

How do we develop nanopharmaceuticals under open innovation?

Michael A.W. Eaton, PhD*

European Technology Platform for Nanomedicine, Berlin, Germany

Received 18 May 2011; accepted 18 May 2011

Abstract

It is incumbent on nanomedicine researchers to understand how to develop their ideas into commercial drugs; success to date has not been as good as funders would have liked. This article attempts to outline, perhaps for the first time, some of the expertise that the pharmaceutical sector has acquired to facilitate translation. It is hoped this explanation will start to improve the planning required at an early stage to develop nanopharmaceuticals and to encourage researchers and their institutions to devise a development plan.

© 2011 Elsevier Inc. All rights reserved.

Key words: Translation; Commercialization; Nanomedicine; Development; Social responsibility

Medicines are therapeutics, administered to patients by clinicians, but manufactured and researched in most cases by for-profit industry. Pharmaceutical production is the most regulated or controlled industrial sector; it is also a sector facing serious market and reimbursement hurdles.

The government approval of medicines is based on scientific evidence and hence on good applied science. The development of drugs has been refined in pharmaceutical companies, but with the arrival of Open Innovation, research partnerships with small and medium enterprises (SMEs), and even among collaborating academic groups, are now possible and actively sought. This collaboration reduces industry's exposure to research costs but the drug development expertise and the associated supporting costs are effectively transferred to the partners. In most cases this circumstance is a recipe for disaster with very little *translatable* applied research being carried out. In some instances this is willful, but in most cases the new partners have no knowledge of drug development or of its requirements.¹ Why is such research funded in this knowledge vacuum? Such research and development were and are now a

global competition. This article attempts to rectify this ignorance but it falls well short of being comprehensive and some information is of necessity too brief.

There are three main areas where projects fail:

1. Choice of research areas — Some are much more developable than others.
2. The selection of therapeutic agent — Most are not developable.
3. The Peer Review Process — Why should academic experts know what is translatable and what is not? Translation expertise is a completely separate skill and a team game in comparison with academic research. To ignore this will lead, unless researchers are lucky, to no useful output.

Nanomedicines of course have the added complications for a drug being branded as “nano”; this is discussed below.

Nano

Nano is more of a political label than a scientific one in the present nano-pharmaceutical context. Declaring 100 nm as the upper level of “nano” sized units is an attempt to quantify what is in effect a continuous function, i.e., drug size; from this point of view, no scientific boundary exists between nano and non-nano scales. These artificial definitions are not recognized by industry, especially when some drugs are likely to be more than 100 nm. Industry, clinicians and patients have no need for a definition of nanomedicines as a category, because marketed nano-drugs do not carry the nano-label, but of course have to be precisely defined, safe and efficacious. Many authors argue

No conflict of interest was reported by the author of this paper with respect to the material published here. The views published here were not supported financially by any organization but are broadly endorsed by the ETP Nanomedicine.

*Corresponding author: European Technology Platform for Nanomedicine Secretariat, VDI/VDE Innovation + Technik GmbH, Department Innovation Europe, Steinplatz 1, 10623 Berlin.

E-mail address: nanomedicine@btinternet.com.

that nanoparticles (NPs) (as drugs) have unusual properties but this assertion promotes the false idea to the public that there is something unusual or uncontrolled in this size range. The properties of nanosized particles are understandable, at least on an empirical level, even if the physics still requires some greater understanding. There has been some recent debate in Europe as to the extent that nano-scientific research should be ring-fenced for funding. Should nanomedicine be distinct from medicine or nano-electronics be separated from electronics?

A better argument is that nanomedicine defines a new type of drug space, one which has only recently started to be explored. Novel chemical entities (NCEs) are the original drugs, as exemplified by aspirin; the 1980s saw the development of larger drugs called biologicals. Nanomedicines can be considered as synthetic drugs even bigger than biologicals (approximately 5 nm) and up to and including regenerative medicine (over 1 micron). This is useful drug space; the space has and will be developed, but there are challenges and opportunities in this area, as we know. Efforts to define the edges of drug space are unfortunately fruitless because drug size is a continuous function, but drug dimensions are mainly at the nanometer scale.

I have attempted above to define nanomedicine. For nanomedicine to make any sense, it is critical in the (near) future that it produces more marketable medicines. For drugs to be marketable, this production has to be planned and designed from the outset of research. Unfortunately many nanomedicine researchers do not have access to the knowledge of how to develop a drug. Although a translational advisory organization would be highly desirable, it does not exist and in its absence, each research group is strongly advised to come up with a strategy to access this largely unpublished information. The European Technology Platform for Nanomedicine in its various reports has made some suggestions about how to do this and these are available on the web.² At the moment the lack of commercial translatability of publicly funded healthcare research is a more important issue than the level of funding.

