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Citation for published version:

Wield, D, Tait, J, Chataway, J, Mitra, J & Mastroeni, M 2017, 'Conceptualising and practising multiple knowledge interactions in the life sciences' *Technological Forecasting and Social Change*, vol. 116, pp. 308-315. DOI: 10.1016/j.techfore.2016.09.025

Digital Object Identifier (DOI):

[10.1016/j.techfore.2016.09.025](https://doi.org/10.1016/j.techfore.2016.09.025)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Technological Forecasting and Social Change

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Conceptualising and practising multiple knowledge interactions in the life sciences

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Accepted by: Technology Forecasting and Social Change (TFSC)

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Highlights

- We introduce a novel approach to the analysis of life science innovation
- With a triangular theoretical framework inclusive of all innovation actors
- We have developed foresighting tools that analyse these interactions

Abstract

This paper presents an approach developed by the Innogen Centre for the analysis of systems of innovation. The approach, developed through the study of innovation in the life sciences, is unique in that it features a triangular view, alongside consideration of the behaviours and interactions between innovators, regulators and policymakers, and advocacy and public interest groups. Furthermore, while the approach can be characterised as co-evolutionary and system-based, it also allows for the user to shift from the macro to micro – considering the impact of institutions on actors and innovation within an institutional milieu, but also considering the individual behaviours and business plans or actions of the actors involved. This paper presents both the approach itself and how the approach was developed.

Keywords: life science innovation; triangular actor framework; scenario tools

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1 Introduction

This paper describes the development and use of a new methodological tool and analytical approach to the study of the life sciences that is rooted in interdisciplinarity. This, we argue, is needed to capture the complexity and interconnectedness of the sector's knowledge production and product development processes that constitute the life science innovation system. Our focus on life science sectors where regulatory and public interests play a key role builds on recent complementary work (Crespi and Quatraro, 2013; Kerr et al., 2013). The approach presented here is unique in that it features a triangular view, and equitable consideration, of the behaviours and interactions between innovators, regulators and policymakers, and advocacy and interest groups. Furthermore, while a co-evolutionary system-based view, the approach also allows for the user to shift from the macro to micro – considering the impact of institutions on actors and innovation within an institutional milieu, but also considering the individual behaviours and business plans or actions of the actors involved.

Understanding of innovation in the life sciences depends on pulling together three dimensions: first, a sense of the intradisciplinary and interdisciplinary complexity of the different disciplines that generate knowledge in the life sciences; second, an understanding of the wide range of science-industrial sectors that translate this knowledge into new products and processes; and thirdly, the social science disciplines needed to understand the social relations of these activities, and to build an integrated overview and effective decision- and policy-making for life sciences. By integrating these three dimensions, and treating the opportunities and challenges of life science innovation as inherently systemic in nature, we developed a novel set of methodological and conceptual tools. These tools better capture and understand the significant changes in the life sciences that are emerging from interactions between three key sets of actors:

- The innovators, the broad group of actors involved in the production of science, technology and product innovations. They may be located in public or private sector research settings, small and large companies, and within new networks and partnerships.
- Policy makers and regulators ranging from narrowly organised regulatory bodies for sub-parts of the innovation system, to those responsible for bridging boundaries and proposing new policy and regulatory innovations to ensure appropriate governance of the sector.
- Citizens and other users (such as patient interest groups and advocacy organisations) that provide an important public ‘check’, but also informed pressure on the other two sets of stakeholders, concerning for example improved food quality and new drugs for rare diseases.

It is the ability to look at the interaction between these three sets of actors, in breadth and depth, and without bias, that provides the value added to Innogen’s approach.

We introduce a selection of the tools we have built, which provide a means of conceptualising and analysing the interactions among the actors with the aim of identifying gaps, weaknesses and opportunities to improve scientific and technological foresighting. We argue that foresight will be more accurate, and therefore have far greater and positive impact on policy, innovation and society, if it is based on a formal integrative approach such as the one we present. The methods section (section 2) describes the evolution of our approach from the late 1980s to date. In section 3 we provide the theoretical underpinnings of the approach. Section 4 shows how we apply the approach to the analysis of innovation in the life sciences, and in section 5 we give a sense of how the approach works in detail with the case of regenerative medicine. We present our conclusions in section 6.

2 Method

Our initial framework was developed over more than a decade from the late 1980s. As early as 1990, Tait suggested that misgivings would grow about the safety of new technologies in agriculture, especially those based on genetic modification (GM). She suggested that the outcome of these concerns would depend on complex interactions between industrial innovation, government policy, risk regulation and public attitudes: ‘In the resulting system, perturbations in any one factor will have a major impact on the others, through a set of feedback loops (Tait, 1990, p 1).’

Tait’s concern, as expressed in evidence she gave for the UK Economic and Social Research Council (ESRC) to a UK parliamentary committee, was that industrial lobbying would destabilise existing risk regulation:

‘[Industrial] lobbying activity ... is also likely to diminish industry’s perceived trustworthiness, and hence reinforce adverse public attitudes. The latter would then feed back, directly and through pressure to increase the level of risk regulation, to cut back on industry investment (1992, p 192).’

She went on to describe the results of a public attitude survey she had conducted concerning new biotechnologies, particularly genetic modification of plants and micro-organisms:

‘The overall levels of concern expressed, among all groups, were high. This leads us to the tentative conclusion, a worrying one from industry’s perspective, that these

negative attitudes may be triggered into overt expression in behaviour by some relatively minor event’.

