

Special Issue: Therapeutic Biomanufacturing

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In-Hospital Production of Medicines: Preparing for Disruption

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In-hospital production of affordable medicines holds potential to address problems of drug accessibility. However, expanding the scope of magistral preparation to include high-cost drugs and complex biologicals gives rise to new challenges. We discuss ethical and regulatory complexities faced by Dutch initiatives defying the current pharmaceutical system through magistral preparation.

Pushing the Regulatory Boundaries

The current pharmaceutical system is increasingly struggling to deliver medicines at affordable costs. Many newly introduced drugs are low-risk innovations and do not sufficiently meet society's needs [1]. Even if new drugs do address an unmet medical need, their sprawling costs pose a substantial threat to the sustainability of health-care systems worldwide [2]. These problems indicate that the current system is in need of disruptive innovations that radically change the way medicines are developed, produced, and delivered. In-hospital production of medicines as magistral preparations could provide a potential solution. Magistral preparation of small-molecule drugs and radiopharmaceuticals is a skill practiced by many hospital pharmacists today. Considering the acceptance of in-hospital production of advanced therapy medicinal products (ATMPs) like complex

gene and cell therapies in the EU [3], local production even of otherwise highly expensive or personalized biologicals lies on the horizon [4–6]. However, such a new practice will give rise to regulatory and ethical complexities and might require a completely new type of governance. In this Science & Society article, we discuss several recent Dutch initiatives of magistral preparation – ranging from the preparation of small molecules to biologicals – to identify the complexities that need to be addressed in preparing for a practice that could potentially disrupt the entire pharmaceutical system.

Recent Initiatives of Magistral Preparation: From Small Molecules to Biologicals?

In late 2017, The Netherlands was caught up in heated public and political debate about pending reimbursement of the newly marketed drug Orkambi to treat patients with cystic fibrosis (€170 000 per patient per year). Amidst the turmoil, pharmacist Paul Lebbink declared he would start magistrally preparing the drug for a fraction of the price. About 1 year later, a Dutch university hospital announced that it had started producing chenodeoxycholic acid (CDCA) to treat patients with the rare genetic disorder cerebrotendinous xanthomatosis (CTX) by directly purchasing the active pharmaceutical ingredients. This small-molecule drug – a bile acid typically used to dissolve gallstones – was prescribed off-label to CTX patients for years. However, over time, all brand variants of CDCA were taken off the Dutch market one by one, only to be reintroduced later by Leadiant Biosciences for the indication CTX under the EU's orphan drug designation program. The 'new' and only registered version of CDCA now costs around €170 000 per patient per year [7]. A similar phenomenon occurred in The Netherlands with the magistral preparation of the radiopharmaceutical lutetium-octreotate to treat patients with rare neuroendocrine tumors. The drug had originally been developed by doctors in a

hospital laboratory and through a chain of events ended up being exclusively owned by Novartis under the brand name Lutathera by 2017 [8]. Lutathera now costs €20 000 per IV drip while, until then, three Dutch hospitals had been producing the drug for no more than €4000. Serious attempts to employ magistral preparation as a way to curb health-care costs or to secure patient access are not limited to well-defined products. In a recent issue of *Nature Biotechnology* a team of Dutch researchers claim that 'bed-side production' of expensive and personalized biologicals will soon be possible [4]. Allegedly, Utrecht University has initiated a pilot program for the production of biologicals in hospital pharmacies financed by the major Dutch health insurance companies. The researchers even allude to the development of a 'bionesspresso', an easy-to-operate, tabletop-sized machine that produces cheap and personalized biologicals with the push of a button [4] (<https://www.uu.nl/nieuws/geneesmiddelen-op-maat-met-de-bionesspresso>). Of course, magistral preparation of biologicals is far more complex than that of well-known small molecules and radiopharmaceuticals. Nevertheless, hospital exemptions for the production of ATMPs could open the door to in-hospital production of highly complex therapeutics, including biologicals.