Among other areas, expertise is needed and should be sought in:

1. Regulatory affairs
2. Analytical methods and instruments
3. Manufacturing, process and scale-up
4. Pharmaceuticals
5. Market analysis
6. Soft information, competitor intelligence, and patents

Pharmaceutical companies have sequestered considerable knowledge about what can be developed and what is problematic (under existing conditions). It is impossible to document this expertise briefly, but the following (often encountered) issues should serve by way of examples only. They are listed under the translatability evaluation criteria shown below:

1. Safety evaluation
2. Technical evaluation
3. Competitive evaluation
4. Regulatory evaluation
5. Reimbursement evaluation
6. Commercial evaluation

Safety evaluation

Safety is about doing no harm, leaving no residues and causing no detectable biological changes in the patient at any level. Elements that have not been in humans before are problematic and have to have a *major* therapeutic advantage for them to be considered seriously. For example substitution of silicon for carbon has been considered by several start-up companies but given the lack of any real advantage, there has been little progress. Quite a few nanomedicines utilize silicon chemistry for linkers, due to their convenience, but this characteristic also makes them difficult to progress. It is essential that researchers consider this point. The argument that these are model systems does not impress investors or move drugs into the clinic expeditiously.

Most metals are similarly problematic, including gold, which tends to leave residues for extended periods and is seen by histology in the liver and spleen. It may well be that these residues are inert, but the government regulators will query the undesirable changes and remember the development costs to get to that point are huge. The exception seems to be iron and its oxides, which have been approved for imaging studies because they are cleared by the body. Many of the other transition elements are known to be carcinogenic.

Carbon nanotubes (CNTs) remain very much in the area of basic research. They must be shown to be quantitatively cleared *in vivo* by analysis of the mass balance; what goes in must be measured going out. Renal clearance is comparatively easily done in comparison with analysis of feces, but an extremely sensitive quantitative assay for the CNTs is necessary. Concentration on dialysis membranes is a good way of concentrating urine, but urine contains quite a few oligosaccharides. CNTs are structurally interesting but they have to have real therapeutic advantages to be worth the risk and cost of development. The advantages have not yet been proven and this remains a very high-risk technology. Novelty is not an advantage.

Although plants use silica structurally, its presence in animals has not been studied extensively. Low molecular weight silicates are renally cleared but the metabolism and clearance of macroporous silica has not been fully studied. Silica NPs are often used as carriers but their *in vivo* clearance needs proving. Especially challenging would be the analysis of silicon in body fluids.

The field of polymer therapeutics is well researched but with the exclusion of PEGylated proteins, few have reached the market. The reasons include:

- i. Analysis of polymers is challenging in a product made under Good Manufacturing Practice (GMP).
- ii. Regulators will ask questions about the metabolism of the linker chemistry. Given the polydispersity of the polymer, it will not be possible to do this using conventional mass-spectroscopy methodology.
- iii. The pharmacokinetics and elimination of nonbiodegradable polymers are difficult to follow using mass spectroscopy. NMR may be useful for some polymers, but polyacrylates do not have such a useful window in the NMR spectrum.

- iv. Some polymers have pharmacology of their own. This could be an opportunity therapeutically, but there are very few published studies.^{3,4}
- v. The cost of GMP polymers can be prohibitive and pharma generally wants multiple sources for raw materials.
- vi. Many polymers such as PEG are not metabolized in animals but the environmental fate of polymers is subject to regulation.⁵
- vii. Polymers such as PEG do not normally leave the blood (after lymphatic drainage) and therefore may not be able to reach the desired site of action except by taking advantage of the enhanced permeation and retention (EPR) effect.
- viii. Polymers by their nature are viscous. If it were to be injected quickly and painlessly using a fine bore needle (in a 1 ml volume), then this aspect of formulation should be considered.
- ix. Unusually the osmolality of PEG is a function of temperature, and this could be an issue for pain-free injections if it is ignored.⁶
- x. Although research is funded into new polymer therapeutics, their drug metabolism and pharmacokinetics (DMPK) properties are largely unfunded by grants; hence, their development is unlikely.
- xi. Immunogenicity and complement activation-related pseudoallergy (CARPA) may be enhanced by forming arrays or multimers.⁷

Naive immune systems often produce natural antibodies to synthetic and natural polymers.⁸ These antibodies have a weak affinity and are not abundant, but they can in some instances negate any therapeutic effect.⁹ It is thought this is one of the earliest defenses against disease and it is a fascinating active research area.

