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Nanomedicines – Ensuring Patient Safety through Regulatory Clarity

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1. Introduction

Science and technology have never moved as fast as now. With personalised medicines and the advent of gene and cell therapy, the standard rule book is clearly coming under pressure. It would appear that the same is true for the understanding and definitions behind the technology of nanomedicines.

Nanomedicines and their follow-on products, also referred to as nanosimilars, are complex molecules and so regulatory oversight must be scientifically fit for purpose. It is important to note that a survey (1) carried out in 2018 reported "…strong regional differences in the regulation of nanomedicines and confirmed the need for a harmonisation of information requirements on nano-specific properties". And so experts believe that the level of data for market authorisations is not consistent across EU countries.

In addition, protocols used in clinical trials are not of a level of detail to allow a full and consistent interpretation of clinical trial results and outcomes. This creates challenges for the capability of the regulatory framework to adequately assess copies.

There is evidence that such "follow on copy" products do not deliver the same efficacy and safety (2).

EU regulatory agencies are becoming more aware of the complex issues surrounding the correct criteria to ensure that follow on nanomedicines are indeed truly similar. Within this context, a centralised regulatory process that addresses this is needed at EU level and, in the absence of a tailored regulatory pathway similar to the biosimilars one, the EAASM strongly believes that all future nanosimilars should go through the Hybrid Application process (10.3) and NOT the generics application process (10.1) (3). This pathway, if consistently applied and aligned to the draft guidance (4) which the EMA has produced for specific types of nanomedicines would ensure that follow-on copies are therapeutically similar to their originator and therefore improve patient safety.

Regulatory harmonisation is needed within the EU but also internationally and the fact that the European Medicines Agency supports international harmonisation of regulatory science standards through initiatives such as International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is to be applauded.

In the absence of clarity on nanomedicines regulatory pathways and a legal definition, more scientific, policy and practice knowledge on the quality, safety, and efficacy of nanomedicines and nanosimilars must be gained among all stakeholders including payers and health care professionals. There is therefore a need to build a consensus dialogue as well as alignment between all players in Europe and beyond. This paper aims to catalyse discussion and galvanise consensus so that existing as well as innovative nanomedicines can realise their full potential and thus take their place in this exciting and new field of medicine to the benefit of patients. We hope very much that the EAASM's endeavours to highlight this area will indeed accelerate this process.

2. New nanomedicines to meet unmet medical needs

Nanotechnology is a compelling and growing scientific field that provides numerous opportunities for life science organisations to develop innovative medicines to address unmet medical needs and create alternatives for many therapeutic areas (5).

Many nanomedicines and nanodiagnostics have already received product licences and are being used in the clinic, and many more are in clini-

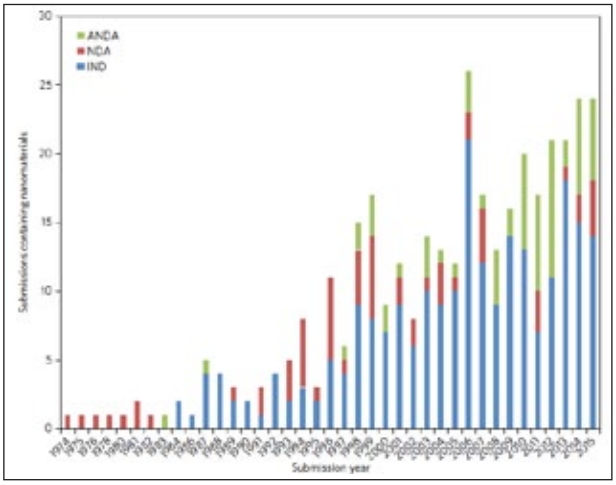

Figure 1 *Number of nanomaterial product applications submitted to CDER by year. Applications are separated as INDs, NDAs and ANDAs.*

cal trials (8). Currently, the most active areas of nanomedical research and product development are in cancer, inflammation/immune/pain, infection, anaemia, imaging, biomarker detection, parenteral nutrition, endocrine/exocrine disorders, cardiac/vascular disorders. With many types of formulations: intravenous, oral, ophthalmic, inhalation (oral/nasal), topical (skin), intramuscular, vaginal, others

Figure 1 clearly shows the increasing number of applications being made.

Nanomedicines have a rich history of clinical success in treating anaemia, cancer and neurological disorders.

However, their physico-chemical properties and biological properties depend on the manufacturing process as subtle structural modifications may effect the stability of the preparation (6,7). This is a crucial point as, if we take the example of intravenous iron products to treat iron deficiency, several iron sucrose similar (ISS) preparations have been introduced in a number of countries worldwide (8) on the basis that they can be considered therapeutically equivalent in terms of safety, efficacy and quality to their originator. Alarmingly this has proven not to be the case. A study carried out in 2009 demonstrated that a "… switch from the originator IS to an ISS preparation led to destabilisation of a well-controlled population of hemodialysis (HD) patients and incurred an increase in total anemia drug costs. It can therefore be strongly argued that prospective comparative clinical studies are required to prove that ISS preparations are as efficacious and safe as the originator i.v. IS".

3. Conclusions and Call to Action

There is a need to build a consensus dialogue as well as alignment between all players in Europe and beyond. A useful comparison can be made with that of the regulatory pathway that was evolved for biosimilars.

The EAASM is therefore advocating for:

a) a scientific consensus on definitions for nanomedicines across Europe whilst at the same time greatly improving education and a fostering of awareness on the complexity and sophistication of nanomedicines among; policymakers, prescribers, payers and patients
b) a harmonization of information requirements of regulators in order to correctly characterize nanomedicines
c) clear regulatory criteria, including clinical trial data, for the approval of follow-on/nanosimilar medicines to ensure patient safety.

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