Making individualized drugs a reality

Huub Schellekens, Herre Talsma & Enrico Mastrobattista

Magistral drug preparation offers a model to circumvent many of the technological, regulatory and financial challenges that prevent provision of the right drug at the right time to the right patient.

Precision (or personalized) medicine promises to improve the efficacy and safety of pharmacotherapy for individual patients. But the truth is that precision medicine today is not tailored to individual patients; it is tailored to groups of patients. Precision drugs are tested on groups of patients that share a disease marker but other differences among patients are not taken into consideration. Once approved, the medicines produced on a bulk scale are prescribed to patients that share the disease marker specified on the drug's label. Built on the twentieth century drug development model, today's precision drugs still require the building of a robust intellectual property position, the negotiation of a complex and stringent regulatory system, and the application of twentieth century manufacturing models, all of which inflate drug prices and prolong product development times.

We contend that technological advances now enable both bedside development and magistral drug production as an affordable, safe and flexible alternative for treating patients with individually tailored biopharmaceuticals. As this magistral model is overseen by a physician for individual patients under their care, it is only minimally regulated. This means magistral drugs dispense with the need for protracted marketing authorization, dramatically reducing development times and costs. Here, we outline the challenges inherent in the current model for precision medicine and propose a new model based on the magistral system that can meet the demands of twenty-first century individualized patient care. Although many questions remain unanswered about the pros and cons of bedside drug production, we hope that this Commentary will stimulate vigorous debate and new thinking about this alternative way of making drugs.

OJO Images Ltd / Alamy Stock Photo

In magistral development, a doctor–patient consultation could be the start of a process in which the right amount of drug is produced for the right patient at the right time.

Huub Schellekens, Herre Talsma & Enrico Mastrobattista are in the Department of Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands.
e-mail: h.schellekens@uu.nl

Vision and reality

In recent years, the average clinical effect of new drugs has been steadily declining[1], notwithstanding the introduction of several breakthrough medicines against hepatitis C, numerous **[AU: seems to contradict "several"; delete?]**rare diseases and cancers. Moreover, for the majority of disorders, drugs continue to be ineffective in a large proportion of patients, while they cause side effects in all patients, including those who do not respond (e.g., ref. 2). The number of patients benefitting from pharmaceutical treatment should be balanced against the patients suffering from serious adverse drug reactions. In the United Kingdom, 6% of all hospital admissions were reported to be caused by side effects of drugs[3].

Precision medicine has been touted as a way to improve the efficacy and reduce the adverse effects of pharmaceuticals[4]. It is defined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR; Lawrenceville, NJ, USA) as "the use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches"[5].

In his 2015 State of the Union address, US President Barack Obama unveiled the Precision

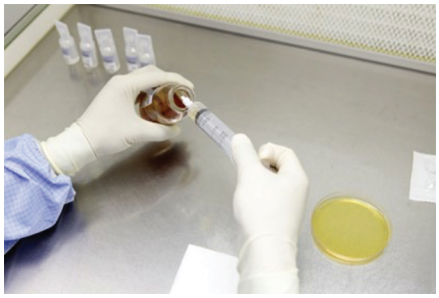

Figure 1 Magistral production in a laminar flow at the Transvaal Pharmacy, a local pharmacy in The Hague, The Netherlands. The pharmacy is owned by P.W. Lebbink, who pioneered individualized medicine on the basis of magistral production. At his practice, Lebbink encountered a small boy who suffered from a very rare serious condition leading to high blood levels of ammonia for which there was no commercially available treatment. On his own, Lebbink figured out a treatment for the boy based on carglumate acid, which he bought from a local chemical company. He kept the boy alive for €3,000 ($3,300) per year. Then in 2007, the biotech company Orphan Europe SARL (Puteaux, France) received marketing authorization to distribute the same chemical as an orphan drug. The company priced the drug at €25,000–€250,000 ($27,000–270,000) per year for a 20-kg child. The company subsequently started several legal cases to stop Lebbink from making the drug via magistral production for the little boy. Although Lebbink won all these cases, he subsequently decided to stop magistral production because the health insurance companies refused to pay for his magistrally produced drug any longer. He is still active in magistral production of other drugs.

