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Anticipating Market Introduction of Nanotechnology-Enabled Drug Delivery Systems

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Additional information is available at the end of the chapter

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1. Introduction

Nanotechnology-enabled drug delivery systems (NDDS) are associated with high expectations regarding their economic and societal value. NDDS are expected to contribute to important issues in healthcare such as enabling novel pharmaceutical therapies which only target the site of the disease and help to reduce costs of healthcare. To date, more than two dozen NDDS have been developed into marketed products and many more are under development [1]. Market forecasts have estimated that the market for these technologies will grow from US\$ 1 billion in 2010 to US\$ 136 billion in 2021 [2, 3].

The pronounced expectations surrounding nanotechnology-enabled drug delivery applications and its claimed market potential suggest that the path toward market introduction is clear. This is however not the case, as is often with newly emerging technologies. While for instance claims have been made about NDDS contributing to a reduction of undesirable side effects of drugs (compared to conventional delivery systems), to date limited clinical data is available to actually support such claims. Uncertainties about the application of regulatory regimes and which methodologies to apply in order to assess novel nanotechnology-enabled drug carriers have created further challenges for firms to introduce new products on the market.

Making promises is almost inevitable in order to attract attention and mobilize resources. However, too broad promises may make sponsors such as large pharmaceutical companies and venture capitalists reluctant. Uncertainties about the performance of specific future drug delivery systems, the demand for such technologies and how they will be evaluated by

regulatory authorities have contributed to impasses, 'waiting games' as we have called them [1, 4] which constrain development and potential market introduction of NDDS.

In such uncertain and ambiguous situations actors need to make sense of what is happening already and what might happen [5], before taking a specific course of action. There are two main strategies available to developers of NDDS to handle this challenging situation. Academic entrepreneurs and firms interested in developing and introducing NDDS on the market may view uncertainties regarding performance and value inevitable and/or postpone such discussions until a later stage and wait for the 'invisible hands' of the market to do its proverbial work. Or, they can anticipate reception of new products and interact with the broader environment to work towards the market introduction of what they consider to be desirable products.

Pro-active interactions will have to go beyond the promotion of promises of nanotechnology-enabled drug delivery systems in anticipation of the opening up of new markets. Market success of newly introduced NDDS products involves more than attractive sales figures. Deuten et al. [6] argued for broadening the notion of market success by thinking in terms of what they call 'societal embedding'. They characterized societal embedding by three dimensions (p. 132): (1) Integration: new technologies need to be integrated in industries and markets; that is, within business practices and repertoires of users, in this case clinicians and patients. (2) Admissibility: new products need to be acceptable according to rules and standards within the sector or set by the government. Think for instance of good manufacturing practices, pre-clinical testing and clinical trials. (3) Acceptance: new products have to be accepted by the public. That is, societal concerns should not be too strong, there should be sufficient articulation in order to make well-informed choices by clinicians and patients, and the product should actually be used.

Pro-active action then requires taking a broader perspective than that of a single actor, saying an academic researcher or a start-up firm with a patent in the field of NDDS. Societal embedding involves a variety of issues which create openings for different actors - who have different interests in, and perspectives on, emerging NDDS - to engage in strategic actions and interactions. In the drug delivery sector, firms, governmental bodies, health insurers, scientists, clinicians and patient organizations are all more or less involved in interactions with respect to one or more dimensions of societal embedding. Thus, important dynamics related to the market introduction of NDDS exist at the level of the drug delivery sector rather than at the level of individual academic or business entrepreneurs. Put differently, for the market introduction of NDDS entrepreneurial individuals and organizations are dependent on interactions with other players in the sector which is beyond their full control. Pro-active action then requires understanding of what happens at the level of the domain and feeding back such insights into individual or collective strategies to further development and market introduction of NDDS.

Anticipation on future market introduction and embedding may seem the wiser option compared to trial-and-error strategies, but is also difficult and precarious. Anticipation on how

new technologies become embedded is difficult in itself, due to uncertainties regarding how new products will eventually look like and their impacts. Anticipation of how other involved actors perceive and cope with parts of the embedding process and what this means for individual actors' strategies then introduces further complexities. Yet, taking into account these perspectives and strategies is exactly what is important in the case of the drug delivery sector, which consists of an intersection of different value chains with a large number of mutually dependent actors. Then how to anticipate future market introduction and embedding of nanotechnology-enabled drug delivery systems? How to support articulation of anticipatory strategies and decision making of, say academic and business entrepreneurs, taking into account other actors' perspectives in the domain of drug delivery systems?

The question of anticipation of future introduction and embedding of NDDS is a common challenge of emerging technologies. Within the field of technology assessment a number of approaches have been developed to deal with uncertainties of emerging technologies emphasizing interactive anticipatory approaches such as real-time technology assessment [7], anticipatory governance [8], interaction research in lab-settings [9] and constructive technology assessment [10]. Such approaches are devised to support stakeholders in their anticipatory competences and to support strategies and decision making. These approaches differ in terms of scope, i.e. which dynamics and actors are taken into account, and in their main target audience, i.e. whose strategy articulation and assessment is actually supported.

In this chapter I will focus on the approach of Constructive Technology Assessment (CTA) which has a particular emphasis on exploring future developments with stakeholders in a domain and feeding insights back to researchers and technology developers. This approach is by now well established and has been applied for different nanotechnologies and their applications. I will describe the methodology of CTA scenario workshops and demonstrate the approach by offering the results of a study [11] where this approach was used to map and support anticipation of opportunities and challenges of nanotechnology-enabled drug delivery technologies.

In section 2 I will start with offering a general perspective on how different types of actors perceive and assess emerging technologies. This is important to recognize when interacting with a variety of involved actors and forms the backdrop against which I position the methodology and approach of Constructive Technology Assessment and its scenario workshops. I will describe the CTA methodology and discuss how to organize and prepare for such interactive workshops. In section 3 I will set the scene for the workshops by briefly describing the main actors involved in the drug delivery sector and the promises of NDDS. In section 4 I will report on the preparation of the workshops and discuss in detail the main lines of discussion in the workshop and participants' assessments of the situation in which the drug delivery sector finds itself regarding emerging nanotechnologies. In section 5 I will conclude by summarizing main findings and reflecting on the merits of the CTA approach for anticipating, and supporting anticipation of, market introduction of nanotechnology-enabled drug delivery systems.

