***IST abstract** for Track 1: 'Whole system reconfiguration across production and consumption'*

Transition to distributed sustainable innovation models

Ellen Moors, Marlous Arentshorst, Wouter Boon, Jarno Hoekman*

**Corresponding author*. Copernicus Institute of Sustainable Development, Utrecht University, Heidelberglaan 2, PO Box 80.115, 3508 TC Utrecht, The Netherlands. e.h.m.moors@uu.nl

e.h.m.moors@uu.nl

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Copernicus Institute of Sustainable Development

Utrecht University

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Introduction

Society faces complex global challenges, such as ageing and unmet medical needs. These 'wicked' problems require to move away from the linear model of innovation towards examining alternative innovation models, in which the nature of problems and solutions co-evolve. Through democratization, digitalization and rising self-actualisation, citizens and consumers are increasingly involved in co-developing innovations (e.g. Bogers *et al.* 2010;. Sha *et al.* 2007; Von Hippel 2005, 2016). They often collectively act in (distributed) communities creating innovation platforms (VanDijck *et al.* 2016), such as web-based patient networks. Furthermore, complex innovations cannot be understood without intertwined institutional practices (Lounsbury *et al.* 2007), as for example case-by-case regulation of personalized medicines shows (e.g. Kukk *et al.* 2016). We need a better understanding of these new distributed innovation models that occur between individuals, organisations and institutions. Therefore, this paper contributes to understanding distributed modular innovation processes by combining insights from innovation studies, STS and institutional sociology.

The empirical context is the pharmaceutical innovation system, as the current system is increasingly struggling to deliver innovative medicines at affordable costs for unmet medical needs (Moors *et al.* 2014). The current system is too complicated, too expensive and too inflexible to support drugs tailored to individual patients. This emphasizes the need for disruptive reform of the current innovation system and alternative ways of

(bio)pharmaceuticals production and manufacturing. Whilst there is still a strong focus on fixing the problems in the current pharmaceutical system, in practice a combination of more disruptive reforms is necessary to make drug development sustainable: i.e. safe, affordable individualized drugs for all in need. Distributed, local, cost-effective production and innovation of biopharmaceutical therapies is one proposed solution direction. Distributed drug production and development offers an alternative innovation model to circumvent some of the technological, regulatory and financial challenges preventing provision of the right drug at the right time to the right patient (Schellekens *et al.* 2017). The aim of this research is to study the different socio-institutional challenges of various distributed drug development technologies regarding their embedding in clinical practices.

Theoretical background

The development and use of medicines is extensively institutionalized through regulations, guidelines, standards, tools and approaches like randomized controlled trials to assess the safety, efficacy, quality and performance of medicines (Timmermans and Berg 2003; Howick 2011; Rafols et al. 2014). However, this evidence-based logic has only evolved over the past decades as a departure from local production, manufacturing and use of medicines (Slezak 1996; Giam et al. 2011). This study shifts attention back towards development, production and use of drugs in a distributed, decentralized way. Historically, distributed production of medicines is performed through so-called magistral production[1]. Such shift inherently leads to misalignments with existing procedures, rules and interests, indicating an 'institutional void' (e.g. Hajer, 2003). Distributed, in-hospital, production of drugs challenges the dominant institutional model of a) centralized authorization of medicines based on evidence from clinical trials, and b) safety monitoring based on big data. In addition, c) roles and responsibilities of the actors involved (such as pharmaceutical firms, investors, insurers, patients, medical professionals, hospital managers, biomedical researchers) will be changing due to the distributed and modular character of these new production technologies, with more autonomy and as far as evidence is concerned for the users of the new technology. To investigate the institutional void and eventually build safeguards to govern it, we take a socio-institutional perspective with the aim to identify different challenges in locally produced and distributed personalised medicine[2]. We identify three challenges:

[1] Magistral production concerns producing medicines that fit the unique need of a patient and implies 'bedside' production in hospital pharmacies, with direct and short connections between laboratory and individual patients.