Tait, then, picked up these concerns, and the need for systemic integrated analysis, well before GM became a public issue and before GM products went onto the market. At the time her suggestion that concerns might arise was not taken seriously. Policy makers and regulators did not sense the growing public concerns about new agricultural technologies. Within a few years, however, the GM ‘debate’ had exploded and was to fundamentally change the nature of European approaches to food production. We decided to focus on analysing these issues. A range of research projects from the mid-1990s to the early 2000s focused on agricultural processes and practices (Chataway et al., 2004; Chataway et al., 2006).

This research was consolidated by the establishment of the UK Innogen research centre (the ESRC Centre for Social and Economic Research on Innovation in Genomics - Innogen) in 2002 to study the new science and technologies emerging in the life science industries – human health, crop and animal. Our approach used and further developed the tools we had applied in the previous decade (Tait, 2007; Wiold, 2008). We based the tools on a triangular framework based on the view that the major changes, and potential surprises that could destabilise innovation policy, would come from crucial systemic interactions between the three main sets of actors. Our research has shown that the interactions and collaborations of the three sets of actors with each other, and not simply their individual characteristics and actions, are important.

For example, our research with drug regulators and producers suggested that the weakening of drug industry innovation models could be reappraised as a mismatch between: the nature of new life science innovations, the nature of the companies that could best exploit these innovations, public and private expectation of new drugs and treatments, and regulatory systems that were designed around twentieth century models of drug development (Tait, Chataway and Wiold, 2008a, Tait et al , 2008b, Wiold et al 2013). Such a research approach involves: knowledge generation from multiple sources in a more ‘open’ way including from users of knowledge, such as patients with rare diseases and their organisations; the sharing and combination of ideas in an interdisciplinary way; and the contextualisation of these triadic interactions in particular situations – each with different and evolving routines.

The evolution of our approach has allowed development of a framework and empirical tools. In this paper we introduce one of these, the Strategic Analysis of Advanced Technology Innovation Systems (STRATIS) approach. The methodology provides an overarching framework that acts as a basis for interdisciplinary integration across academic disciplines, actor perspectives and across a wide range of areas of application.

3 Theoretical underpinnings

Our early research on the life sciences made it clear that simple analysis of the relationship between science and industry did not pick up the reasons why innovation was taking place in the life science sectors. Similarly, a focus on public attitudes alone, or only on regulators, did not allow rigorous analysis of the changing regulatory environment. A focus on both ‘policy’ and ‘public’ interests was

necessary (Burawoy, 2005, Mastroeni et al., 2012). In order to pull together analysis of the various scientific disciplines and the complex social interactions, our approach to theory building began by working from in-depth analysis of our empirical data on complex situations. It was informed by four theoretical underpinnings: (1) specificity of the life sciences, emphasising the complex role of multi interest stakeholders; (2) how this specificity influences the sectoral nature of the life sciences; (3) its co-evolutionary approaches; and (4) its systemic characteristics.

3.1 Specificity of the life sciences

Our theoretical approach acknowledges and classifies the multi-stakeholder nature of the life science sector in order to capture its specificity and its strongly value-oriented environment.

The stakeholders include important non-market actors (such as universities, public sector research institutes, as well as patients, consumers, and health services). Even the nature of science is different. For example, Dupre (1995) argues that biological knowledge differs in its complexity and scientific disunity from sciences such as physics and chemistry. It does not appear to have the methodological unity or underlying theory to link its disparate fields. Such analyses may lead to a new unity of knowledge that is more complex and involves a wider range of actors (Wield et al, 2013). If we take the science and innovation together with the complex governance systems and public and non-market actors, we have a sector with complex knowledge interactions.

We add our triadic approach to a systems perspective to deal with complexity. Historically, the first category, 'innovator', has been treated as a firm-based activity with markets as the main testing ground for innovation success or failure. However, in the life sciences, innovation happens in a wide range of social and economic activities, many beyond that of the single firm. Life science innovation increasingly involves 'a wide range of external actors and sources to help them achieve and sustain innovation' (Laursen and Slater, 2006, p131). Although pharmaceutical companies are still the dominant actors in health, and agro-chemical and seed companies in agro systems, innovation in the life sciences includes a relatively higher degree of non-firm and non-market actors and interactions. Scientific labs in universities and large public research institutes are major actors, as are public health systems. There are a range of complex institutional arrangements such as public-private partnerships for rare and neglected diseases and patient-induced research networks. Our research on innovation dynamics suggests there is a broadening conceptualisation of innovation strategies.

Innovation now requires knowledge from multiple sources, in a more 'open' way, including from users. OECD evidences an 'explosion in the development of knowledge networks and markets' and suggests this has led to increased enabling of open innovation (OECD, 2012, p 11). It requires different sources of knowledge co-evolving during the innovation process, each context being different and specific, with its own routines and traditions. It is clear, for example, that big pharma requires a wide range of science, clinical trial, and other outsourced producers. (Wield et al, 2013; Wield, 2013; Rafols et al., 2014; Mittra, 2016). On occasion, openness allows significant power to be devolved to multiple actors, even though the stronger (usually big pharma) partner can capture more value from

collaborations (Gambardella and Panico, 2014). The category of innovator is complex, containing firm-based, private, market oriented actors, but also public, non-firm, non-market actors.

