Book chapters in “Non-Biological Complex Drugs - The Science and the Regulatory Landscape”

Introduction: Defining the Position of Non-Biological Complex Drugs

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Abstract In the first chapter of this book the concept of non-biological complex drugs (NBCDs) is introduced. These are complex drug products but don.t fall in the category of ‘biologicals. NBCDs were earlier defined as: medicinal products, not being a biological medicine, 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 physico-chemical analytical means. The composition, quality and in vivo performance of NBCD are highly dependent on the manufacturing processes of the active ingredient as well as (in most cases) the formulation (Crommelin et al. 2014). Examples of NBCDs are iron-carbohydrate complexes, glatiramoids, liposomes, polymeric micelles, swelling polymers and many (other) nanomedicines. A number of these (and related) NBCD-families are dealt with in 8 chapters of this book. As complex drug products request sophisticated analytical means for characterization of their structure and in vivo performance, ample attention is paid to the analytical challenges in two separate chapters. Finally, a perspective regarding NBCDs is given from the regulatory side.

Chapter 1, (p1-8)

Iron Carbohydrate Complexes: Characteristics and Regulatory Challenges

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Abstract Iron carbohydrate complexes for IV therapy consist of nanosize range particles with a polynuclear Fe(III)-oxyhydroxide core and a carbohydrate shell. They are pro-drugs. The iron complexes are stable on the shelf and are modified upon intravenous administration. The iron carbohydrate nanoparticles interact with cells of the innate immune system for uptake and release of iron into the physiological iron metabolic pathways: i.e. phagocytosis by cells of the RES, cleavage of the carbohydrate shell from the iron core which has to deliver the iron to physiological pools after release into and transport through the blood. They are non-biological complex drugs (NBCDs) i.e. showing polydispersity (non-homomolecular structures), cannot be fully characterized, and are highly dependent on a well-controlled manufacturing process.

Iron carbohydrate complexes are nanomedicines or nanocolloidals. Absorption, distribution, metabolism, and excretion (ADME) profiles have to be investigated and defined by appropriate in vivo test systems. The “nanoparticular” properties are key to their specific disposition which also influences pharmacodynamics and therefore efficacy and safety.
Sensitive biomarkers to correlate fate, efficacy and safety of the products have to be defined and used to ensure therapeutic equivalence when comparing products, especially also follow-on versions developed with reference to an innovator product. These follow-on versions, called nanosimilars, have to undergo a stepwise similarity approach to establish their therapeutic equivalence.

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Published in :
Non-Biological Complex Drugs - The Science and the Regulatory Landscape; AAPS Advances in the Pharmaceutical Sciences Series, 2015, © Springer International Publishing Switzerland
doi: 10.1007/978-3-319-16241-6_1
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