[2] Personalised or precision medicine is tailoring diagnosis and therapy to individual patients based on their predicted response to therapy or risk of disease (Collins & Varmus, 2015). It is expected that tailoring leads to

First, in the current medicines regulatory framework medicines evaluation agencies authorize medicines based on an assessment of benefits, risks, and quality of production. Magistral production of drugs in hospital pharmacies operates outside this model as these therapies are not subject to external evaluations. Magistral production draws on the professional competences of the medical specialists and pharmacists. Such a decentralized approach challenges a traditional evaluation of a drug's benefit/risk ratio by medicines agencies and prescription of a medicine produced by a pharmaceutical firm versus a medicine locally produced by the hospital pharmacist. We argue that this distributive approach requires innovative 'regulatory science' (Jasanoff 1995; Irwin et al. 1997; Hamburg 2011; Hayden 2012) to inform treatment decisions. Questions arise about the need and feasibility of clinical trials to underline the efficacy and safety of locally-produced precision medicines, and about the possibility to use novel research designs such as n=1-trials, i.e. studies with only one patient enrolled. In addition, regulatory questions will be raised about the distributed production of medicines in a local hospital pharmacy context. In addition, increased knowledge about genetic causes and mechanisms of diseases may lead to the local production and development of personalized or precision medicines. By taking into account individual variability in genes, environment and lifestyle, tailor-made treatments and far-reaching patient stratification becomes increasingly probable (Collins and Varmus, 2015). Given this personalized nature of the therapy, also questions exist about (expected) variability in drug response and the possibility to extrapolate research findings from one patient to others.

Second, in the current regulatory paradigm, safety is monitored on a systemic level. Medicines agencies search for potential safety signals in big datasets and take action after a signal has been validated and discussed in expert committees (Ebbers et al. 2011; Raine et al. 2011). Yet, in bedside production risk monitoring and management tend to take place under the exclusive professional responsibility of a medical practitioner, influenced by peer evaluation. It is unclear whether additional risk governance structures are necessary to manage these risks (Boon et al. 2014). Examples could include intensive monitoring of patients (e.g. Meijer *et al.* 2014), making products fully traceable for the specialist, pharmacist-producer and patient, and collecting data through patient registries. Insights from the risk governance literature (Stirling 2003; Renn 2008; Renn et al. 2011) can be helpful to discern conditions under which risks for locally-produced and distributed personalized

improved treatment efficacy and safety. Despite these high expectations, the developments in personalised medicine has been slower than expected (Kukk et al., 2016; Joyner & Paneth, 2015).

medicines can be managed and monitored in a responsible way. In other words, the *scalability* of the modular, distributed manufacturing technologies matters.

Third, a STS and innovation studies approach supports further uncovering the (perception of) new roles and responsibilities of distributed stakeholders and maximizing the quality of deliberation and the experimentation process itself (e.g. Owen *et al.* 2013).

Methodology

In order to better understand distributed manufacturing technologies we followed a 2-step research approach: First, we did a literature review of various distributed drug manufacturing technologies. We zoomed in on biopharmaceuticals. PubMed, Embase and Scopus literature databases were searched systematically for publications describing alternatives for large-scale industrial production of biopharmaceuticals. Articles were deemed eligible if they: described a model or method for end-to-end therapeutic drug manufacturing; addressed problems of affordability of drugs; focused on local/ distributed/ miniaturized/small(er)-scale manufacturing and/or scalable/on-demand processes in the period 2007-2017 (covering most recent developments). The shortlist of publication titles was further downsized by applying the inclusion and exclusion criteria to full text screening. Additional sources were located through hand-searching and backtracking of citations in the reference lists of the reviewed articles about novel practices of drug manufacturing. Of each article, key passages were annotated and coded in Covidence according to predetermined variables: brief technical description of the distributed drug development model or method, its stated aims and expected advantages. In addition, information was extracted about the considerations mentioned regarding implementation in practice. These could be, for example, technical challenges, regulatory and safety aspects, or suggestions for organizational structures. Subsequently, we assessed the timelines of each technology in terms of its anticipated realization in practice. If there were examples or actual case studies described, we briefly outlined these. Lastly, we identified white spots, which we defined as (regulatory, ethical and societal) issues that are not addressed but that are relevant to successfully implement innovations in the larger system of pharmaceutical innovation.

The second analytical research step was to define the incentives, roles and responsibilities of stakeholders involved through desk research. Stakeholders involved in distributive production of drugs include clinicians, technology developers, pharmacologists, patients, pharmacists, hospital management officials, regulators and other users. After the desktop research, we included actual consultation of these stakeholders via interviews and focus group

discussions. The researchers actively challenge stakeholders to articulate their ideas, problem definitions, normative objections and reflections. This line explored institutional, normative and ethical considerations. The articulation was facilitated by interactive action research: preparatory interviews and field work provided input for the creation of scenarios and visions of how the implementation should look like. These visions were then discussed in focus groups to learn about (in)congruencies and to articulate first governance guidelines for responsible bedside production and distribution of (personalized) drugs.