Technical evaluation

This should be an easier area for evaluation than others, but the requirements for academic publications are significantly less than those demanded by regulators. The main reason that many researchers' ideas are nontranslatable is that they cannot be scaled up for large-scale manufacturing. It is essential that if a drug were going into development its chemistry must be defined precisely and must be repeatable. I have seen failures due to the product specification being defined during development. The new drug must also be stable with regard to chemical and physical changes over at least a year. Chemical changes include hydrolysis, which may not change the drug's efficacy but does change its stated specification. All impurities greater than 1% should be known and measured, with maximum impurities of 3%; above this level it is not the same product and the batch will be discarded. Analysis of the product is simplified if site-specific chemistry is used to join entities together, rather than random attachment. If non site-specific linkage chemistry is used, it does raise the question to regulators whether all isomers have the same activity and poses the problem of whether that could be proven.¹⁰

Hydrolytically labile linkers (pH sensitive) are used in academic laboratories but these can be very problematical indeed in manufacturing, where consistency is essential. There is unfortunately no practical pH at which there is no hydrolysis, and expensive batches can be lost in manufacturing due to less control at scale-up. Another common linker chemistry that is problematical during storage is the maleimide – thiol adduct, a succinimide linkage. Both maleimides and succinimides are known to be susceptible to slow hydrolytic ring opening.¹¹ Appropriate substituents can alter the rate, but it remains a problem awaiting a proper solution.

Disulfide linkages are also often used in research labs but their manufacture to GMP at scale can be challenging due to disulfide interchange.

Nanomedicine drugs are generally injected, and this requires that the therapeutic dose be in one milliliter as this is the maximum tolerated volume. Consideration should be given to ensure that any carriers or excipients do not occupy too large a percentage of this volume, leaving no room for the therapeutic entity. Targeting entities, like antibodies, have a very small (by mass) carrying capacity, and the choice of drug is determined by this consideration. This limits the choice to a very small class of extremely potent agents.

Technical evaluation should define the success translation metric in the particular disease in question. For oncology, animal models with reduced tumor volumes are less impressive than xenograft models, with 100% survival against a control.

Nanomedicine can involve materials with a high cost; process costs associated with complicated processes can dwarf such considerations.

Competitive evaluation

It is normal commercial practice for manufacturers to know where their competition is likely to be when their putative drug enters the market. If a manufacturer is first or second to the market, it is not so hard to secure substantial market share, but after that, it is a difficult sell except via price, or there must be a major clinical advantage, which is often difficult to predict. An improvement in potency is not enough, because that is only a question of dose. Causing fewer side effects does not always guarantee reimbursement, but a measurably better therapeutic outcome is advantageous.

Regulatory evaluation

Regulations for approval are constantly changing, and similar earlier technical approvals are no guarantee of acceptance later. An example might be that detailed knowledge of *in vivo* polymer fate is required, but historically that was not requested because the required analytical science had not been developed.

Nanomedicines often take advantage of the EPR effect in entering inflamed or tumor tissue with a two- to threefold typical increase in the local concentration in rodents.¹² Unfortunately clinical studies would have to be quite large to see this comparatively small change in humans.

Regulators want to see quantitative evidence that all the constituents of the nanop pharmaceutical are excreted intact or

metabolized. This is very problematical for many of the rather exotic academic NPs being explored. This requirement is not industry being conservative; it is just impossible to progress drugs whose *in vivo* fate is unknown, or worse still, impossible to quantify. Such systems are dead ends and should be recognized as such, and not funded as applied research or effort must be put in to produce the data required.

The fate and impact of the nanopharmaceutical in the environment are also required to be known, this issue having arisen with silver NPs.¹³ Polymers like PEG are not metabolized by animals but are fortunately degraded by micro-organisms.

Some NPs (e.g., gold) are frequently defended as causing no biological problems because they are inert. However, they reside for a long time in some organs and show up as altered histology; this would lead to a difficult approval process.

These are not problems created by industry but by the existing regulations established to protect patients. The regulators are flexible, especially if there is the prospect of a significant improvement in the prognosis of a serious disease, but this is not often the case. Industry is not being conservative and indeed, as a sector, it is seeking new approaches, but it is a safety gatekeeper before the regulators.

Reimbursement evaluation

Researchers often think that getting their ideas to the clinic as quickly as possible is the solution for patients. However, reimbursement can often stop drugs from reaching patients due to the drug's cost. These costs reflect in part the cost of goods, but more important, the costs of earlier research and development failures and in getting the drug to the market. The therapeutic dose determines the cost of goods but generally once the cost of goods approaches more than \$100 per gram or monthly treatment costs of more than \$1,000, then cost becomes an issue. Surprisingly, clinical-grade polymers can be very expensive; process costs can be prohibitive and more than material costs if the process is not simple. A complicated process with many different elements in a final product is probably not feasible to manufacture.