2. Constructive technology assessment & scenario workshops

2.1. Perspectives on emerging technologies

There are structural differences in how actors perceive and interact with novel technologies. In our modern societies there exists an asymmetry between those who develop new science and technology and those who are impacted by these developments. For one this is related to a difference in timing between the development and actual introduction of new technologies; for another it is related to differences in involvement and perspective of a variety of actors which to some extent is institutionalized in a historically grown division of labour regarding novel technologies. That is, there exists a separation between individuals and organizations involved in either the generation or the uptake – ‘selection’ - of technologies. For instance, technology actors have had ‘a mandate’ to develop new technologies and could confront society with new technologies when linked with ideals of progress. Even if this mandate is not taken for granted anymore, it has led to institutions and divisions of labour with respect to the promotion and selection or regulation - ‘control’ - of new technologies which cannot easily be undone [12].

For understanding actors’ perspectives and interactions regarding (emerging) technologies the actor typology developed by Garud and Ahlstrom [13] is helpful. Garud and Ahlstrom emphasize the structural difference in the ways actors assess technologies. They relate differences in views and action perspectives to two different positions: insiders and outsiders with respect to technologies. To emphasize the difference in position and style, rather than inside/outside boundaries, the terms enactors and comparative selectors have been proposed [14].

As we formulated in the yearbook *Nanotechnology in Society* [15], enactors, i.e. those who promote and aim to realize novel technologies “construct scenarios of progress, and identify obstacles to be overcome. They thus work and think in ‘enactment cycles’ which emphasize positive aspects. This includes a tendency to disqualify opposition as irrational or misguided, or following their own agendas. For nanotechnology, enactors now also anticipate obstacles similar to the ones which occurred for GMO (Genetically Modified Organisms) in agriculture and food, cf. Colvin [16].”

Enactors will identify with a novel technology and its applications such as nanotechnology-enabled drug delivery systems and may believe that the world is waiting for these products, e.g. because of its attractive performance characteristics and ‘a good product sells itself’. However, for ‘the world’ the product is just one of many options and it may see alternatives. This group takes a position of comparing and selecting different technological options, thus act as ‘comparative selectors’. While enactors may downplay considerations regarding costs and risks, selectors will often take broader evaluation frames where these considerations are put upfront [13: 40].

There can be different types of such so called ‘comparative selectors’. This act of ‘comparative selecting’ can be done on a professional basis, such as health insurance authorities deciding which novel drugs are worth reimbursing and to be included in insurance packages on the

basis of cost-benefit analysis, or the Food and Drug Administration deciding whether or not to grant market access to novel drugs. It can also be done by actors who are less tied to certain methods such as patients and their individual experience with specific medication. Public interest groups may act as selectors, for instance organizations which have opposed the introduction of GMOs or those who have called for more control and regulation of nanotechnologies such as the ETC Group [17].

These different positions may, and sometimes have to, interact with each other. For instance in the case of drug delivery, firms aiming to introduce novel drugs will at some stage have to interact with the US Food and Drug Administration and/or the European Medicines Agency or other regulatory body. Firms acting as enactors of drug delivery systems will have to act with pharmaceutical companies who (then) may act as selectors, choosing between different delivery devices to be used for their pharmaceutical agent. They may also meet each other at conferences or in dedicated discussion platforms which may be set-up to foster mutual understanding.

Actors pursuing promotion activities and actors pursuing selection activities will interfere anyway, eventually. The next step then is to identify where and when these activities interfere and what happens there. That is, what do these different actors learn at these occasions from each other. How does that shape how they view the novel technology under consideration and what does this imply for their strategies regarding development or uptake of novel technologies. Garud & Ahlstrom (1997) call such occasions 'bridging events' and discuss some examples.

The important point here is that such bridging events can be created on purpose. This can be done by technology enactors themselves who for instance engage in market research, or by selectors such as regulatory authorities who invite sponsors of new pharmaceutical therapies to discuss their future products and how to evaluate them. It can also be done by academic researchers or more disinterested actors who are working with the perspective of Constructive Technology Assessment (CTA).

2.2. Constructive technology assessment

The approach of Constructive Technology Assessment (CTA) has been developed since the 1980's and has become a key methodology within the field of technology assessment. It aims to broaden design, development and implementation processes rather than only assess impacts on novel technologies [18]. In CTA, technologies and their impacts are not seen as given. "For CTA, the dynamics of the process are central, and impacts are viewed as being built up, and co-produced, during the process of technical change. Many technology studies have shown that impacts are not just passive effects of a given technology on its environment, but are actively sought (or avoided) by technology producers, users, and third actors such as governments, unions, and pressure groups alike" [18, p. 257]. Technologies and their impacts co-evolve, and actors involved try to shape this process and make assessments of what is happening or could happen.

CTA does not aim to introduce assessment – as enactors/selectors are making assessments the entire time- but rather to modulate ongoing processes of assessment and feedback into actor decisions and strategies with respect to technology development and introduction. In particular it aims to broaden actors perspectives by offering an overview of actors and aspects involved in development and embedding of emerging technologies [19]. Second, it aims to enrich actors understanding of the dynamics of such processes, for instance the role of reimbursement in health care innovations. By broadening and enriching perspectives of actors, CTA interventions aim to support individuals and organizations in identifying their role and impacts in the overall innovation processes. This helps actors to evaluate effects of their strategies and consider what they may need to change in their activities in the present and near future in order to work towards desirable outcomes (for instance to improve chance of market success of new NDDS).

While CTA events are an intervention, they are also a tool to understand what is happening in a particular domain of technology. They provide an entrance point to elicit perceptions of enactors and comparative selectors in an interactive setting. As we formulated it [15], it is creating and orchestrating spaces where interactions occur, even if the interactions between citizens/consumers and technology developers and promoters will always be partial (because of their difference in perspective). There will be “probing of each other’s realities” (as Garud and Ahlstrom (1997) called it), with more or less contestation.

The CTA workshop which convenes stakeholders in a particular domain, is a micro cosmos which reflects parts of the macro cosmos, in this case the drug delivery sector, through participants’ interactions and their assessments of the force fields in which they find themselves. The workshops provide a space in which actors with different socio-cognitive positions, which I summarized as enactors and comparative selectors, can interact. Thus, the temporary space is a bridging event, and is designed as a bridging event.