Challenges to Magistral Preparation

A philanthropic organization donating €5 million to the CDCA initiative, health insurers, and even the Dutch Ministry of Health have expressed their dedication to advance magistral preparation [9]. Magistral preparation of Orkambi and CDCA and the idea of a bionesspresso were covered by the media with considerable optimism. Nevertheless, to date no patients are receiving magistrally prepared CDCA, Orkambi, or biologicals. Lutathera is still prepared by hospital pharmacists, but they worry that this practice may not last for much longer [8]. So what are the challenges faced? In the CDCA case, Leadiant

had submitted an enforcement request to the health-care inspectorate about the legality of in-hospital production. The investigation by the inspectorate suggested concerns about the purity of the raw materials used and the production of CDCA was subsequently suspended. However, in its report the inspectorate explicitly stated that magistral preparation of a registered product is legal on a named-patient basis, when in small quantities and using only acknowledged raw materials [10]. Pharmacist Lebbink was forced to search for a new supplier of the raw materials to produce Orkambi after his original supplier retracted. Lebbink says he now plans to perform extensive analyses on the raw materials to assure their quality. Magistral preparation of Lutathera still happens, but soon might run into a similar problem with respect to obtaining lutetium. As Novartis appears to have recently bought the only acknowledged supplier of lutetium worldwide, hospitals fear that they may soon be deprived of the necessary resources to continue producing the magistral variant of Lutathera for their patients [8].

Ethical and Regulatory Complexities

The challenges faced in the Dutch cases point toward three complexities. First, there is a lack of guidance on how to interpret the conditions for allowing magistral preparation. Dutch legislation – which follows from EU law – demands that magistral preparations be based on a medical prescription for the individual patient attending that particular pharmacy and that preparations may be only ‘small scale’ [11]. However, ‘small scale’ has not been defined so far. Magistral preparation of CDCA for all approximately 50 Dutch patients could be considered small scale, but at the same time it meets the needs of the whole patient population of a country. Also, if CDCA capsules are to be produced in batches, this would defy the claim that the product is magistrally prepared for a named patient. Second, there is no well-defined system for

oversight. As magistral preparations are exempted from marketing authorization, these do not have to comply with requirements for commercial manufacturers. As such, no documentation is needed that validates product quality or provides insight into preparation methods and conditions. Despite Good Manufacturing Practice (GMP) partly covering quality issues, the lack of insight into quality by design is a major issue for authorities. Especially considering the shift toward batch production of more complex products, new governance is likely to be required to assure quality, safety, and efficacy. Third, the cases indicate that the existence of competing interests simply cannot be ignored. Commercial manufacturers and representatives will protect their business interests and will not shy away from legal or financial action. A key question seems to be whether magistral preparation should be viewed as complementary to or a substitute for commercial product development. Currently, it is unclear how the availability of a registered or patented drug relates to magistral preparation. While EU legislation does not rule out preparations of registered drugs, patent law does protect manufacturers against patent violations. The Royal Dutch Pharmacists Association (KNMP) specifically states that only when treatment with the commercially available drug is not possible or sufficient, pharmacy preparations may provide an alternative (<https://www.knmp.nl/patientenzorg/geneesmiddelen/apotheekbereidingen/knmp-richtlijn-bereiden>). The Dutch Minister of Health issued a policy letter emphasizing the position of magistral production but also saying that using registered medicines remains the norm, ‘of course against a reasonable and acceptable price’ (<https://www.rijksoverheid.nl/documenten/kamerstukken/2019/04/08/brief-magistrale-bereidingen-aan-tweede-kamer>). The Dutch Association Innovative Medicines has already emphasized the importance of collaboration with industry to arrive at sustainable solutions. In

particular, industry articulated that in-hospital production will impede innovation and eventually undermine the whole basis of the pharmaceutical system.