The second category is centred on public actors, such as regulators, though these operate largely within market based environments. Although regulation is an important part of the activity in many industries and sectors, it is a more important part of the life science industries. Our theoretical underpinnings give regulation a key role, perhaps not controlling but certainly central to explaining the dominance of the conventional drug discovery innovation model. We have shown that the dominance of the large pharmaceutical firms is, in large part, explained by their ability to invest the huge amounts needed to take drugs through the clinical trials process (Tait, 2007; Mitra, 2016). Start-up biotech firms cannot do this, as they do not have the resources and the venture investment model prefers shorter-term pay-offs from selling at earlier stages in the clinical trials process.

Regulatory systems can, by a set of incremental changes over time, get out of step with the regulated area, and also become extremely complicated so that further change has unexpected implications (Tait et al., 2007; Chataway et al., 2006). As a regulatory regime becomes more complex, its practices are likely to become more fragmented. Regulators operate within a network of actors with competing interests, values and power. Regulation can therefore be analysed in a similar way to more open innovation processes, and thus on the interactions between the triad of actors.

The final category, citizens and public stakeholder groups, contains a rich combination of interests and values. The anti-GM advocacy groups and anti-animal experimentation groups are strongly against some new biotechnologies, for example, whilst rare-disease patient-interest groups are more closely allied to those innovators and regulators that are working towards new therapies (Wield et al 2013). We, like Burawoy (2005), clearly separate professional 'policy' from 'public' approaches.

We have analysed this latter category in two ways. First, through an interests/values type approach (Tait, 2001). Values play a key role in most fields of the life sciences, from GM food, cloned animals, to various new health therapies, and issues around ownership of intellectual property (IP), bringing strong opinions that cannot be changed by negotiation. Interests on the other hand, allow for a more nuanced and pragmatic approach to decision-making. An example of the latter is the efforts to negotiate 'benefit sharing' for communities affected by IP arising from local medicinal plants.

Second, we use the concept co-production, where citizen's groups can often be co-producers of knowledge concerning new therapies. Epstein's work (1996, 2007) illustrates the importance of public 'patient' knowledge in the development of new therapies. His first work, concerning the development of AIDS therapies to AIDS associated retrovirus (ARV) therapies (1996) described the levels and layers of knowledge of non-scientists AIDS activists, and how they gained a voice in the scientific world. 'The vigorous participation of self-educated activists – and more broadly, the rise of knowledge-empowered communities that monitor the course of the medical research – has had momentous effects on the development of AIDS treatments. These treatments have transformed the procedures by which drugs are

tested, in which test results are interpreted, and the processes by which those interpretations are then used in the licensing of drugs for sale' (Epstein, 1996, p33). A further breakthrough was the role of clinical trials and the pressure from activists to 'bring the patients back in' (Epstein, 1996, p40) which led to fast track legislation and rare disease and orphan drug legislation. Epstein (2007) noted the growing inclusion of 'more and more ordinary citizens, often organised into patient interest groups or broader social movements, have demanded a say in how scientists and health professional groups go about their work, tossing aside the presumption that technical matters are best left up to the experts' (p20-21) but also emphasises that 'these policy changes were not brought about by a lay social movement, pure and simple, but rather by a hybrid coalition linking health advocates with experts, bureaucrats and policymakers' (p21).

In addition, Haddow et al.'s research, which focused on the Scottish genetic data base, showed how participant involvement and knowledge could improve effectiveness of data collection and use (Haddow et al., 2008). Patient support groups have added a major dimension to the knowledge base on which new therapies are developed and regulated. Epstein and Haddow et al.'s insights provide strong evidence that public advocacy can influence the production of knowledge in the life sciences.

3.2 Sectoral approaches to the life sciences

The specificity described above affects the sectoral nature of the life sciences, covering the new discoveries in biotechnology and genomics, building on a broad range of science disciplines – biochemical, chemistry, computer sciences, IT, synthetic biology and, cell biology. The knowledge generated is translated by a wide range of industrial actors and subsectors into new products and processes. The life sciences as a sector has commonalities but also important differences: agro-biotechnology including GM crops, pharma and biopharma, industrial biotechnology, devices and new therapies. Malerba advanced the concept of sectoral innovation systems as a way of building a coherent analysis of sectors of economic activity, previously not well studied either methodologically or theoretically (2002). Malerba proposed that a sectoral system of innovation and production is 'a set of new and established products for specific uses and the set of agents carrying out market and non-market interactions for the creation, production and sale of those products Sectoral systems have a knowledge base, technologies, inputs and demand. The agents are individuals and organizations at various levels of aggregation, with specific learning processes, competences, organizational structure, beliefs, objectives and behaviours (p248)'. Malerba's approach, therefore, captures the specificities that each sector faces.

Our research, building on the work of others (Orsenigo et al., 2001; Henderson et al., 1999) showed that the life science sector has some key characteristics (Tait et al 2002, Chataway et al, 2004). For example, it has a strong science base, including university and public research lab knowledge. This knowledge base has been linked closely to firm-based R&D systems, including via big pharmaceutical companies, agrichemical and seed firms, and spin-out biotechnology firms. These knowledge-based inter-organisational sectors are linked with formal intellectual property rights, including

patents and seed rights, which are strongly defended, including in high profile legal actions. The life science technology regime is thus science- and IPR- based.