Preliminary results and implications

The literature database search resulted in 2866 unique records, with 73 articles reviewed in full by two assessors. Once fully reviewed, a further 62 were excluded mainly because a) these articles did not describe and end-to-end manufacturing process or b) large-scale production was the ultimate goal. Hand searches resulted in one extra record included in the analysis, leaving 12 sources for data extraction and analysis. With one exception, all reviewed papers were published within the last four years (2013-2017). After analysis of these 12 papers it became clear that each paper related to either one of three categories of alternative technologies for biopharmaceutical production: 1) modular and flexible platforms; 2) plant biotechnology or molecular pharming; or 3) 3D-printing. For each category we briefly describe the technology, the aims, the expected advantages and the implications described for implementation in practice (Table: tbd). We also provide an overview of examples described and, when indicated, the timelines estimated for realization in practice.

From this review into alternative, cost-effective ways to locally produce biopharmaceuticals, three categories of technologies emerged from the literature: modular and flexible platforms (n=8); plant biotechnology (n=2); and 3D-printing (n=2). Each category can be viewed as a type of disruptive innovation as they pose radical challenges to the current pharmaceutical innovation system.

In terms of timelines, the initiatives and proof-of-concepts presented in the literature demonstrate that modular and flexible manufacturing platforms are most likely the first to become a reality in the near future, possibly within the next 5 to 10 years. Integrated table-top systems which require minimum actions will likely take longer time to develop. 3D-printed drugs have been encouraged by regulatory authorities, and the first printed small-molecule product was licensed two years ago. Although 3D-printing of biopharmaceuticals is substantially more complex, we infer from the literature that it might not be long before

technical hurdles are overcome, which could mean 3D-printed biopharmaceuticals might become a reality within the coming decade.

Our results demonstrate that distributed manufacturing technologies are already permeating practice, from proof-of-concept exercises and pilot studies to the first products receiving regulatory market approval. Given their disruptive character, these innovations inflict on the practice and governance of traditional biomanufacturing. Three important (socio-institutional) challenges of distributed manufacturing of drugs are identified:

a)Ensuring sufficient levels of safety, efficacy and quality. The reviewed publications elicit varying degrees of detail when it comes to a description of considerations for implementation in practice. Some pose helpful questions for shaping new practices. Choi *et al.* (2015), for example, call upon the professional community of hospital pharmacists to evaluate their readiness to adopt new manufacturing platforms "for the betterment of patient care". Schellekens *et al.* (2017) ask the community to conceive of a new—but supportive—regulatory framework for the novel practice of bedside production. Liaw *et al.* (2017) highlight regulatory issues in terms of safety and quality. Other publications mostly elaborate on the benefits and opportunities of distributed manufacturing technologies, but remain relatively silent on a number of aspects relevant to societal implementation (Excell 2013; Almhem *et al.* 2014).

b) *Scalability: large-scale, local versus distributed manufacturing*: Diblasi *et al.* (2007) specifically foresaw a new role for modular platforms in the biopharmaceutical industry, and in many of the other publications, it seems implied that distributed production processes still have a place in designated manufacturing facilities, though much smaller in size and considerably cheaper to build and operate (Almhem *et al.* 2014). However, others point towards the potential of the innovations outside the context of traditional manufacturing facilities, such as in hospitals, remote areas and battlefields (Choi *et al.* 2015; Lewin *et al.* 2016; Schellekens *et al.* 2017). This raises the question: who might be potential manufacturers? Traditionally, developer and manufacturer are the same entity, but with these new technologies it is imaginable that developer and manufacturer might be different. It might even mean that manufacturer and prescriber will overlap.

c) *Changing roles and responsibilities of medical professionals*: Since the distributed technologies are envisioned at the point of care, also the roles of doctors, pharmacists, patients, the pharmaceutical industry and regulators may change. Schellekens *et al.* (2017), for example, envision bedside production as a practice exempt from regulatory manufacturing requirements, as they categorize it as drug compounding. Nevertheless, these authors do

concede that it will be "important to introduce regulations ensuring a quality control system", but that these regulations should be preferably implemented at the institutional level (Schellekens *et al.* 2017).

As innovative distributed manufacturing technologies are technically and economically feasible, they will most likely change the current practice of biopharmaceutical production in the near future. To maximize the expected advantages/benefits (e.g. personalization and global on-demand production with lower investment costs and shorter development times) and minimize unintended consequences, reflection is warranted on the implications of potential new manufacturers, settings, responsibilities and governance structures.

The task now will be to evaluate how new distributed manufacturing technologies may be established in existing structures, or whether current structures warrant adaptation (e.g. Faulkner & Poort 2017). The transfer of complete end-to-end manufacturing platforms from developers to manufacturers elsewhere—including practical skills and know-how—raises questions about rights and ownership, and how it will be ensured that manufactured biopharmaceuticals indeed remain affordable and that such systems are sustainable in the future.

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