Ways Forward

To move in-hospital production of medicines forward in a responsible and sustainable manner, a new type of governance is likely to be required. For this, a clearer taxonomy of magistral production is needed, accounting for relevant differences in motives, types of products, and the technologies used. A locally produced capsule of CDCA is something evidently distinct from a personalized product emitted from a bionepressor. Clear rules that safeguard the quality, safety, and efficacy of the products should be established in co-creation with different stakeholders, at least including pharmacists, doctors, inspectorates, regulators, and reimbursement agencies. We suggest that good governance is a system covering the entire production chain, from the sourcing of raw materials all the way to delivery, patient monitoring, and registries. In such a system, health-care inspectorates and regulatory authorities are aware of the balance between their distinct roles and responsibilities. Moreover, a broad political discussion is needed – nationally and at the EU level but perhaps even globally – about what is societally desirable when it comes to affordable access to safe and effective drugs. Ultimately, involving patients is paramount. To assess public acceptance, we need to identify patients’ views, needs, and preferences. In the face of ever-decreasing patient access to affordable medicines, moral obligations exist to maximize the potential of promising alternatives through timely incorporation of regulatory and ethical complexities.

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Forum

Minicircle DNA: The Future for DNA-Based Vectors?

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Minicircle DNA (mcDNA) is a smaller and safer version of non-viral DNA

vectors that results from a cutting-edge *in vivo* recombination process to excise prokaryotic sequences from plasmid DNA (pDNA). Considering the molecule's potential and increasing interest as a non-viral DNA-based therapeutic, bio-manufacturing methodologies need to be improved, especially in downstream processing.

mcDNA

mcDNA has attracted significant attention as a gene therapy vector, DNA vaccine, or intermediate in cell-based therapies due to its strong performance and safety as a non-viral DNA vector [1], especially in comparison with the popular pDNA vector (Box 1). Although mcDNA was designed specifically to overcome the limitations of pDNA, its origin derives from a pDNA-like structure called a parental plasmid (PP). A PP contains specific sequences, such as *att*, *loxP*, *MRS*, or *attP/attB* recombination sites, that allow its recombination into two different molecules: mcDNA and miniplasmid (mP) (Box 2) [2]. Despite the well-documented potential of this outstanding biopharmaceutical, showing better performance than pDNA in cell transfection and gene expression in different fields, little attention has been given to mcDNA manufacturing restrictions and recent progress that has been made to overcome them. These points are crucial to understand how to further improve the yield and purity and reduce the costs of mcDNA manufacturing to reach its large-scale potential.

mcDNA Processing

Upstream Processing

While a mP inherits all the prokaryotic sequences necessary for PP amplification within the prokaryotic system, including the replication origin and selection markers, mcDNA retains the eukaryotic sequences required for the therapeutic

effect, such as the promoter and gene of interest [2]. PP production begins similarly to pDNA production, and induced *in vivo* recombination of the PP into mP and mcDNA follows. Simultaneously, in some particular systems, certain events can occur to promote the cleavage and elimination of mP and unrecombined PP impurities (Box 2). Each system can have a different impact on its downstream processing since variable mcDNA, PP, and mP content can result from the recombination process, affecting not only the final mcDNA yield but also its contamination degree.

Downstream Processing

Due to its peculiar production features, mcDNA upstream processing still requires optimization since mcDNA is often contaminated with the PP. Moreover, the methods used to purify pDNA are not as efficient for purifying mcDNA. This unfortunate situation is mainly due to the similar genetic composition of the mcDNA, PP, and mP molecules. The PP and mP impurities contain analogous structural and chemical properties to mcDNA, which hampers the purification process because the impurities interact similarly with the chromatographic matrix. These drawbacks have prompted the use of affinity chromatography to isolate mcDNA.

Backbone Modification

Until 2016, the methods used to purify mcDNA strongly depended on custom backbone modification. For instance, in 2008, a strategy for mcDNA purification was developed that involved modifying the PP backbone to include a lactose operator (LacOp) sequence in the mcDNA template [3]. The sample would be loaded onto a chromatographic column modified with a LacOp repressor protein. Given the specific LacOp sequence, mcDNA would bind to the column, while the remaining contaminants would be eluted. However, this approach requires full PP recombination since the presence of the