Less emphasised is the 'D' in 'R&D', the technology regime elements around the clinical trials and agro-production trials. These trials are intimately connected with the regulatory systems that have grown in depth and breadth over the years: deepening the stages needed, and broadening out to many types of innovation product, trajectory and process. There is a paradox, however, since increased openness of the innovation process in the life sciences goes together with increasing constraints from regulatory complexity, which lowers the capability of small innovative companies and cements the power of big pharma over the life science value chain. We argue that it is these less emphasised parts of the sectoral system which have led to the increasing difficulty for new entrants to develop and succeed in the sector.

Malerba (2002) mapped out four areas for future research, each of which we researched for the life sciences. First, progress in understanding of firm heterogeneity, structure and change within sectors, and on the role of sectoral institutions which we have mapped (Chataway et al, 2004; Orsenigo and Tait, 2008; Wield 2013). We have also built understanding of barriers to entry and the impact of regulatory systems on the lengthy clinical trials process which are important for Malerba's second and third areas of future research: the need for taxonomies of sectors; and research on the relationships between elements of a sectoral system (eg Mitra and Williams, 2007; Orsenigo and Tait, 2008). Malerba's fourth area, the need for public policy proposals on the transformation of sectoral systems to identify mismatches and blockages, is exemplified by our work on policy proposals concerning the need for improved regulatory systems (smart regulation) and on new approaches to the development of public-private and more open innovation systems (eg Chataway et al 2006, Tait et al 2007). We have, in the process, focused hard on non-firm activity that can enable firm based innovative potential, showing the importance of open and complex knowledge management approaches (Wield 2013, Wield et al 2013).

3.3 Co-evolutionary approaches

Following directly from our finding that three broad sets of actors have shaped evolution, is the conclusion that these groups co-evolve in the changing life science sector. That is, life science industrial innovation is inter-dependent with policy and regulatory actors and with public actors. Mitra has described the body of knowledge developed over the last decade as: 'a complex and distributed innovation eco-system ... [that] highlights the interdependencies between different actors and organizations that co-produce new scientific knowledge, technologies and therapies' (Mitra, 2016, p3). Geels has also suggested a triple embeddedness framework aiming to get beyond firms, markets and evolutionary economics (Geels, 2014; Penna and Geels, 2012), supporting our view that industry markets and technology co-evolve (our 'innovation actors') with civil society and broader polity. He postulates the need to get beyond market environments and introduces a second external environment – the institutional environment.

Geels' industrial regime is closest to our 'innovator category' to which we would add his task environment. We, on the other hand, have characterised socio-political

environment into two: regulation/policy; and publics. That is, we treat the policy/regulatory system and civil society as separate partners in the governance process. The specificity of the life sciences is one reason for such an approach, but also we think that these two categories are better analysed separately, since public associations and actions have very different characteristics to policy institutions.

Thus, for Geels, with his attempt to understand better how firms get to grips with markets as well as environmental change and other highly disruptive changes, the co-evolution is between industry, markets and non-market forces. For us, with our attempt to understand the social forces propelling life sciences and innovation, the co-evolution is not so easily separated between market and non-market drivers. The growth of biological knowledge and its application in food and health has increased the importance of non-market actors, especially public actors. One major implication is that the management of knowledge creation and appropriability becomes ever more complex (Brown and Duguid, 1998) and knowledge sharing/collective understanding increasingly important (Cook and Brown, 1999).

3.4 Systemic interactions

Finally, we underpin our approach with emphasis on the systemic characteristics of the life science sector. Tait (2007) summarised the theoretical underpinnings of our systemic approach. She analysed different systemic approaches in the innovation literature (including complex, technological, regional, local, national and sectoral systems) in terms of their different perspectives on the boundary of the system. She argued that the conceptual embodiment of each innovation perspective was outlined in the initial system description which then suggested a specific set of appropriate methods Tait used the sectoral systemic approach, arguing that markets and regulatory systems should not be seen as integral components within a dynamically interactive network, but rather as external to the system within the environment of the system 'influencing and/or controlling it and by definition outside the control of the innovation system itself (2007, p. 259). 'Relationships between these systemic and environmental components determine the nature of the boundary and the ease with which components can cross it, either to come under the control of the system or to leave its control (p 261)'. Tait felt that, although sectoral innovation systems thinking had described well the innovation system as a network of actors and relationships, focusing on the systems boundary would tighten analysis of the overall behaviour of the system.

She used the drug discovery blockbuster innovation model to explain her thinking. Contrary to the usual thinking that new biotechnology firms would eventually bring a new wave of disruptive innovation, she included new biotech firms within the blockbuster model, not an alternative to it because biotechs were almost entirely within the dominant system's control. There is little possibility at present that biotechnology companies will break the mould and produce a wave of creative destruction in the life sciences. Tait also argued that the regulatory system was outside the boundary and strongly influencing the nature of drug innovation. Each incremental change in regulation has been incorporated into the existing innovation system in a way that reinforces the dominant position of the multinational pharmaceutical companies, making it virtually impossible for any new entrant to break through 'far less to develop an alternative innovation system that challenges

that of the existing multinationals (op cit, p 262)'. So, the more open innovation system has not led to a broadening in the number of successful drug producers.