Within this general framing, CTA workshops are tailored towards stimulating actors’ anticipation of embedding through broadening and enriching actors’ assessments of ongoing dynamics, and actors’ articulation of possible embedding strategies. Facilitating interactions, especially mutual ‘probing’, between enactors and selectors is one of the mechanisms. At the same time, interactions between enactors and selectors offer insights into what is happening in a domain. Supported by careful preparation – ‘pre-engagement’ [20] – CTA workshops then provide a ‘window on the world’ to the participants; their world as it is, and might be in the future. The articulations in this micro cosmos then will offer a view of potential developments in the domain. On the other hand, the temporary (and protected) space of the workshop will not fully reflect the force fields in the macro cosmos. Still, the patterns that are found in actors’ articulations and their assessments of force fields affording actions, offer good indications. One reason is that participants probe into or comment on each other’s positions and considerations, introducing checks on what happens in the drug delivery sector.

In interactive workshops, probing and commenting can be supported by socio-technical scenarios. In the case of nanotechnologies, socio-technical scenarios are necessary to address their doubly fictional character [15]. Many of the expected applications enabled by nanotechnologies (and nanosciences) are still envisioned, part of ‘science fiction’. The eventual impacts

of such applications are unclear, and attempts to find out about impacts amount to social science fiction. Socio-technical scenarios capture ongoing dynamics and develop assessments of future developments. They show the effects of interactions between enactors and selectors which provides more substance to interactions in workshops as actors can draw upon the scenarios for inspiration.

The use of scenarios and interactive workshops has further effects. They provide participants in workshops with competences to support anticipation and strategy articulation. Tools such as scenarios, which are based on insights in ongoing dynamics and debates during interactive workshops, provide actors with understanding of the overall situation and clues for how to take into account ongoing developments and future impacts. So, while actors will likely value anticipation of embedding as a prudent strategy relevant for their own activities, they now are also provided with some skills to fill in such strategies.

2.3. Workshop design and preparation

To prepare for a CTA workshop, the actual 'engagement' between stakeholders, the organizers of this event need to prepare themselves, or 'pre-engage' with the technologies and domains under consideration, in this case NDDS in the drug delivery sector. Preparing for the workshops clearly includes an organizational component, such as identifying possible collaborators, preparing input documents for the workshops themselves, and interactions with participants and actors potentially interested in participating in the workshop. Preparing also requires analysis to support anticipation in a situation filled with uncertainties. This helps to focus the discussion on key issues and be more productive while at the same time the organizers should remain open for other themes and questions.

The organizers of a CTA event need to have a thorough understanding of the emerging science & technology. What are the dynamics in its development, to what extent is there still room to change the course of technology developments and how these technologies can be integrated in business practices, and how they are perceived by regulatory authorities and further individuals and organizations in society. A second requirement is that organizers need to have a sense of various actors' willingness to anticipate future developments and tune their activities with other actors in the domain. For instance some companies may not be willing at all to engage in co-ordination activities with other companies or societal actors. A third requirement is to identify, select and position potential participants which is related to their role in the overall technology development and embedding process. For instance large pharmaceutical companies are important in the overall innovation process and should ideally be included in such an exercise. For a productive discussion the workshops benefit from an appropriate mix of participants with an enactor or selector perspective toward the technologies under consideration [19]. Finally, the organizers should be aware of broader dynamics which may not always be immediately obvious to actors involved in developing novel technologies. In the case of the drug delivery sector, one may consider involving health insurers as they may be not directly involved in developing new options, but will definitely be important when new pharmaceutical options are introduced on the market.

The design of a CTA workshop can take different shapes, see also [19, 21], but will often be geared toward eliciting actors' perspectives on societal embedding of emerging technologies and to stimulate broadening and enriching of understanding of dynamics in development and future introduction of these technologies. To do so the workshop can be structured around two themes which will be recognizable for participants: (1) identification of challenges, opportunities and directions for development of emerging technologies in a specific domain; (2) identification of ways to cope with challenges and opportunities of these technologies. These are broad themes in order to simulate actors to articulate linkages between emerging technologies like NDDS and aspects of societal embedding and prevent too early lock-ins into particular options or strategies. Such open-ended character will often be unavoidable considering the emergent character of the application of technologies. It was intentionally open-ended in order to allow for open discussion

Some reduction of the open-ended character of these two discussion themes will be important in order to have a productive meeting and attract participants. In CTA workshops this is often done by means of a preparatory document which will be given to all participants, justifying and framing the meeting. To link up with interests of potential participants, such a document can identify key issues and dilemmas which will be recognizable to at least part of the participants. In addition the document will contain the scenarios about future developments. These scenarios depart from major challenges in the present situation and explore strategies to overcome them, including the possible responses of actors involved, for scenario methodology see also [15, 20, 22]. In this way the scenarios help to make anticipations of future developments concrete and can support actors in their formulation of strategies.

Finally, to stimulate an open discussion and overcome possible concerns regarding confidentiality, a CTA workshop can be held under the 'Chatham House rule'. This rule is as follows: "When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed" [23]. By adopting this workshop rule, the organizers aim to create an informal atmosphere and stimulate an open discussion.

Before I will discuss the results of the workshop discussions I will briefly introduce the drug delivery sector and nanotechnology.

3. Setting the scene: Nanotechnology in the drug delivery sector

The drug delivery sector consists of different value chains related to the technology under consideration. A drug delivery system is a formulation or device "that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s). The system, on its own, is not a therapy, but improves the efficacy and/or safety of the therapeutic agent(s) that it carries."¹ These delivery devices can not only be used as carriers for drugs but can also be applied for medical imaging purposes and as carriers for food ingredients. The

¹ From www.drugdel.com/glossbot.htm

drug delivery sector, then, is an intersection of two product value chains involving the ‘primary manufacturing’ of the active pharmaceutical ingredient (API) and the ‘secondary manufacturing’, i.e. the formulation (including drug delivery systems) and packaging. Both stages of manufacturing can occur within one (integrated) firm or be outsourced to contractors [24].

