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How to Deal with Complexity of Nanomedicine in Practice

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1. Introduction

Nanomedicine is a promising innovation path for drug research and development with increasing reality over the last decades; a high number of nanomedicines is in clinical evaluation. Copies of the first generation innovator nano products, called nanosimilars in the EU, aim for market access to substitute or being interchanged with reference nanopharmaceuticals. Biological and non-biological complex drugs (NBCDs) belong to these nano drug products. They are highly complex regarding the non-homogenous composition, and structure. Critical Quality Attributes (CQA) define the profile *in vitro* and *in vivo*, ultimately dependent on specific not fully understood structure-function correlations originating from a critical drug manufacturing process (fig.1).

In contrast to biologicals, the regulatory evaluation and approval of the synthetic NBCDs is highly jeopardized by the not defined equivalence assessment for their copies and a globally not harmonized approach. Selection and use of such nanosimilars in practice has revealed unexpected equivalence problems asking for guidance, knowledge-based standards, and practice to guarantee safe, reliable, and consistent nanopharmaceuticals and similars based on a sufficient regulatory simi-

larity / comparability exercise to allow only switching or interchange for therapeutically equivalent products (2-5).

2. Nanomedicine opportunities and characteristics

Nanotechnology and nano size render drug products different from existing, well-defined small molecular drug products. These aspects have an important impact on improved drug dissolution and reliable drug bioavailability (e.g. by nanocrystals) and on a specific drug targeting by overcoming tissue barriers leading to better efficacy and safety (e.g. by liposomal or solid nanoparticle drug products, fig. 2). Such nanopharmaceuticals are able to address so far not achievable therapeutic needs with better tolerability and effectiveness of nanopharmaceuticals in the individual patient (personalized medicine). These drug products show a high variety and complexity in (surface) structures, composition, and their modifications and are strictly governed by the difficult to control and mostly intellectual property-protected manufacturing process with defined ranges of specific characteristics for batch-to-batch consistency (fig.1,2). There is no universally accepted definition of nanomedicine. However, this discipline covers the science and technology of delivering nanosized drugs or drug carriers to specific cell types and structures not targeted by conventional drug products. Nanopharmaceuticals or nanomedicines are merely defined by their size only, although a critical size factor of 1-100nm is recommended by the EU (6). FDA considers

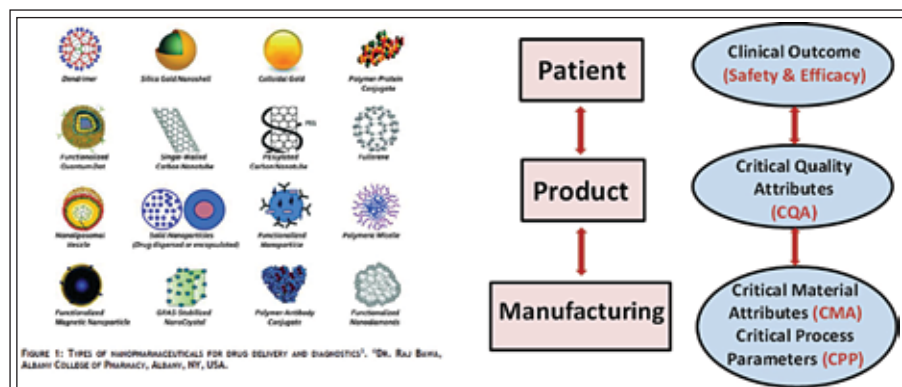


Figure 1 Structure variety and critical attributes showing the complexity of nanopharmaceuticals (1)

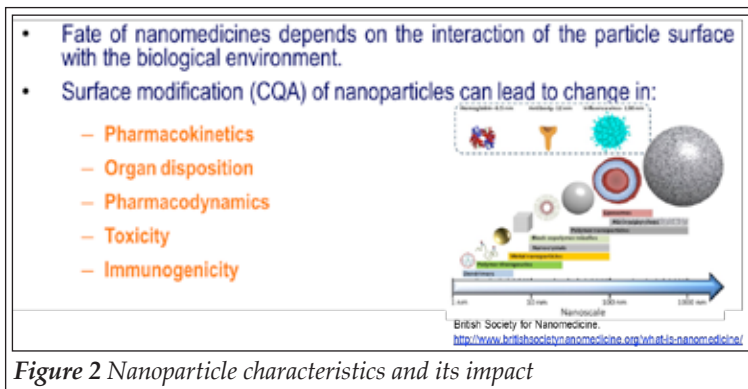


Figure 2 Nanoparticle characteristics and its impact

if either a material or end product is engineered to have a dimension/structure in this nanoscale range or exhibits properties attributable to its nanoscale dimension ranging up to $1\mu\text{m}$ (7).