Tait was able to show that specifying a system boundary suggested that some innovations had the potential for disruptive innovation, for example that stem cells could have this property in innovation, regulation and in markets but that this potential will depend on regulatory changes and whether new firms can break into the pharma dominated arena. Certainly, it seems that new business models are needed to accommodate new collaborative and knowledge systems

Teece (2010) proposes that good business model design involves determining: which market segments should be targeted; what benefits the product/service will deliver to the customer; which features/technologies will be embedded within it and how they can best be assembled and offered; and how value will be captured and competitive advantage sustained. Teece argues that these issues are interrelated and that a business model is a conceptual rather than a financial model of a business. Several issues arise in applying these ideas to the development of new cell therapies. There is no pre-defined business model or body of experience that can be refined to give competitive advantage. The chosen tactics and strategies will define the business model rather than being defined by it – the business model has to be developed de novo (Mastroeni et al, 2012). The concept of dominant design is important here. Experimentation will be needed before a dominant design emerges (Tushman and Murmann, 1998).

The bottom line of our theoretical underpinnings is that there is no pre-determined business model for such disruptive innovation, creating a challenging foresight-related task for innovators.

4 Application to life science innovation systems

These theoretical underpinnings allow the development of a series of evolving analytical approaches to the study of life science innovation. We have evidence that such approaches are both ambitious and also practicable. Ambitious, in the sense of understanding the structure and dynamics of the agro- and bio-medical industries and science knowledge systems, the role of regulatory and policy regimes in shaping innovation trajectories, and the potential for public involvement in knowledge creation, management and use. Practicable, in the sense of ability to navigate a decision-making route through the complexity of the multi-actor, complex institutional dynamics of the life sciences.

The approach evolved initially through analysis of existing sectoral innovation systems - the agro-food sector, then the pharmaceutical industry. Then, we analysed incremental changes to those sectoral systems with orphan drugs and fast track regulation (Milne and Tait, 2009). This work led us to reconceptualise by better integrating our theoretical framework based on sectoral innovation systems, systemic interactions, life science specificity and co-evolutionary approaches. We also analysed the early development of potential new therapies to address major needs but with no clear market.

Our analysis of the pharmaceutical sector began with the obvious that the major companies depended on a blockbuster model of drug discovery innovation which was highly stylised around identification of promising drug targets; conducting

multi-phase clinical trials that got increasingly complex over time, and became much more expensive at later stages when large numbers of humans were needed, leading to a small number of marketable drugs (Mittra et al., 2011; Wiold, 2013). We described the lower productivity rate of R&D; high attrition rate of active compounds and rising cost of each successful drug given the large numbers of drugs 'lost' during the clinical trials process (Mittra et al., 2011).

We were able to illustrate the increasing ossification of the regulatory system which has led to an increasing crisis in this form of innovation, albeit within an industrial system that has high volumes of profit, even as profit levels decrease, allowing big pharma to acquire innovative smaller companies and to give funds back to shareholders rather than invest. One important result from our research was that the sclerotic regulatory system had increased the monopoly power of big pharma. New biotechs, for example, cannot survive the long and expensive clinical trials. Milne and Tait report that, of the nearly 2,000 active biotech medicines in preclinical development in 2009, only 15% were owned by the top 20 pharmaceutical companies, 'yet big pharma owns nearly 40% of projects in late development and over 70% of the biotech medicines that have actually reached the market over the last 20 years' (2009, p 734). The long development times involve too much risk for SMEs. Thus, we show the increasing monopolisation of a decreasingly profitable sector. The blockbuster innovation model is showing symptoms of strain in terms of R&D efficiency, profitability and public image.

More open innovation models are gradually taking on the old model as a way of analysing changes (Wiold, 2013). The drug regulatory system is now opening up somewhat and becoming somewhat more flexible to accommodate more radical innovation. One 'trend' is the large increase in new therapies as a result largely of the FDA's orphan drug and fast track programs. The US Orphan Drugs Act 1983 was a radical departure in regulatory system that proactively encouraged the development of new drugs for rare conditions. Since 1983, 1,700 orphan designations had been granted and about 300 orphan drugs approved (Milne and Tait, 2009, Wiold, 2013). The fast track designation, begun in 1998, gives opportunity for priority review for development of products for serious and life threatening conditions, illustrating that the blockbuster innovation model can be changed by changing governance systems, which itself is a result of changing public participation and pressure from patient interest groups, with patients increasingly integrated into knowledge production processes.

More recently, evidence has emerged that research into rare diseases may offer learning that will improve drug discovery processes more generally. Milne and Tait (2009) argue that the orphan drug/fast track 'regulatory opening' can be generalised both to bridge market gaps, and to provide a safe accelerated authorisation process. Another example is the major initiative from 2000 to build new institutional collaborations to bridge the gap between needs and access in developing countries. For example, public-private partnerships have attempted to develop 'products and processes relevant to the developing world' where 'it is tragically obvious that the private sector ... cannot or will not address the needs of the sickest and the poorest' (Chataway and Smith, 2006, p16).

These experiments have brought insights to the study of the opening of, and inter-organisational collaborative nature of innovation, such as the importance of innovation integrators in more open innovation systems (OECD, 2012). 'Innovation in the life sciences requires knowledge from multiple sources, in a more "open" way, including from users of knowledge, such as patients' (Wield et al, 2013). This type of innovation involves co-evolution of different sources of knowledge interacting in a shared and combined way.