Dynamics in the sector then come from both chains and their intersection, but also from the broader health care environment in which these chains are embedded. For embedding new drug delivery systems, enactors, e.g. business entrepreneurs, not only need to deal with business dynamics in the world of pharma, but also with broader developments in health care such as overall pressures on cost reduction of treatments, debates on reimbursement. In addition to firms, there are knowledge institutes, clinicians, patients, governmental actors and health insurers. Figure 1 offers a (simplified) overview of actors in the drug delivery sector.

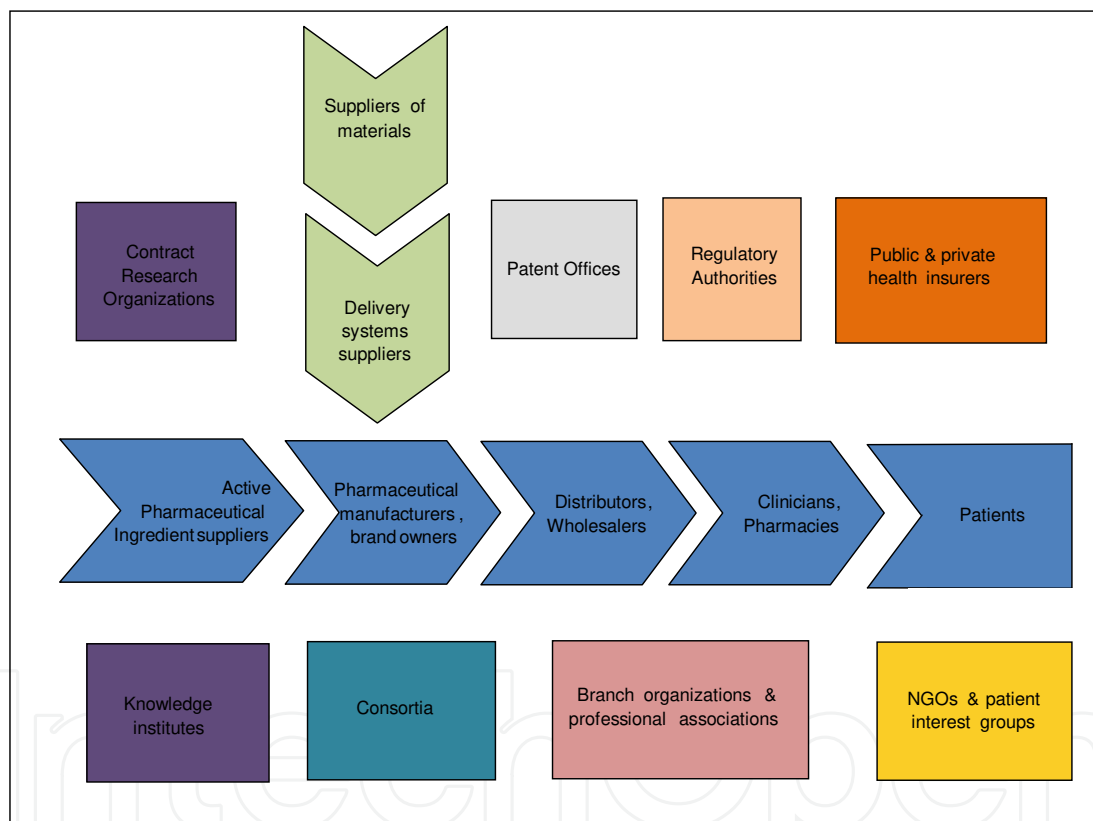


Figure 1. Organizations in the drug delivery sector

The development and introduction of nanotechnologies plays against a backdrop of increasing difficulties of pharmaceutical companies to develop and market new drugs [25, 26]. Nanotechnology-enabled drug delivery systems promise new solutions. The application of nanotechnologies which has attracted the most attention is the promise of releasing drugs at a particular target. While there are other targeting approaches, nanotechnology engineered delivery systems are considered to be particularly promising. In a conventional delivery system, the drug is distributed systemically across the body, but this may not always be

sufficiently (therapeutically) effective or have adverse toxic effects. For targeted drug delivery there are two general approaches. Drugs can be released near the desired location in the body or drugs can be designed for active or passive targeting purposes. In both cases the application of nanotechnologies (devices and molecules) promises to contribute to targeted delivery.

The promise of targeted delivery is not entirely new. The concept of drug targeting is linked with Paul Ehrlich’s idea of ‘Zauberkekeln’, ‘magic bullets’ introduced over a century ago. The ‘magic bullet’ refers to the idea of homing in on the target and being effective - in this case affecting only the diseased tissue. Work on what are now considered to be nanotechnology enabled drug delivery systems has evolved since the 1960s [27-29] – although not exclusively related to targeting. Systems which are currently labeled as ‘nanovehicles’ have existed for some time, such as liposomes and polymer micelles (1960s), nanoparticles and dendrimers (1970s) [30]. The connection with the term ‘nano’ can thus be considered as a relabeling of what was already occurring.

Pharmaceutical challenges	Expected solutions from NDDS
Difficult or unacceptable pharmaceutical format due to poor solubility or toxicities linked to particular excipients.	Enhancing drug solubility, e.g. by micelles and liposomes providing hydrophilic and -phobic environments.
Undesirable side-effects caused by extravasation (e.g. by leakage) of drugs from diseased to surrounding tissues.	Regulated drug release can reduce or prevent tissue damage by extravasation.
Loss of activity of drugs due to rapid breakdown in the body.	NDDS protect drugs from premature degradation and may enable use of lower doses.
Loss of activity due to too rapid clearance of drugs.	NDDS can reduce clearance and may enable use of lower doses.
Undesirable side-effects due to too widespread distribution in the body affecting healthy tissues.	Particulate character of NDDS lowers distribution and helps to reduce side-effects.
Suboptimal therapeutic effects due to use of low concentration of drugs to reduce side-effects.	NDDS can increase drug concentrations by passive and active targeting (EPR-effect, targeting ligands).
Insufficient drug absorption and intracellular penetration.	NDDS can improve absorption through epithelium and improve intracellular penetration and distribution.
Difficult or unacceptable excipients to stimulate immune responses in case of vaccines.	NDDS can be engineered to stimulate immune response, e.g. virosomes and virus-like particles.

*Modified and expanded from Allen and Cullis [31] with items from Couvreur and Vauthier [32].

