars. Published reflection papers (EMA) and (draft) guidance documents (FDA) reflect close views from both sides of the Atlantic Ocean but are not always aligned [8, 9]. The World Health Organization (WHO) has taken the initiative to draft a WHO regulatory protocol for biosimilars [10], but has not started such an initiative for NBCD follow-on products. Ehmann and Pita mention other bodies as well (International Pharmaceutical Regulators Forum [IPRF] and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH]), but no concrete results have been reported so far. The scientific basis for regulatory protocols for NBCD products should be further developed

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with a global discussion platform enabling an open exchange among experts in the field. Special emphasis should be put on the identification of the physicochemical parameters leading to clinically meaningful differences. In Europe, relevant clinical differences of the performance of supposedly equivalent nanomedicine follow-on products compared to the originator drug were described (see above). Very little, however, is known about the experience in other parts of the world. But would this problem be restricted to Europe? Very unlikely so! Here again, one should strive to create a database filled with data on the (pre)clinical outcome of therapy using NBCD follow-on products from all over the world, and published in reputable journals.

## Conclusions

In our opinion, the title of the Ehmann and Pita article should be accompanied by a question mark. In principle, EMA may have the legal basis to deal with NBCD products and their follow-on versions, but in practice there is a list of *desiderata*. On the top of this list are: 1) Strengthening the science base in the public domain to demonstrate equivalence of these products, for Europe as well as for the rest of the world; 2) Taking appropriate actions and guidance when therapeutic inequivalence of products has been proven; 3) Intensifying global harmonization efforts of reflection papers/guidance documents; and 4) Assisting in and support of educational actions to spread awareness and increase knowledge on the topic especially towards healthcare professionals to eventually assure optimal patient benefit by rational and correct drug treatment.

In our view, a harmonized regulatory approval pathway similar to, but distinctly separate from, the 'biosimilarity pathway' should be considered. Because of the complex nature of NBCD products, a step-wise comparison of test to reference drug with respect to analytical characterization, animal studies and clinical studies is essential. This will facilitate the assessment of therapeutic interchangeability.

## Authors' comment

The views expressed are those of the authors and should not be understood

or quoted as being made on behalf of or reflecting the position of the individual organizations or the NBCD Working Group as a whole.

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## References

1. Ehmann F, Pita R. The EU is ready for non-biological complex medicinal products. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2016;5(1):30-5. doi:10.5639/gabij.2016.0501.008
2. Rottembourg J, Kadri A, Leonard E, Dansaert A, Lafuma A. Do two intravenous iron sucrose

- preparations have the same efficacy? *Nephrol Dial Transplant*. 2011;26(10):3262-7.
  3. Martin-Malo A, Merino A, Carracedo J, et al. Effects of intravenous iron on mononuclear cells during the haemodialysis session. *Nephrol Dial Transplant*. 2012;27(6):2465-71.
  4. Agüera ML, et al. Efficiency of original versus generic intravenous iron formulations in patients on haemodialysis. *PLoS One*. 2015;10(8):e0135967.
  5. European Medicines Agency. Intravenous iron-containing medicinal products [homepage on the Internet]. [cited 2016 Oct 20]. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous\\_iron-containing\\_medicinal\\_products/human\\_referral\\_000343.jsp&mid=WC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous_iron-containing_medicinal_products/human_referral_000343.jsp&mid=WC0b01ac05805c516f)
  6. European Medicines Agency. Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product [homepage on the Internet]. [cited 2016 Oct 20]. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_001408.jsp&mid=WC0b01ac05806403e0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001408.jsp&mid=WC0b01ac05806403e0)
  7. U.S. Food and Drug Administration. FY 2016 Regulatory Science Initiatives Part 15 Public Meeting [homepage on the Internet]. [cited 2016 Oct 20]. Available from: <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm489572.htm>
  8. Authors are Steering Committee members of the NBCD Working Group hosted at the Dutch not for profit organization Lygature, the Netherlands. *Generics and Biosimilars Initiative*. EU guidelines for nanosimilars [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Oct 20]. Available from: [www.gabionline.net/Guidelines/EU-guidelines-for-nanosimilars](http://www.gabionline.net/Guidelines/EU-guidelines-for-nanosimilars)
  9. GaBI Online – Generics and Biosimilars Initiative. US guidelines for follow-on NBCDs [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Oct 20]. Available from: [www.gabionline.net/Non-Biological-Complex-Drugs/Guidelines/US-guidelines-for-follow-on-NBCDs](http://www.gabionline.net/Non-Biological-Complex-Drugs/Guidelines/US-guidelines-for-follow-on-NBCDs)
  10. World Health Organization. Guidelines on evaluation of Similar Biotherapeutic Products (SBPs) [homepage on the Internet]. [cited 2016 Oct 20]. Available from: [http://www.who.int/biologicals/areas/biological\\_therapeutics/BIOTHERAPEUTICS\\_FOR\\_WEB\\_22APRIL2010.pdf](http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf) © World Health Organization 2009
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