5 *Application to a framework of analytical tools and guidelines?*

This section shows how we have used the Innogen framework and underpinning theory to develop a set of foresighting tools. We have developed a framework (Figure 1) along with a series of guidelines that allow actors within each of our three categories to map the likely future outcomes of their actions as they will affect, and be affected by, the other two categories, the overall focus being on the success or otherwise of the innovation trajectory as mapped along the value chain. Conceptual or quantitative scenarios, or a combination of the two, can be used to incorporate analysis of the positions and trajectories of the relevant actors operating along the value chain as they interact with elements of the innovation ecosystem (Mittra *et al.*, 2015). The degree of the foresight challenge will depend on how early in the foresight process (i.e. how far from market delivery) is the innovative development and the degree of disruption of manufacturing processes or of markets involved.

5.1 *Strategic Analysis of Advanced Technology Innovation Systems (STRATIS)*

The STRATIS approach, the core of the framework, allows analyses to be made from the perspective of scientists/innovators but also to consider the roles of regulators/policy makers and/or public/citizen stakeholders (Fig 1). It uses three levels of analysis, business models, value chains and the innovation ecosystem, and uses scenarios to identify key factors and interactions that may determine the success or failure of a novel innovative development.

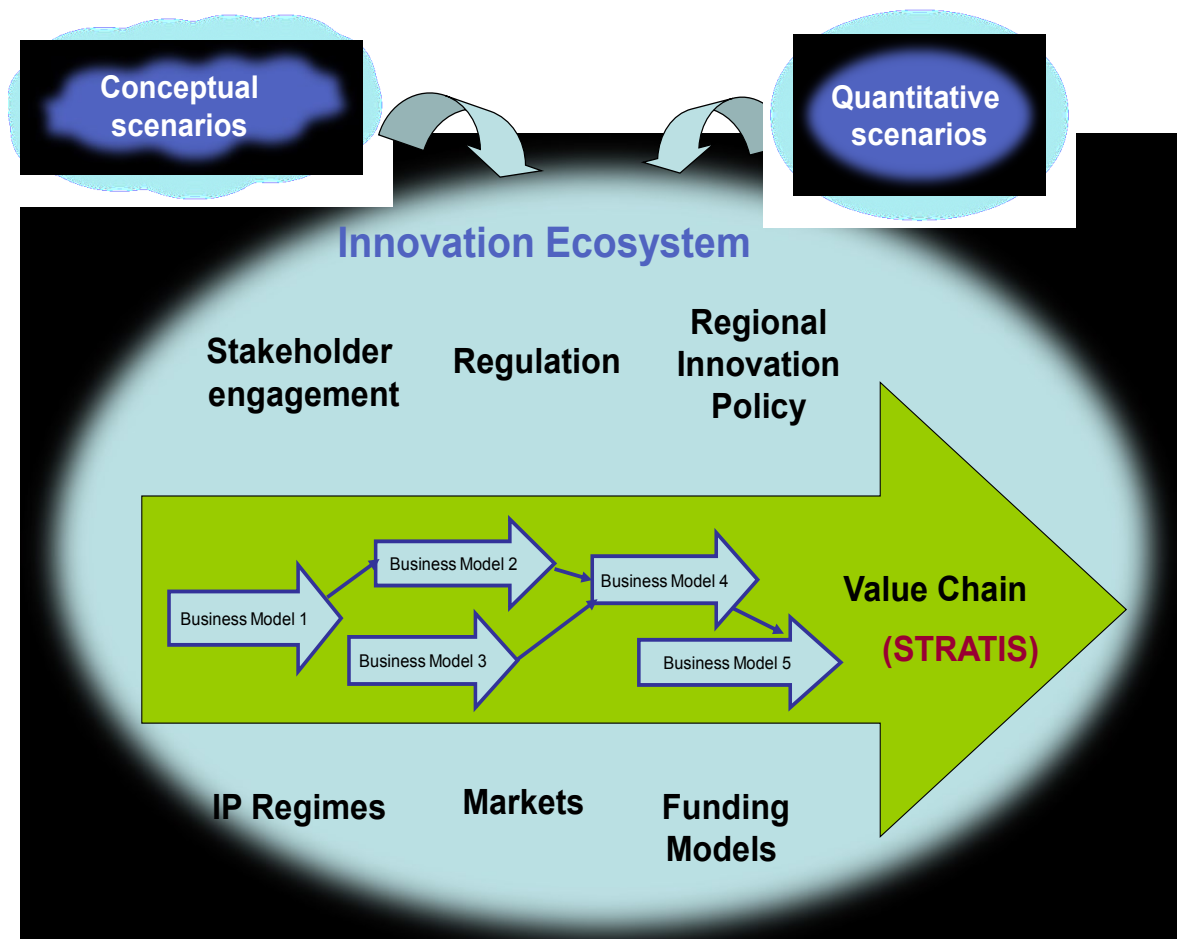
- *Business model*: a generic model based on in depth understanding of the range of business plans being developed in a specific sector or sub-sector within an overall value chain; it determines how firms within a sub-sector can create, capture and deliver economic value.
- *Value chain*: the range of activities required, and of businesses involved in taking an innovation from conception to end use, including the linkages between business models needed to reach the end-market. The value chain is likely to include several different business models, in sequence or in parallel.
- *Innovation ecosystem*: the wider economic, regulatory and political environment that may enable or constrain the ability of actors to deliver a new product or process, including cultures and identities of collectives and individuals.

The overall framework is designed to support decision making at various levels, including companies developing business plans for a specific therapy; groups of firms involved in strategy development towards constructing a value chain; policy makers considering the impact of a regulatory initiative for a new technology; and patient interest groups involved in decision-making on new therapies (Mittra and Tait, 2012; Mastroeni et al., 2012; Mittra et al, 2015). The approach can be used by

actors in any category to consider the impact of their actions on others operating at the appropriate level of analysis, and/or to think through how actions in any realm may affect their interests and planned actions. It also allows planning for the integration of business models along the value chain, as well as taking account of how environmental factors can act as enablers or constraints on innovation (Tait et al, 2015).