Medicine Initiative, which has a goal of galvanizing the accrual of data from a million patients to move the concept of precision medicine into every day clinical practice (https://obamawhitehouse.archives.gov/precision-medicine). Under the umbrella of this initiative, the US government allocated $215 million in 2016, mainly to the US National Institutes of Health and the US National Cancer Institute, to expand research into the pathogenesis of cancer, standardize data collection and promote private-public partnerships. President Obama and other proponents of personalized medicine promised it would not only optimize treatment of individual patients, but also stimulate the economy, optimize the involvement of patients in their treatment and save healthcare dollars[6].

All this belies the reality of the commercial development of precision medicine, which has been heralded for decades, but is only slowly making an impact on patient care. Since the completion of the first draft of the human genome sequence in 2001, we have witnessed approval of only a handful of personalized treatments[7]. Indeed, the development of new drugs based on what is known of the molecular mechanisms of disease has proceeded at a glacial pace[8–10]. **[AU:OK? (to avoid using 'basis' twice)]**The slow progress in precision medicine is attributable to several factors.

First, for a long time, there was little economic impetus for industry to market drugs solely to responders when its existing pharmacoeconomic models incentivized companies to sell as much drug to as many patients as possible, regardless of whether those receiving medication were responders or nonresponders. By definition, commercial drug development is driven by the profit incentive as much as by whether patients fail to respond to a therapy (although now these pharmacoeconomics are changing as regulators and payers increasingly demand efficacy in return for approval and reimbursement, respectively). Wastage is also driven by regulatory requirements that require drug package volumes of expensive intravenous therapies to be larger than needed for the treatment of an individual patient[11]. Second, there is a lack of standardization of the collection, storage and analysis of large amounts of genetic, serological, histological and population data to enable patient stratification in clinical practice. Third, there is an absolute scarcity of properly validated biomarkers and a glut of poorly validated biomarkers to sort through. And fourth, when a validated biomarker exists, few developers have the expertise and financial resources to develop both a companion genetic test and a new drug, either of which must navigate stringent and protracted regulatory oversight.

How regulation constrains individualized medicine

The twentieth century regulatory system for drug manufacturing and marketing authorization was introduced after the occurrence of a small number of major safety incidents ascribed to drug industry products[12]. **[AU:OK?]**These comprehensive and detailed regulations cover all aspects of drug development and manufacture, and have had a major positive impact on the safety and quality of pharmaceuticals produced on a large scale. On the other hand, the many guidelines designed for twentieth century drugs have now become an obstacle for the development of twenty-first century precision medicines. Today, it takes years of research and development to collect the data necessary to submit a request for marketing authorization for precision drugs or any new drug. In addition, on average, it takes three years from submission of a new drug application to marketing of a drug[13]. These timelines are difficult to reconcile with the development of a medicine tailored to the individual needs of one patient. They are totally at odds, for example, with the development of

Table 1 Drugs and indications suited for magistral production

Drug class	Why suitable	Possible obstacles	Timeline for implementation
Existing drugs			
mAbs	Platforms for efficient production already exist	Lack of infrastructure and trained personnel	Now
Small molecules and biologics to supplement innate deficiencies	Relatively low amounts needed. Marketed bulk-produced drugs extremely expensive	Lack of infrastructure and trained personnel	Now
Treatment for ultra-orphan diseases	Extremely high prices if developed by industry	Lack of infrastructure and trained personnel	Now
Novel individualized medicines			
Replacement proteins for ultra-orphan diseases	Market too small for commercial development	Lack of infrastructure and trained personnel. Clarification of efficacy/safety testing for new molecule	2–3 years
Individual tumor specific mAbs for hematological malignancies	Relatively easy screening system available. Development time of product needs to be as short as possible	Lack of infrastructure and trained personnel. Needs efficient transient expression systems. Clarification of efficacy/safety testing for new molecule	2–3 years
mAbs for rare forms of pediatric solid tumors	Market too small for conventional drug development	Lack of infrastructure and trained personnel. Identification of suitable markers. Clarification of efficacy/safety testing for new molecule	2–3 years
Individualized mAbs to overcome resistance to pre-existing bulk-produced mAb therapy	Development time of product needs to be short	Lack of infrastructure and trained personnel. Heterogeneity of resistant tumor. Clarification of efficacy/safety testing for new molecule	2–3 years

Box 1 What are key safety issues for magistral biologics?