Table 1. Expectations of nanotechnology enabled drug delivery systems

Considering the history of drug delivery systems, promises of the application of nanotechnologies may not be very effective in mobilizing actors. According to Boyd [27] the claim that “advances in nanotechnology are stimulating a ‘revolution’ in colloidal drug delivery” should be reconsidered given evolutionary developments over the last decades. Available funding

related to rhetorics of nanotechnology in general and for drug delivery in particular, as well as advances at the level of materials, have created new openings for pursuing targeted drug delivery.

The application of nanotechnology-engineered drug delivery systems (NDDS) is expected to be beneficial for the generation of novel pharmaceutical therapies and thereby appealing to current pressures on pharmaceutical companies to generate novel therapies. The idea of the magic bullet enabled by nanotechnologies is a powerful image. There are further expectations of the application of nanotechnologies which link up with issues in the drug delivery sector, in particular the challenge of sustaining pharmaceutical business: (1) creating new drugs or extension of patent life of existing drugs by providing new and improved formulations with respect to therapeutical effectiveness and safety; (2) enabling formulations for API's which are difficult to develop pharmaceutically, including promising new biopharmaceutical therapies such as those based on genes. In table 1 an overview of expectations of the applications of NDDS is presented.

4. Workshop results

4.1. Preparing the interactive workshop

To prepare for a CTA workshop on NDDS it is important to have a solid understanding of dynamics related to the development and introduction of these emerging technologies. To do so I addressed the pre-engagement requirements mentioned in section 2.² Table 2 summarizes major findings in the pre-engagement phase. For an in-depth discussion of dynamics in the drug delivery sector, nanomedicine and pharmaceutical developments more generally, see also [1, 33-35].

For the organization of the drug delivery workshop I co-operated with two (regional) branch organizations. One of them was an association of companies, including large pharmaceutical companies, who develop new pharmaceutical products. The other organization was an association of companies and organizations involved in biotechnology, including pharmaceutical applications. For the former, nanotechnology was not a central topic as it was not (yet) an important theme for its members. Its members are relatively little involved in R&D activities and therefore activities in this area are limited almost by definition as many nanotechnologies are still in a pre-clinical stage. For the other the situation is somewhat different. Biopharmaceutical companies are likely to be interested in nanotechnologies considering the promises for (difficult) delivery of macromolecules such as siRNA.

² Mapping of dynamics linked to nanotechnologies and the drug delivery sector was completed by analyzing relevant reports, papers, conducting interviews and attending international conferences on nanomedicine. Interviews were conducted with experts in the field in order to map opportunities, challenges and dynamics. In addition, interviews were used to find out about existing activities to develop new framing conditions, rules and practices and attempts at co-ordination with respect to nanotechnologies and drug delivery systems [11].

Pre-engagement requirements	Findings
Understanding of dynamics in the domain	Focus on promises of targeting applications, but also on other promises such as longer circulation time of drugs. Long history of development and few products on the market yet. Nanotechnologies not high priority on drug delivery sectors' agenda.
Actors' propensity to co-ordinate development and embedding of NDDS	Waiting games between actors in the value chain. Emerging consortia and platforms for drug delivery researchers and other actors interested in drug delivery (often linked to nanomedicine). Uptake of notion of 'translational research'.
Selection and position of actors	Big pharma as gatekeepers regarding development of new options. Important to involve and link academia, industry and clinicians
Assessment of broader dynamics	Linkages between drug delivery and imaging sector; between drug delivery and food sector. Attention to regulatory and clinical aspects, less on broader issues such as patient involvement, reliability and liability. Overall developments: reimbursement pressures; mergers and job cuts at large pharmaceutical companies; perception of nanotechnology risks

Table 2. Summary of pre-engagement drug delivery workshop

I expected that attracting workshop participants would be difficult. Large pharmaceutical companies might not be interested due to waiting games and the low priority for nanotechnologies. Clinicians might not be interested, due to their limited involvement until now. It indeed proved difficult to attract participants from large pharmaceutical companies and, for that matter, biopharmaceutical companies, to attend the workshop on drug delivery - despite efforts by the co-organizing branche organizations. Nanotechnologies were not a high priority for potential participants and caution in discussing R&D developments were provided as important reasons for not attending the workshop. Attracting clinicians also proved to be difficult, albeit for different reasons. While some clinicians were interested in the phenomenon of nanotechnologies, but not able to attend due to busy schedules, others were sceptical about the value of nanotechnologies and not interested in participating in the workshop. These observations are relevant as they already give indications of possible difficulties in bringing about co-ordination in the field regarding emerging NDDS.

While eventually no clinicians or participants from large pharmaceutical companies attended, participants from different parts of the chain were present at the workshop, including some who had experiences with interactions with pharmaceutical companies and clinicians. Participants from knowledge institutes, suppliers of delivery systems, and a drug development firm were present. In addition, a firm involved with microsystem technologies and a governmental organization involved with nanotechnologies were present.

To prepare for the discussion and support participants thinking about current and future developments, three scenarios were crafted. One scenario explored two different (and

contested) development paths. A consortium of researchers anticipated that demonstrating clinical value would convince investors in the added value of targeted drug delivery systems which would contribute to overcoming the current impasse. To do so the consortium focused on incremental improvements of carriers with which there was already a lot of experience with regarding safety and effectiveness. Another set of actors disagreed with this approach and anticipated that big steps were needed in order to fulfill the promises of nano-enabled drug delivery. This group of actors formed a more ambitious consortium working on theranostics. The scenario speculated that the eventual fate of the consortia was not so much determined by its technological achievements but due to contextual factors. Concerns about possible risks of nanotechnology enabled drug delivery systems and gaps between diagnostic and therapeutic possibilities co-determined the fate of the two development paths. In the end the ambitious consortium was disbanded.

The two other scenarios explored initiatives which more directly worked on improving co-ordination across actors in the drug delivery sector. One of these scenarios described the formation of a broad platform involving material and pharmaceutical researchers, clinicians and people from industry. Discussions and differences of opinion among the platform participants about how to co-ordinate technology developments and their future introduction forces the platform to abandon the initial broad scope and focus on specific carrier systems. While the platform is successful in attracting a broad variety of stakeholders, including interested actors from outside the nanomedicine world, attempts at co-ordination across the domain are met with criticisms. One of the co-ordination mechanisms proposed by the platform is a stage-gate model which articulates criteria for the development and clinical introduction of novel targeted medicines. According to critics the stage-gate model is too restrictive: commercially uncertain, but potentially interesting and promising technologies are too quickly shifted aside – effectively constraining opportunities for breakthrough technologies.