3. Nanosimilars: regulatory consequences for substitution or interchange

These complex biologics and NBCDs are different in size, structure, stability, and immunogenicity compared to fully defined low molecular drugs. Follow-on versions of nanopharmaceuticals are only similar and cannot be evaluated according to the established generic paradigm where pharmaceutical equivalence (PE) plus bioequivalence (BE) indicate therapeutic equivalence (TE). These complex drugs cannot be fully characterized *in vitro*. Their follow-on versions are not the same requiring an extended and challenging equivalence assessment (8). The bio-similar pathway represents a separate regulatory evaluation procedure, initiated and established by EMA and universally agreed and applied. In contrast, synthetic nanosimilars do not have such a well-defined or world-

wide accepted evaluation pathway. NBCD similars, by definition, cannot be considered as biosimilars and a different regulatory assessment has to be used for these nanoparticulate follow-on versions. The difficulty to evaluate and compare pharmaceutical and clinical properties, a lacking centralized procedure in the EU and in other regions together with missing awareness of their nano properties, led to inconsistent national authorizations of nanosimilars with insufficient TE to the reference product. This was only shown, e.g., for iron sucrose similars, after their approval and use in practice for substitution and interchange. The lacking well-defined abridged regulatory approach for nanosimilars induces an increasing use of the hybrid pathway in the EU (art. 10(3)). Although compliant with requirements, this approval cannot claim chemical identity (PE) and substitutability (1,2,8,9). The missing understanding of the regulatory approval among health care professionals (HCPs) including the hospital pharmacists (HPs) is crucial for the practical drug selection and use of nanosimilars in the drug formulary and the absence of guidance for drug handling and use. Patients on stable nano drug regimens might be exposed to safety and efficacy risks and increased therapy costs upon interchange. The insufficient knowledge and inappropriate use of colloidal iron sucrose and their similars by HPs was revealed in French and Spanish hospitals (8). Lacking interchangeability was also demonstrated on obvious quality differences when diluting similar and innovator i.v. iron colloids for ready-to-use administration (10). Specific

Pharmaceutical quality	Efficacy/safety	Manufacturer considerations	Product considerations	Hospital and patient factors
<ul style="list-style-type: none"> • Chemical composition • Identity • Quantity • Pharmacopoeial specifications • Particle size and size distribution • Particle surface characteristics • Unchanged pharmacological active moiety fraction • Storage stability 	<ul style="list-style-type: none"> • Pharmacokinetics <ul style="list-style-type: none"> > Uptake > Distribution • Clinical data • Range of indications • Immunogenicity • Potential for therapeutic interchange • Number of similar agents on formulary • Pharmacovigilance requirements 	<ul style="list-style-type: none"> • Supply reliability • History of drug shortages • Supply chain security • Anti-counterfeit measures • Patient assistance programs • Reimbursement support • Manufacturer services, expertise 	<ul style="list-style-type: none"> • Product packaging and labeling • Bar coding • Compatibility with CSTDs*, robotics • Ready-to-use preparation and administration <ul style="list-style-type: none"> > Stability for ready-to-use administration • Storage requirements 	<ul style="list-style-type: none"> • Economic considerations <ul style="list-style-type: none"> > Hospital > Payer > Patient • Transitions of care • IT and medication system changes • Educational requirements • Pharmacovigilance requirements

Figure 3 Formulary selection criteria for nanosimilar drug products (11)

additional evaluation criteria for nanopharmaceuticals are requested for the hospital formulary selection (fig.3). Documented guidelines must ensure appropriate storage and handling including a carefully evaluated and restricted substitution or interchange policy.

4. Conclusion

Education on nanopharmaceuticals for HPs and HCPs is an urgent need to properly deal their complexity in practice.

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