Life science innovation system stakeholders developing potentially disruptive innovations must begin forecasting business models at very early stages of product development, often ten to fifteen years ahead of market launch. Scenario analysis is a useful tool for planning at this early stage, often based conceptually on qualitative data but sometimes data can be used to develop quantitative models. Data for our cases come from published and unpublished literature, workshops, and interviews with scientists, regulators, companies and public interest groups such as patient groups.

Figure 1. STRATIS approach



Source: adapted from Mastroeni et al, 2012)

The STRATIS approach has been used so far to study, for example, the development of clinical grade pluripotent stem cells, a bio-artificial liver device, the production of red blood cells (detailed in Mitra et al, 2015), and stratified medical products (detailed in Mitra and Tait, 2012). For new regenerative medicine (RM) therapies there is as yet no routinized business model, or any straightforward way to tie new business approaches to existing business strategy and tactics. Since a good business model design is central to sustainable competitive advantage, it is important to build scenarios that produce insights on possible ways to capture value. Projected business models will be experimental, leading to failures and new versions before robust models begin to emerge.

Business models will also depend on successful negotiation of relations with other businesses in other parts of the value-chain as the value chain takes shape (Nature, 2002). Mason and Manzotti (2009) have argued that there are serious challenges for companies wishing to develop RM therapies, which are disruptive of existing business models and value chains. New product and process approaches will be

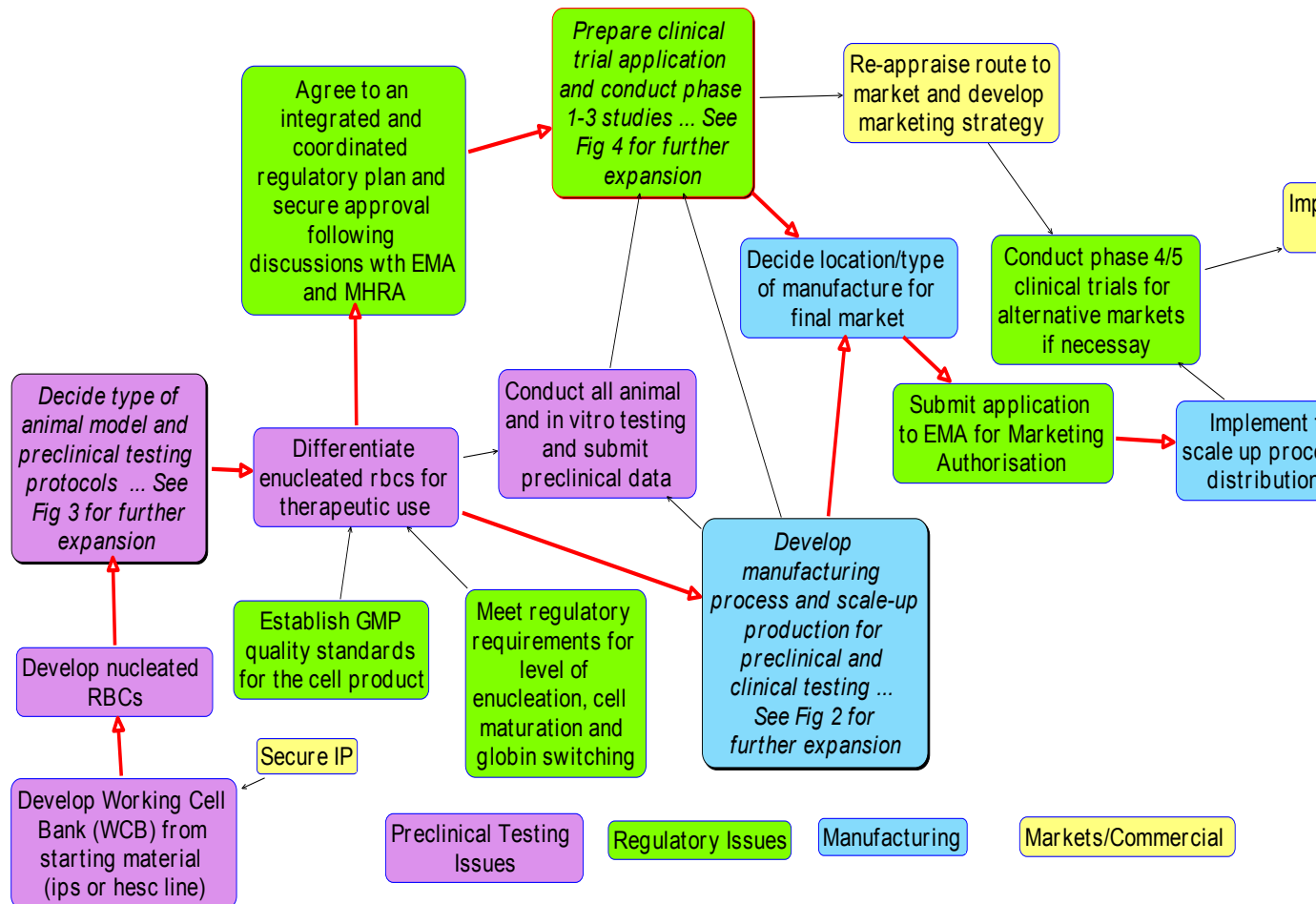
needed together with a service infrastructure to support implementation of the therapy – that is, not only new business models but new value chains will be created (Mastroeni et al, 2012). Such value chains, in turn, will depend on the new innovative specialist RM companies finding ways to collaborate with existing big pharma and health care providers.