The third scenario explored attempts at stimulation and co-ordination from the demand-side. An alliance of patient organizations, knowledge institutes and firms is forged with the general aim of stimulating demand for cancer medicines with little side-effects. The alliance develops a broad research programme and actively involves itself in political circles and decision processes on the restructuring of the health care system and reimbursement policies. The broad focus on stimulating demand for reduction of side-effects of medicines attracts various alternative technology solutions. Only with help with the reference to cancer medicines, nano-enabled targeted drug delivery system remain on the agenda within the research programme which is eventually funded. First clinical evidence suggests that complexity of cancer requires different forms of drug delivery systems which may be commercially less attractive because of limited market volumes. Involved patient organizations are disappointed and press for applications fitting their specific diseases. The push of the alliance for medicines with less side-effects then starts to lose its momentum. The emphasis on cancers as the major disease area now appears to be less effective to mobilize resources.

To inform the participants a preparatory document was distributed one week before the workshop. This document contained: (1) a program of the meeting; (2) a short introduction

into and justification of the topic of the meeting; (3) a brief analysis of the current situation of development and embedding of nanotechnologies for drug delivery; (4) the presentation of scenarios; and (5) a list of identified dilemmas where strategic choices about development and societal embedding of nanotechnology-enabled drug delivery systems had to be made. The document aimed to create common ground for participants, and offer ideas for discussion. In particular the scenarios and dilemmas were offered as ways to think about future developments and strategies. It was emphasized that the scenarios were controlled speculations [22], i.e. imagined developments but based on what was happening in the drug delivery sector already. Participants were invited to modify and add to the scenarios during the workshop.

4.2. Discussions during the workshop

The workshop consisted of a half-day of intense discussions which took place in an informal atmosphere.³ While the workshop discussions covered a variety of themes, there was a strong focus on the clinical value of nanotechnology-enabled drug delivery technologies. Sectoral issues of co-ordination between disciplines and across positions in the chain emerged as the most important challenges to be overcome. They were recognized and were actually highlighted by some participants in the workshops as being a key factor holding back embedding processes of nano drug delivery technologies. The lack of clinical evidence of (significant) therapeutical effectiveness was positioned as the reverse salient for furthering developments in the field. Strategies to stimulate and improve further developments in the field of nano-enabled drug delivery revolved around the challenge of demonstrating clinical value.

Interactions during the targeted drug delivery workshop are characterized as a series of exchanges on diagnosing the key challenges in furthering developments in the field of nanotechnologies and drug delivery, and on the best methods to cope with those challenges. While there was no explicit consensus on which strategies should be pursued in the future, the emphasis on problems of co-ordination and lack of clinical evidence effectively constituted a lock-in in the discussion. To show how participants in the workshops assessed current dynamics and anticipated future developments relevant for the commercialization of nano-enabled drug delivery systems I will report on salient items in the discussions.

4.2.1. *The unique character of nanotechnology and the pharmaceutical sector*

Puzzles about the unique character, if any, of nanotechnology engineered drug delivery technologies set the stage for a series of exchanges. The discussion was initiated by a participant wondering about specificities of the application of nanotechnologies and how these contributed to reluctance in uptake and development of nanotechnology-enabled drug delivery technologies. A participant from a drug development company replied by pointing out uncertainties about the unknown safety profile of nanoparticles. Whether this meant that there was a lack of testing methodologies and knowledge about distribution and effects of nano-

³ The quotations in this chapter are anonymized, and used with permission of the participants. The quotations were translated into English by the author.

particles in the body – which would suggest the existence of specific nanotechnology related challenges - or required more efforts during testing was unclear.

This question regarding safety of nano drug delivery technologies prompted a participant, working for a company supplying drug delivery systems, to frame the question differently by asking about the status of knowledge and methodologies for assessing ‘conventional’ pharmaceutical materials. This participant considered questions regarding safety to be the responsibility of their customers and not a topic for his firm. However, by asking about evaluation criteria for their customers’ products, his understanding of broader developments increased.⁴ In that respect, this participant did consider broader developments rather than only customer-supplier exchanges.

Delivery systems supplier: May I ask a simple question? We discussed that we cannot observe where nanoparticles are travelling to, but this is also unknown for pharmaceutical substances, molecules. Also in these cases one doesn’t analyze in detail whether particles travel to the liver, or to.

Knowledge institute 2: Well, well

Delivery systems supplier: They do?

Knowledge institute 2: There is pre-clinical pharmacokinetics, tissue distribution; this should all be done.

Governmental organization: But that is not different for what needs to be done already for pharmaceutical substances.

Delivery systems supplier: Hence, my question. If this is already being done for small molecules, why would this be problematic for nanoparticles?

Governmental organization: Because for non-nanoparticles, let’s call them that way, for other chemical substances, not necessarily pharmaceutical compounds, already a number of patterns are known. [...] The case of nanoparticles is becoming a totally different story for us.

Even if questions concerning the unique character of nanotechnologies for drug delivery were unsolved, the link between general conceptualizations of the term nanotechnology and drug delivery was problematized. Participants from research institutes and a drug development firm pointed out that the associations of targeted drug delivery with the umbrella term ‘nanotechnology’ also, albeit incorrectly, implied connections with discussions of ‘disadvantages or risks’ linked to nanotechnologies in the public domain. According to these participants, such associations could provide nuisances for nano drug delivery technologies. This type of reasoning shows that these enactors take broader aspects into account, yet in a way which resembles other patterns which have been called by Rip [14] as ‘folk theories’: taken for granted patterns, which have not systematically been checked. In this case, the expectation that nanotechnologies may suffer from the same public backlash as what happened to GMOs.

⁴ During my post-workshop interviews this participant expressed that understanding in this area helped the firm to assess their business plan forecasts as uncertainties in this area might slow down introductions of their customers’ products, and therefore the participants’ sales volume.