Biologics (proteins, peptides and mAbs) as a whole have a good safety record. They mostly act on extracellular targets by binding to a specific receptor or ligand in the cell membrane. They are either excreted and/or catabolized into amino acids, sugars and other natural products and recycled. Unlike small molecules, which exert their toxicity intracellularly, the systemic adverse effects of biologics are most often the pharmacodynamic effects of the drug and therefore closely related to their potency[26,27]. This does not mean, however, that product safety can be assumed. One need only look at the CD28 superagonist mAb TGN1412, which led to life-threatening multiorgan failure in all six volunteers administered the drug during phase 1 testing. This incident led to a revision of the first-in-man trial principles with ascending doses and a low starting dose that also can applied for the dosing of patients with precision biologics[28].

Immunogenicity is considered the main safety issue for biologics[29]. Nearly, all the biologic products are immunogenic, although the incidence differs widely. Most biologics are copies of human proteins, and their immunogenicity is considered breaking tolerance. Aggregation has been identified as the cause of breaking B-cell tolerance. Aggregates occur in every protein therapeutic, but the amount and characteristics of aggregates necessary to break tolerance have not been established. It may be the result of the production process or the formulation, packaging, storing or handling of the protein product.

In general, immunogenicity leads to a transient, low level of binding antibodies with no clinical consequences. Sometimes a high level of neutralizing antibodies in the patient may lead to inhibition of product efficacy. The immunogenicity of some mAbs results in the formation of immune complexes, which may lead to transfusion reactions and serum sickness. If a biologic induces antibodies that cross-neutralize an endogenous factor in the patient, serious clinical consequences may ensue, as happened in the case of Eprex discussed above.

With the above factors in mind, potency and purity are the two factors most important in determining the safety of a biologic. These are, therefore, the characteristics that would need to be carefully controlled and tested in magistral production of a precision medicine.

targeted drugs to address a rapidly evolving malignancy in a cancer patient.**[AU:OK?]**

The submission and evaluation of a marketing authorization and the maintenance of good manufacturing practices (GMP) and auditing for bulk production demand vast resources from both the biopharma industry and the regulatory authorities. Even the largest companies can afford only a limited number of new drug submissions per year. The main target of the US Precision Medicine Initiative is cancer. However, the number of new drugs needed to meet this ambition is daunting. The personalization of these drugs implies higher specificity—and higher specificity leads to an increase in resistance to therapy, which also will evolve in time. So precision therapy for a cancer patient is expected to consist of at least three different drugs.**[AU: OK? Meaning for each individual?]** There are about 200 different cancers, and there are currently 250 cancer drugs available[14]. About 1,200 drugs are currently estimated to be in the pipeline. Assuming a combination of just three of these drugs,**[AU: 250 plus 1,200? Please clarify]** the possible permutations are >280 million. Most of these combinations will make no clinical sense, of course, but even if corrected for unlikely combinations, it is clear that the number of combinations that require clinical testing, submission to the regulatory authorities and subsequent evaluation is beyond the means of both industry and regulating bodies.

Perhaps the greatest disadvantage of the current outmoded regulatory approach is the forced lock-in of technology early during product development, which is contrary to the personalization of a product to an individual's needs. Regulators expect the product and its use not to vary,**[AU:OK?]** especially during preclinical and clinical development. Any change in the product and the way it is applied may lead regulators to request repeat testing with the modified product, dosage and any other changed elements.**[AU:OK?]** These data are then the basis for new labeling of the product, which means individual adaptation of the use of the product in the context of precision medicine would be off-label use. This has potential legal, financial and administrative consequences.

