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Complex Drugs: What Are They and Why Do They Need Special Attention?

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1. Introduction

The rise of bio- and nano-technologies has accelerated the development of complex medicines, and at the same time it has revealed new hurdles in regulatory science and accelerating patient access to new therapies. Complex medicines include biologics (e.g. vaccines, gene therapies, recombinant proteins) and non-biological complex drug products (NBCDs). Their diverse nature poses challenges for the development of regulatory guidelines. While complexity is not new in medicines, our technical capacity to measure and analyze data has increased. This requires a determination of which measurements are relevant to demonstrate therapeutic efficacy and safety. Further, many obstacles remain in regulatory harmonization across global authorities, given their different approaches and legal frameworks.

To advance research and build consensus, it is necessary to engage together key stakeholders from academia, regulatory bodies, industry, and drug manufacturing. The Non Biological Complex Drugs Working Group hosted at the not-for-profit Foundation Lygature was established to do exactly that. Three action lines were defined:

- Create awareness of the intricacies of complex drug products
- Build understanding of the challenges with characterization of complex drug products, including the determination of Critical Quality Attributes
- Aim for alignment across the globe on rules and regulations for complex drug products.

Over the years, many scientific publications have been published with the involvement from scientists of the NBCD WG. The papers have identified the best scientific approaches for complex medicines development and regulation, have out-

lined outstanding challenges in the assessment of equivalence, and touched upon how to improve timely patient access for new medicines. The discussions continue to facilitate the translation of scientific findings into advancements in medicine for the benefit of patients.

2. Results

The basic assumption for regulating small molecule medicines is the full chemical and physical characterization of the active pharmaceutical ingredient. The active pharmaceutical ingredient in the innovator or generic product are equal or identical. However, there is a fast-growing category of complex drug products where such full characterization is not possible.

Biologics are loosely defined as medicinal products produced by living organisms and are typical examples of these complex medicines. There are also non-biological complex drugs (NBCD). These NBCD products stand out for a number of reasons: 1) they are not produced by living organisms, 2) they cannot be fully characterized, 3) full control over the details of the manufacturing process is critical for the reproducibility of their clinical performance. Examples of NBCD product families are liposomes, glatiramoids, iron-carbohydrate complexes and a growing number of nanomedicines.

For complex drugs the small molecule generic drug paradigm in which pharmaceutical equivalence plus bioequivalence leads to therapeutic equivalence needed adjustments. For generic versions of small molecule medicines, the terms 'equal' and 'identical' are key words, for complex drugs 'similar' is considered more appropriate. That leads to still ongoing discussions on the question: how similar is similar?

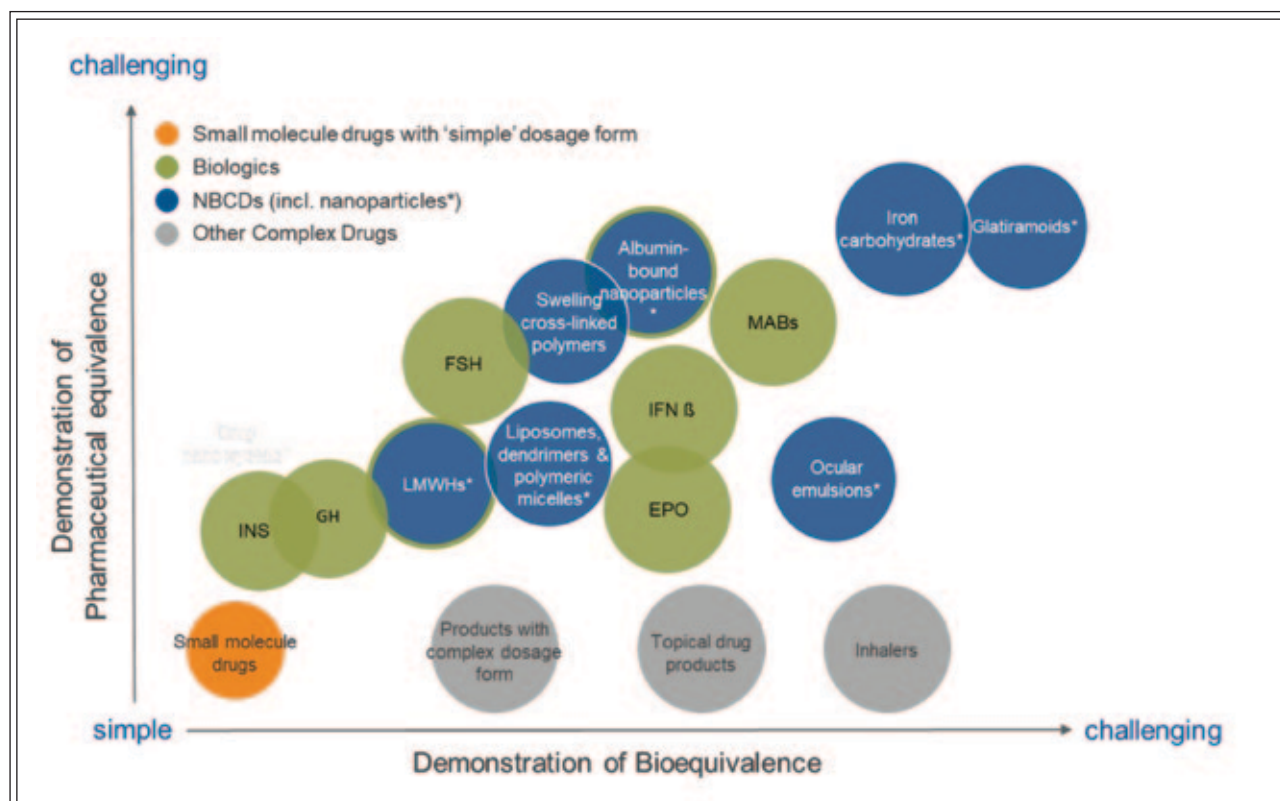


Figure 1: The complex drug landscape (illustrative). Drug products are positioned on the basis of the challenge to assess pharmaceutical equivalence (PE) and bioequivalence (BE) of two drug products (i.e., the reference product and its generic version). Conventional low-molecular-weight drugs that can be fully characterized are shown in orange; demonstration of PE and BE is relatively simple. Biologics are shown in green, NBCDs are shown in blue, and other complex drugs are shown in grey. Albumin-bound nanoparticles and low-molecular-weight heparins are blue with a green outline (classification of these drugs varies across the globe). Adapted from Hussaarts et al.).

4. Conclusions

In conclusion, the regulatory processes for the approval of complex drug products are evolving fast. So is the complexity of products, being biologic or non-biologic. The growing importance of biotech products will increase our experience with biosimilars and lead to adjustments of our present views.

Experts start to realize that additional attention to the review process of these complex drugs has to be paid. The publication of guidance documents and reflection papers is proof of that growing insight. Significant differences exist between the policies to regulate this type of products in the EU and the US. During the DDRS2020 meeting, more attention will be paid by various speakers to this topic.

5. Acknowledgements

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