A series of interactions followed in which a participant from a governmental organization questioned this implicit pattern. This participant pointed out that specificities of the drug delivery sector would limit possible risks of nanotechnologies. Exposure to nanotechnologies through pharmaceutical therapies would be well controlled and registration procedures would check, among other things, toxicity. In addition, access to consumers – patients – would be regulated through intervention of clinicians. Furthermore, authorities had already considerable experience with delivery systems such as liposomes, suggesting that registration procedures should not pose particular difficulties. However, the participant acknowledged, patients might think differently about risks than experts do.

The point about regulatory expertise was contested by one of the participants who had experience with regulatory authorities, puzzling over whether existing evaluations were sufficient – even for liposomal formulations. The participant speculated that more knowledge about risks of nanotechnologies might lead to re-evaluating existing registration procedures. This prompted a reflective comment from the participant of the governmental organization, noting that there were tendencies in society to reduce and solve all uncertainties and problems linked to nanomaterials. While such an objective might be laudable, the participant warned that one should not increase risk assessment criteria for nanotechnologies beyond what was presently accepted.

4.2.2. Challenges in co-ordination across the innovation chain

During the discussion the point was made that the development of linkages between research on drug delivery materials and specific diseases was difficult. A participant from a knowledge institute suggested that research programmes should stimulate the improvement of interfaces within a chain of activities involved in developing these linkages. At the same time, this participant observed that developing linkages would not be straightforward, for different reasons.

Knowledge institute 1: There are also groups that only focus on researching their own chemical entities and do not develop them further. While, clearly, further development of these substances should be considered. In which area do you want to have an application? Then you also need a partner to do this. We, as material developers, are all confronted with the problem that we have difficulties in reaching those people, particularly the industrial actors which are interested in these materials.

According to a participant from another knowledge institute, the difficulty in bringing the field of nanotechnology enabled targeted drug delivery further was rooted in the lack of clinical evidence. This would make it difficult for researchers and drug delivery firms to link up with large pharmaceutical companies. Later, the participant commented that big pharmaceutical companies were to some extent dependent on these new technologies. So, we see here a waiting game at work, considering that researchers and firms are to some extent dependent on large pharmaceutical companies for funding and further exploitation of nanotechnology enabled delivery systems.

Knowledge institute 2: There is still too little on the market that convinces large companies to put effort in this area. There is very little data on the clinical benefits. Real, concrete proof. And that is what the

industry is waiting for [...] but big pharmaceutical companies are not in-active altogether. On the one hand there is a development which forces them to pay attention to these type of products, eventually. Because there are increasingly less blockbusters. [...] Big pharmaceutical companies do have interest in these [nano drug delivery] type of systems. Watch it carefully.

According to participants from research institutes, big pharmaceutical industries were reluctant. This led the participant from the governmental organization to probe into big pharma's considerations. While no participant from big pharma was present, participants replied by referring to big pharma's waiting strategy, which was considered to be independent of nanotechnologies. A participant from a drug development company pointed out that, among other commercial considerations, clinical proof established in Phase II studies was required to demonstrate the added value of a new pharmaceutical technology. The participant from the governmental organization challenged this claim. The participant probed whether clinical studies were really required in order to convince pharmaceutical companies to invest in nanotechnologies. This was confirmed by a number of participants and not questioned by others.

Focus on convincing large pharmaceutical companies by acquiring – hopefully – significant clinical data (for a specific drug – delivery systems – disease combination) was an important topic in the workshop. The consideration of evaluation criteria from pharmaceutical companies (acting as future selectors of concepts generated by research institutes) by participants from research institutes and firms implies that these actors did take into account broader aspects. Still, the discussion was focused on pushing forward nanotechnologies (from the world of research). The overall strategy itself is predicated on the assumption that convincing firms and health insurers that clinical evidence is 'out there' and that expected benefits only need to be harvested – after which new drug delivery technologies will enter into the clinics. This type of reasoning resembles a typical enactor perspective.

One of the participants pointed out further sectoral dynamics. The participant argued that big pharma had a strong focus on blockbuster drugs and that novel nanotechnology enabled drug delivery technologies would not likely fall under that class of drugs. This then led to a series of interactions regarding structural features in the drug delivery sector constraining development of new pharmaceutical technologies in general. During this set of interactions one participant, who emphasized clinical proof, suggested that if the clinical value would be convincing, actors (which were left unspecified) could not dismiss these technologies. The emphasis on benefits, which would overcome all barriers, is a typical enactor perspective. But this was not left unchallenged. One participant remarked that patients then probably needed to take action as health insurers might be reluctant to pay for new (costly) therapies. Here, we see a typical selector argument, pointing out that benefits alone might not be sufficient, as issues of costs were known to limit introduction of new pharmaceutical therapies.

Participants raised further points to open up the discussion, thereby moving away from the lock-in on clinical value of drug delivery technologies, which was pushed by a number of participants. One of the participants challenged the idea of initiating technology development trajectories from a disease oriented point of view.

Knowledge institute 3: I would like to react to your comment to take diseases as a starting point. There are of course many material research groups which start to think from their technology. [...] If you assert that one needs to start to think from the clinical picture, this means that you actually need to involve all groups in that discussion. [...] For each disease there are then several delivery systems. Whereas one could also say that one should start thinking from delivery systems and whether they are toxic or not.

Knowledge institute 2: Yes, but eventually we develop, we produce [...] not things that are safe. No, we produce things that have to work effectively and which have to help patients [...] Look, it is a bit like, disease searches for a device, or device searches for a disease.

Microtechnology firm: It is an interaction.

Knowledge institute 2: It is an interaction. And actually I am also in favor of broad academic research. But, if one takes the step to, let's call it, valorization, then one needs to make a small value chain and this should be done by spin-offs.

[..]

Knowledge institute 1: You need them both, of course. You need to have a lot of knowledge about particles in order to know how and for what you can use them. [...] So, there is a disease and there is a material, and these should be brought together. How would you like to improve this? Then one would say, for these connections, these points, there should be programs that support them.

The conclusion that interfaces between actors needed to be improved can be interpreted as a call for translational research, although the term itself was not employed. The conclusion shows a non-typical enactor perspective; enactment of new technologies is guided by a diagnosis of what happens at the level of a sector and what should be improved upon.