The innovation ecosystem, the environment within which the value chain is embedded, includes complex regulatory, marketing and public/patient interactions. An example of a problematic element of an innovation ecosystem for RM products is the regulatory system, which is based on that for pharmaceuticals. This regulatory system evolved within an innovation ecosystem that increasingly honed clinical trials for mass drug use and creates problems for highly stratified and rare disease therapies. But, at the moment, the RM regulatory system has tended to use the unsuited drug regulation as its model for all new therapies. Mitra et al (2015) give a more detailed explanation of the problematic regulatory system for RM products.

In the cases studied so far, we have used this three level approach, together with scenarios analysis (Van der Heijden, 1996) to build and test conclusions about potential future RM value systems.

Using a software tool (Banxia Decision Explorer) strategic maps were developed. Figure 2 gives an example of a summary map, showing critical points in the pathway at which scale up and manufacturing would need to be finalised. Similar maps can be developed for other types of decision around life science innovation. Research and evaluation has also taken place of the extensive public engagement elements of product development in these cases. For example, King (2013) undertook detailed research on the public engagement programme of red blood cell product development, showing both the communication and interactive skills developed by scientists and also the ways in which they used the knowledge they gained.

Fig 2 Value chain critical points for production of cultured red blood cells



Source: (Figure 1 From Mitra et al., 2015, New Biotechnology)

The approach has proved effective. As noted above this approach involves foresighting future business models and makes it possible for participating researchers and companies to better conceptualise and visualise future business models. The approach also allows for new data to be integrated to improve modelling and for comparison of different business models – of different companies and sectors. Based on the research, stakeholders had a better understanding of their potential future business models, and of the challenges to be overcome and of the order in which they would need to be addressed.

6 Conclusions

We have aimed to demonstrate that it is possible to develop new and useful approaches to the analysis of future science and technology in areas of major concern to complex groups of stakeholders. The paper began by evidencing the complexity of

the multiple disciplines that generate knowledge in the life sciences. The rise of biology has radically changed the nature of knowledge production in the life sciences, but so has the rise in the number of social actors involved. The paper went on to show that multiple industrial activity is involved in translating science into new products and processes, well beyond the large pharmaceutical and agro-chemical companies that dominated in the past. Such changes have increased the complexity of social interactions between different types of actors. We make the case for a systems approach that requires sectoral specificity, holistic analysis of interaction between three broad groups of actors: innovators; policy-makers and regulators; and publics, bringing co-evolutionary results as knowledge and innovation are generated. We go on to argue that new tools are needed and we describe one of the tools used in analysing and re-conceptualising innovation in the new life sciences. We developed a framework and tools which allows application of theoretical perspectives (sectoral specificity, co-evolutionary and systemic interaction analysis) to specific cases of business model development of new life science products. We worked with stakeholders at three levels from ecosystem to value chain and in innovative life science business model developments. Specifically with RM products, negotiation of product development involves constant inter-organisational adaptation as new RM companies find ways to collaborate with existing big pharma, health providers and regulators.

Various insights have emerged from our analysis that build on our theoretical underpinnings (section 3).

- 1 We demonstrate a new approach to social and natural science interdisciplinary collaboration to foresight product development pathways. The bringing together of natural and social science knowledge is essential if sense is to be made of new business models and value chains in development for new RM therapies;
- 2 We have illustrated Teece's argument that a business model is conceptual rather than financial. Not only that but since the business models for new life science therapies do not yet exist, the STRATIS approach is a means to experiment with, and visualise, potential business models and potential designs for new products;
- 3 We have shown the importance of open innovation approaches if a complete value chain is to be shaped. We show (as does Cooke, 2005) the importance of the inter-organisational knowledge value chain (containing exploration knowledge, examination knowledge and exploitation knowledge) and the absorptive capacity requirements for success of such open innovation systems;
- 4 The STRATIS methodology has brought together a range of aspects of value chain analysis for the development of RM therapies, including: market identification, complex manufacturing processes and their scale and location in the value chain, distribution processes for vulnerable living materials, partner selection and collaborative/networking approaches, intellectual property and access to cell lines, managing clinical trials and other regulatory approval processes, controlling costs and identifying alternative sources of value;

- 5 Our triadic approach to the life sciences emphasises the importance of integrating regulatory and public stakeholders to avoid antagonistic approaches to future technology especially at early developmental stages when hype and promise can be fed by the huge uncertainties over what might be possible in the middle and distant future. The hype and promise associated with new life science technologies can, we found, be attenuated through analyses like that of STRATIS integrating business models and value chains with enabling and constraining factors in the innovation ecosystem.

We propose that these insights will be of practical, methodological and theoretical benefit to analyses of complex innovation systems in life sciences and other new technologies. The next step is to use the tools in a diverse group of sectors, to learn and to adapt them.

Acknowledgements

The authors would like to acknowledge and thank the UK Economic and Social Research Council (ESRC) for its centre grant to the ESRC Centre for Social and Economic Research on Innovation in Genomics (INNOGEN) (Grant number RES-145-28-0002).

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