

Translational research in Nanomedicine: 30 years of clinical practice, the Science, the regulatory path and the challenges.

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Nanomaterials intended for clinical use have to be evaluated under very strict requirements existing for all clinical products. Within different regulatory frames the most strict is certainly the one devoted to medicinal products. During the last three decades of clinical experience, more than 40 products were given final approval for clinical routine use and hundreds given partial authorization under the approval of specific clinical trials in different stages (Phase I, II or III). The requirements for clinical use (under clinical trials or in final marketing authorization) are known and have been tested against different technologies and materials. It's a very good example of how an existing regulatory frame can incorporate technological innovation and deliver adequate scientific appraisal preserving patients/populations safety, incorporating risk management approaches.

The toxicity/immunotoxicity of the product as a whole and all the components (they may ultimately be released by degradation/metabolism) must be considered in the context of the proposed route of administration from the beginning. A recent statement "interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient" was not a well-informed observation. Over many decades, pharmaceutical scientists from academia and industry have studied the general toxicity, hematocompatibility, complement activation, immunotoxicology, pharmacokinetics, toxicokinetics, and metabolic fate of novel materials proposed for use as components of advanced drug delivery systems. Moreover all the nanomedicine products entering clinical development must be subjected to rigorous, often "good laboratory practice" (GLP), preclinical evaluation. There are important points to make in relation to the complex, novel, and often hybrid nanomedicines emerging now. Some researchers often claim that their material or technology is "biocompatible" or "biodegradable" without any robust scientific experimentation (in vitro or in vivo) to back their statement. (In the context of a medicinal product rather than a biomaterial the term "toxicity" is more appropriate than "biocompatibility" as they have different meanings). Cytotoxicity studies often use short time frames (hours) chosen to match in vitro pharmacological experiments without any consideration of likely clinical pharmacokinetics (patient exposure can be hours, days, or months), and the concentration range used is too low to define an inhibitory concentration for 50% cell kill (IC₅₀). Such statements promote dogma that pervades the literature. Claims of biodegradation are rarely qualified by time frame or the mechanism. Many natural polymers, e.g., alginates, chitosans, dextran, are poorly degraded by mammalian enzymes, and many materials actually never access the physiological compartment (maybe intracellular) where the target mammalian catabolic machinery resides. Additionally, chemical functionalization can render a natural polymer effectively nonbiodegradable. Misuse of the terms "biocompatibility" and toxicity is also exemplified by the frequent misuse of the term GRAS (generally recognized as safe). The FDA term GRAS is a designation given to a specific material (designated specification), for use at specific doses and via designated routes of administration.

There is frequently failure to realize that materials approved for topical or oral administration maybe entirely unsuitable for parenteral use.

Techniques used to evaluate nanomedicine safety continue to evolve. Screening often uses in vitro cytotoxicity testing (e.g., polymers, dendrimers and polymeric nanoparticles) to give an early indication of the material suitability for a particular use. Microscopy (TEM/SEM and light) is also used to highlight subtle cellular changes, but such techniques require careful interpretation as sometimes methodology used can introduce artifacts ("seeing is not always believing"). It has been noted that when synthetic polymers and nanomaterials are administered together with noncovalently or covalently conjugated cytotoxic agents, DNA, or antigens, they can markedly alter genetically controlled responses, and this has given rise to studies designed to explore polymer genomics. To note, for useful data to come from biological assays, nanomaterials must be reproducibly manufactured and well characterized. Putative parenteral nanomedicines displaying acceptable toxicity in vitro must then be

subjected to rigorous investigation of their antigenicity, immunotoxicity, and potential to activate complement.

Development of specific in vitro assays that can be validated for nanomaterials is to be applauded, but the establishment of meaningful high-throughput screening, especially in the context of safety evaluation that can be optimal for all nanomaterials, is not without challenges. For each nanomedicine it is essential to choose a specific portfolio of tests and the assays used must be carefully optimized, for example by (i) using time frames that are relevant to material's pharmacokinetics (single time point readouts can easily give false positive or false negative results), (ii) using the cell lines to which the material will most likely be exposed (primary cells may be needed, and all cells in vivo will be exposed to serum), and (iii) using analytical techniques only where it is known that the analyte does not interfere with the assay readout.

All nanomedicines must display an acceptable risk_benefit with respect to proposed use, and early safety studies should be used as a stop_go checkpoint to decide whether or not the technology has promise for further development toward clinical trials in the context of the proposed use.

Current developments in the research landscape of nanomedicines brought the attention to the fact that as an already well established area of clinical practice, it now faces also some questions previously addressed by new chemical entities and biologicals. The current regulatory path has to be perceived in order to understand exactly the implications coming from the legislative and regulatory European frame.

We will discuss the issues bringing together the regulatory path and the underlying Science.

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