Commercial evaluation

It is important that researchers take scientific social responsibility for their research. It should have real impact on science, as well as societal benefit or benefit for patients. This section is about commercial evaluation, but some projects may have significant societal value, though they will not be major commercial successes. Industry will determine whether the market is viable, given an approximate overall cost of \$1 billion to bring new drugs to the market.

Some drugs occupy niche markets and given the market's size, researchers must know how they will improve significantly on an existing therapeutic. Photodynamic therapy is a case in point, it is important that researchers understand the market to date.

Industry knows the history of areas where technical failures have occurred, such as molecularly imprinted polymers. These work out to be more expensive than antibodies and more

difficult to manufacture. Antibody production is very scalable and relatively cheap, in comparison with a complicated synthetic manufacturing scheme, as is required for synthetic oligonucleotides. Other areas where current industrial interest is weak are boron neutron capture therapy and radioimmunotherapy. Neither has shown great commercial success to date for different reasons.

The path to development

Nanomedicine experts must be responsible in their claims and know where they are on the development path. In many cases they may not even be on the path. Industry has evolved a series of decision points, milestones or gates for projects. These acceptance criteria are inevitably somewhat flexible for each project when moving from stage to stage, but it is useful to understand or know someone who understands the process.

The pharma sector milestone development with key decision points are shown below starting with the research stage. (The supplementary material, which *can be found in the online version of this article*, shows in greater detail the type of data required at each point. This covers the full development path from decision point 1 (shown in yellow) to the first time in humans (FIH), decision point 5.

It is hoped that describing the problems of pharmaceutical development of nanomedicines will not discourage researchers. Industry wants new products and these may come from “blue-sky” research or applied research. At the end of the day industry wants innovative products to ensure reimbursement. It is important for all concerned that communication about how to convert applied research to marketable drugs is available and, most important, considered seriously by healthcare researchers. It is vital to improve communication dramatically between the stakeholders if this field is to fulfil its potential, as quickly as patients' demand. Researchers should be mindful that their research, often paid for by the taxpayers, must deliver some value to society and that the debt be repaid.

No institution will have all the technical knowledge and the developmental knowledge; therefore each organization should consider how best to address these problems. The European Technology Platform for Nanomedicines has and continues to advise on this matter and much advice is contained in various reports that are available on its Web site and elsewhere.²

Appendix A. Supplementary data

Supplementary materials related to this article can be found online at [doi:10.1016/j.nano.2011.05.015](https://doi.org/10.1016/j.nano.2011.05.015).

References

1. Eaton M. Nanomedicine: industry-wise research. *Nat Mater* 2007;6: 251-3.
2. Nanomedicine: The European Technology Platform. <http://www.etp-nanomedicine.eu/public>. Accessed July, 2011.
3. Ackland G. Patent WO 2008/001053 A1 2008.
4. Ackland G, Gourine A. Patent WO 2008/001055 A1.

5. Parton T, King L, Parker G, Nesbitt A. The PEG moiety of certolizumab pegol is rapidly cleared from the blood of humans by the kidneys once it is cleaved from the Fab'. *Inflamm Bowel Dis* 2009;15:S56.
6. Winzor DJ. Reappraisal of disparities between osmolality estimates by freezing point depression and vapor pressure deficit methods. *Biophys Chem* 2004;107:317-23.
7. <http://www.seroscience.com/>. Accessed July, 2011.
8. Sauerborn M, Schellekens H. *Curr Opin Biotechnol* 2009;20:715-21.
9. Armstrong JK, Hempel G, Koling S, Chan LS, Fisher T, Meiselman HJ, et al. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy in acute lymphoblastic leukemia patients. *Cancer* 2007;110:103-11.
10. Junutula JR, Raab H, Clark S, Bhakta S, Leipold DD, Weir S, et al. Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index. *Nat Biotechnol* 2008;26:925-32.
11. Khan MN. Kinetics and mechanism of the alkaline hydrolysis of maleimide. *J Pharm Sci* 1984;73:1767-71.
12. Palframan R, Airey M, Moore A, Vugler A, Nesbitt A. Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis. *J Immunol Meth* 2009;348:36-41.
13. Asharani PV, Wu YL, Gong Z, Valiyaveetil S. Toxicity of silver nanoparticles in zebrafish models. *Nanotechnology* 2008;19:255102.

AUTHOR'S COPY