How economics holds back individualized medicine

According to some proponents, precision medicine will lead to a decrease in healthcare costs by increasing drug cost-effectiveness: fewer non-responders will receive needless treatments and medical procedures required to ameliorate side-effects will also be reduced[15]. But this seems unlikely for several reasons.

In terms of healthcare economics as a whole, the main contributor to soaring costs is innovation in a market that is driven by what is offered, rather than by medical need[16]. There is no reason to expect this dynamic to change, despite the advent of precision medicine. If economics are driven by fee-for-service rather than by medical need, there is no reason why existing models of precision medicine would alter cost-effectiveness.

To illustrate this, one need only look at drug prices for recent drugs introduced for cancer and orphan indications. The highest price charged in the Netherlands is currently for Glybera (alipogene tiparvovec), a gene therapy against lipoprotein lipase deficiency, which costs €1.2 ($1.3) million per patient, despite its relatively meager clinical efficacy[17]. As mentioned above, precision medicines have only a very limited market in terms of patients. In current reimbursement systems based on perceived value of a treatment, the limited markets for precision or personalized drugs will be similar to molecularly targeted orphan indications like lipoprotein lipase deficiency. This will drive up drug prices, rather than reduce them. One need only look at the 50 'targeted' drugs currently authorized by the US Food and Drug Administration (FDA), which cost between $70,000 and $130,000 per treatment cycle[14].

Given spiraling drug prices for precision medicines in our current healthcare systems, it is remarkable that the issue is not more widely acknowledged or seen as a hurdle for wide adoption of precision therapies. A search in PubMed (April 2017) using the term "personalized medicine" resulted in 36,029 hits. In contrast, the combination of the terms "personalized medicine" and "affordability" yielded only 19 hits. In the few papers discussing affordability and cost-effectiveness, several solutions are suggested with the common theme being better collaboration between the diagnostic and pharmaceutical companies, regulators, funding agencies, payers and patients[18,19]. However, it is difficult to imagine how such aspirational solutions will lead to cost control, considering the underlying causes of spiraling drug prices.

Bedside or magistral production as a complement

It is becoming evident that the current pharmaceutical system is too complicated, too expensive and too inflexible to support medicine tailored to individual patients. Innovative and

creative new approaches and business models are necessary if we want sustainable healthcare that enables affordable individualized medicine for all.

One solution to the regulatory and economic challenges of precision medicine is to retool the development and production of drugs so they are as close as possible to the patient. There are several reasons why we believe our magistral model is a better fit for individualized medicine, healthcare economics and the future of patient care.

First, if a treatment occurs in the same legal entity as the production of a drug, no restrictive, expensive and time-consuming marketing authorization would be necessary. Such a scheme would combine healthcare provider and drug manufacturer into the same entity, increasing the incentive for drug pricing to be cost-effective.

Second, the magistral approach could be tested, compared and validated using existing approved drugs as a test case first and then expanded to test its utility in the discovery and development of new drug entities (**Table 1**). It may be that only certain types of new drugs—perhaps biosimilar versions of existing drugs or drugs that existing commercial developers find less interesting because their markets are too small—would be suitable for magistral production. Whatever the case, removing the need for patent protection of the product and the requirement for regulatory oversight would radically reduce timelines for magistral drug development compared with industry's timelines of 10–15 years.

Third, there is also the question of whether an academic center producing and administering a drug to an individual patient remains under patent protection and can be sued for patent infringement. In our view, it is unlikely that such litigation would be successful. In the patent legislation, there is an exemption for personal use that may be applicable for magistral production. Also, any individual treatment will be covered by doctor–patient confidentiality and will not be in the public domain, denying the patent holder the possibility to discover administration**[AU: restate for clarity]** and make a legal case. Moreover, if a doctor or pharmacist ran bedside production with the possibility of producing a lifesaving drug for an individual patient, their professional duty to help might override any restriction by the patent legislation to produce and administer the drug.

