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David Ebsworth[1,2]

[1]Vifor Pharma Ltd, Switzerland

[2]University of Surrey, UK

Challenges with Non-Biological Complex Drug (NBCD) products and their follow on copies: Complex drugs in a complex environment

NBCD products are synthetic innovator-driven drug products and their copy versions. NBCD products typically also use nano-technology to exert their specific clinical effect. Examples include drug carrying liposomes and emulsions, iron-carbohydrate complexes and glatiramoids. Their complexity is high and their characteristics are defined by a complicated manufacturing process which has to be well-controlled to reproduce the drug product. In contrast to a well-defined small, low molecular weight drug, the comparability exercise of a NBCD follow-on version with the reference innovator drug product is difficult and the therapeutic equivalence assessment of the two drug products is challenging. A totality of evidence approach and an absence of clinically meaningful differences will define the place in therapy. In contrast to the regulatory equivalence evaluation which is well established for classical generics and biosimilars, the approval and post-approval standards for NBCD products are globally unaligned. Copies of NBCDs are similar to but not the same as the reference product, they have more in common with biosimilars. Discussions are ongoing in the United States, triggered by an analysis requested by the Energy and Commerce Committee of the House of Representatives as to which is the appropriate approval pathway. Intravenous iron sucrose (IS) formulations present an example of a NBCD product family where different regulatory strategies for follow-on versions were and still are being followed in different parts of the world. In the early 2000 iron sucrose similars (ISS) have been authorized based on the generic paradigm in a number of EU countries (decentralized procedure). IS is considered a simple small molecule and the complex, nano-colloidal character of the IS dispersion is not recognized. In the post-approval period non-clinical and clinical comparison studies with ISS and the IS original were published showing significant differences between the drug products. In 2011 EMA published a reflection paper (RP) on iron-based nano-colloidal products developed with reference to an innovator drug which was updated in 2015. This RP indicating that quality characterization on its own would not provide sufficient assurance of the similarity between the two products. Quality, non-clinical and human PK studies are needed for the evaluation. The RP on parenteral iron nano-colloidals must be read in connection with other EMA documents e.g. on liposomes and with ICH guidelines for biotechnological drug products. FDA also has issued industry guidance documents on intravenous iron colloidal dispersions to address the complexity of these products and the challenges when using the equivalence paradigm of generic complex drug products. Differences in physicochemical properties may result in differences in stability or distribution pattern *in vivo* like in iron-carbohydrate complex drugs. For NBCD nanomedicines scientific gaps have to be filled to understand the observed and reported differences between the performance of innovator and follow-versions. This science base should help all stakeholders: regulatory scientists, industry scientists, academics, medical professionals to develop globally aligned science base standards for approval of NBCD follow-on products to ensure product efficacy and safety for the patient. The approach taken for biosimilars is a model which can be adapted to NBCDs.

Recent Publications

1. D J A Crommelin, J S B de Vlieger (eds) (2015) NBCDs, the scientific and regulatory landscape. AAPS Advances in Pharmaceutical Sciences Series Springer International Publishing Switzerland. ISBN 978-3-319-16240-9.
2. S Mühlebach, B Flühmann (2015) Iron carbohydrate complexes: characteristics and regulatory challenges. In: DJA Crommelin, JSB de Vlieger (eds). NBCDs, the scientific and regulatory landscape. AAPS Advances in Pharmaceutical

Sciences Series vol 20. Springer International Publishing Switzerland. ISBN 978-3-319-16240-9.

3. N Zheng, D D Sun, P Zou, W Jiang. (2017) Scientific and regulatory considerations for generic complex drugs products containing nanomaterials. AAPS J doi:10.21208/s12248-017-0044-1.

Biography

David Ebsworth has over 35 years of experience in the Global Pharmaceutical industry, largely with Bayer AG covering senior management roles in Leverkusen, Germany, the US and Canada. Aside from Bayer, where he worked for over 19 years, he spent two years as Chairman of A&D Pharma-Holdings NV in Bucharest, Romania. He also served as Chief Executive Officer of Oxford Glycosciences (OGS), a biotech company listed on the LSE and NASDAQ stock exchanges, which was acquired by Celltech plc (now part of UCB) in 2003. OGS was the world leader in proteomics and had development compounds for Gaucher's disease and cancer. He has served on a number of Boards within the pharma, biotech and venture capital sectors, in the UK, Germany, the US, Austria, Italy, Israel, Netherlands, and Japan. During the past five years, he has held directorships at Xention Ltd, Wilex AG and Intercell AG. He was CEO and Chairman of Executive Committee; responsible for the Galenica Group, coordination of Sante Business and CEO of Vifor Pharma for almost three years until August 2014, after which he remained for an year as Executive Vice President, supporting two new CEOs.

david.ebsworth@web.de

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