4.2.3. Anticipatory strategies: next steps in mobilizing R&D funds and research

The relatively focused discussion created time and space for discussion and articulation of strategies. Discussions focused on the question of how to further develop nanotechnologies in the drug delivery sector. Overcoming what was seen as the reverse salient in the overall development, the lack of clinical evidence, was a central theme in that part of the discussion. Participants explored possible strategies of co-ordinating developments in the sector, including the creation of a nano drug delivery exemplar which – if successful – might convince the field of drug delivery of the value of the application of nanotechnologies. Toward the end of the workshop participants expressed interest and enthusiasm in adopting the discussed strategy in order to try to actually implement them

Other strategies were explored well. One is particularly interesting as it appealed to the promise of reducing undesirable side-effects. In the interactions that followed, not only researchers, enactors, of drug delivery technologies were articulating this strategy, but also the participant of the governmental organization. One of the participants rebutted this strategy by referring to negative experiences with large pharmaceutical companies. According to this participant, the strategy of re-evaluating problematic drugs did not fit with big pharma's practices. By providing an account of those experiences, the participant also provided further insights into the world of large pharmaceutical companies:

Knowledge institute 1: There is also an opportunity in which one could make up for some costs. There are of course many pharmaceuticals which in the end have not made it due to side-effects. Targeted delivery offers an opportunity to avoid such toxic side-effects. The therapeutic effect will probably already have been demonstrated very clearly, but in the end they have not made it due to the side-effects. In that respect one may skip some developments, or at least short-cut them and focus on whether one can reduce these side-effects through targeting.

Knowledge institute 2: Yes, yes, but you can also evoke them [side-effects] via targeting. That automatically appears, safety, you can not eliminate that, because through linking...

[...]

Knowledge institute 3: Big pharmaceutical companies have many pharmaceuticals on the shelves [which cannot be used due to drug delivery problems].

Governmental organization: Yes, [...] one should also have a look at the deleted products.

Knowledge institute 2: We have already tried that many times in the past. [...] And eventually it works, pre-clinically, and they [big pharmaceutical companies] do not do anything with it. Because it doesn't fit with their block buster model eventually, and it is too laborious, costs too much money and finally they pull out. We had spoken already with a number of big pharmaceutical firms in the past about creating a better life for interesting pharmaceuticals, problem medicine. And, that is, ... well, yes, big pharma does not think that way.

During the discussion of strategies to further the field, also the question of mobilizing resources for such strategies was put forward for consideration. Toward the end of the meeting the moderator pointed to one of the scenarios in which patient foundations and organizations were involved and asked whether that would be a feasible option. Patient organizations can be involved for financial but also symbolic (moral) support. Participants from research institutes and the governmental organization were hesitant and argued that it might be too early to involve them for funding and moral support. Too-high expectations based on too little evidence and uncertainties over risks were mentioned as reasons (without making explicit the expected effects). Between the lines, the analyst can see a folk theory of a hype-disappointment cycle at work.

Interestingly, one of the participants from a firm not directly involved with drug delivery technologies responded to this discussion by pointing out that little involvement of patient organizations might induce a pattern reminiscent of the biotech discussions. A pattern, argued the participant, in which little information by enactors of new technologies is distributed, leaving civil society organizations to guess what is happening and perhaps leading to a rejection of new technologies. This was acknowledged by one of the participants from a research institute as something for which an answer should be developed, but not as something directly important for the question of furthering the field. This participant considered this theme as off topic and (again) emphasized the importance of clinical evaluation of new delivery technologies.

By convening participants at various positions in the chain and facilitating mutual understanding of each other's positions and perspectives, the workshop supported the participants

in getting a richer understanding of what happens at the level of the drug delivery sector. This was acknowledged by one of the participants after the workshop who remarked that the meeting discussed the big challenges at the level of the domain which was usually not done as people tend to be preoccupied with their day-to-day affairs.

5. Conclusions

The approach of Constructive Technology Assessment offers a useful methodology and set of tools such as scenario workshops to support researchers, firms, policy makers and other stakeholders in identifying dynamics in innovation processes and anticipating plausible future developments. In this chapter I have described this approach and showed how to actually do this in the case of nanotechnology-enabled drug delivery systems.

A key finding from the scenario workshop on NDDS is that participants' assessments of development dynamics and future market introduction of nanotechnology-enabled drug delivery systems often took into account what was happening at the level of the sector. That said, participants did discuss nanotechnology specific aspects, often in the context of uncertainties about performance, risk and demand for nanotechnology engineered products. Still, during interactions and positioning of actors, broader considerations about sectoral dynamics and circumstances came to the fore. Participants discussed patterns of interaction between actors in the chain and developments at the level of the sector that were independent of, but relevant for, nanotechnologies. In this way, participants drew from a general repertoire of embedding issues in their sector, independent of specific emerging technologies, as part of their anticipatory competences. Discussing dynamics at the level of the sector rather than focussing on a specific NDDS technology was appreciated by participants as they usually did not look at NDDS from such a perspective.

Occasionally participants also discussed issues transcending sectoral aspects such as overall changes toward dealing with risks of (new) technologies in general and nanotechnology as an umbrella term. These broader discussions will offer further, though non-specific clues, such as general pressures to take into account risks of nanotechnologies and take into account ethical and societal aspects during the development of nanotechnology-enabled products.

Present uncertainties of performance of emerging NDDS will make concrete anticipation of societal embedding difficult. Then, considerations about sectoral conditions and patterns of interactions between actors in the sector are likely to be highlighted. This is relevant as a variety of actors and interests are involved during the development and market introduction of novel NDDS. Understanding of sector-level patterns linked to drug delivery technologies in general then offers clues as to what will be important to take into account when working on the development and introduction of specific combinations of drug delivery devices, pharmaceutical agents and diseases. Scenarios offer playgrounds to experiment with specific cases of NDDS which will anyway be embedded in dynamics of the intersecting supply chains of pharmaceuticals and delivery systems.

By organizing an interactive discussion involving participants at different positions in the value chain, supported by well-prepared scenarios, analysts or practitioners adopting CTA methodologies can support articulation of anticipatory strategies and decision making. Whether the insights gained during such events actually make a difference is more difficult to determine, among others because this depends on how much opportunities and room to maneuver participants have after the workshop. The workshops will however contribute to an emerging shared understanding of dynamics and issues which cannot be easily ignored by the individual participants. This will be different than before the workshop and in that sense the workshop will already have effects on how actors will anticipate market introduction of nanotechnology-enabled drug delivery systems.

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