Fourth, industry now has over a century of experience producing small molecules and a >30-year track record producing recombinant replacement proteins, peptides and monoclonal antibodies (mAbs). Antibodies and other recombinant biologics are now commonplace, with numerous examples of approved drugs now complementing traditional small-molecule drugs. The production and purification methods for different biologics are highly comparable. This is especially true for mAbs, which are often of the IgG1 type and share >95% sequence homology. The expertise for producing drugs should no longer be the sole domain of industry; indeed, many people with expertise in drug R&D are being dismissed by larger drug companies increasingly focused on clinical development and marketing. Perhaps such individuals could now be coopted to support magistral drug development in academic medical centers.

Fifth, a relatively standard small-scale culture and purification unit should be sufficient to

Box 2 Outstanding issues for magistral individualized medicine

We have been discussing our pilot project (**Box 3**) with experts and colleagues from many different fields, including patient advocate groups, regulators, policymakers and other stakeholders. The issue that comes up first in nearly all discussions is how to ensure safety, especially if the bedside production expands into less experienced hospitals. The lack of regulation for magistral production is seen as a disadvantage in this scenario.

No process for producing drugs is completely safe. The FDA receives at least 3,000 reports yearly of drug manufacturing or quality control incidents, in most cases the result of human error[30]. Although as we have noted, the risks associated with magistral production are relatively low, human errors will certainly also occur in the hospital pharmacy. Therefore, if bedside production becomes feasible, it will be important to introduce regulations ensuring a quality control system to avoid these human errors as much as possible. However, these regulations— preferably institution-level—should be open, adaptable, based on common sense and smart, using the opportunities provided by information technology. Regulating magistral production should avoid the pitfalls of the standard drug relations that stifle innovation.

We also think the dedicated tabletop production units with integrated quality control based on prefilled cell culture cassettes (**Box 3**) will provide the opportunity to standardize the production and purification and, if well designed, will contribute to the consistency of the products within and between hospital pharmacies. It has not escaped our notice that a whole potential business sector could spring up to supply such tabletop production instruments and reagents.

One other important discussion with the stakeholders has been the question of how to pay the bedside development. Currently, the major Dutch health insurance companies are funding our pilot project through their innovation investment funds. With total projects costs that are only 20% of what the bedside production will save in reimbursement costs of a single orphan drug every year, we had no major difficulties in getting them involved. They also pledged part of the savings in the coming five years to invest in the development of precision medicine approaches and the small production unit.

Cost savings are the main incentive for the involvement of the Dutch companies; this has raised suspicion in the media that our main driver for proposing magistral manufacture is to challenge big pharma. This is not our goal. Instead, we seek to facilitate individualized medicine and to introduce a model that would complement bulk drug discovery and development by existing commercial manufacturers. In time, we hope that some companies may also embrace our model; however, we do not think the current biopharma industry is incentivized to deliver the scientific and medical promise of individualized medicine (for the reasons outlined in this article).

Bedside development and magistral production will not be the solution for all deficits of the current pharmaceutical system. The pharmaceutical industry and its products will remain essential for creating drugs against novel intracellular targets or indications where large-scale production and distribution is necessary.

Another question is whether this approach should be limited to biologics. After all, there have been many developments in chemical synthesis allowing automated small-scale manufacture of small molecules that could be extended to hospital pharmacies[31–33]. One could imagine, for example, bedside development of Kalydeco (ivacaftor) against different genetic forms of cystic fibrosis.

Box 3 Toward a proof of principle

Utrecht University in the Netherlands has initiated a pilot program for producing biologics in hospital pharmacies financed by the major Dutch health insurance companies. The goal of this project is to study whether magistral production can form the basis of a sustainable system for development and production of affordable precision/personalized medicine.

Several replacement protein products have been selected for the treatment of orphan diseases. These will represent alternatives to existing products ('biosimilars'). We also intend to develop a new recombinant replacement protein for the treatment of a very rare orphan disease.

The biosimilars were selected because they provide a reference for the quality and efficacy and the economic feasibility of bedside production. Because they will be the first products of this new approach, their safety and efficacy will be evaluated in clinical trials. One of the trials will be performed in the developing world, where > 99% of children with this lethal orphan disease cannot be treated because of the extreme price of the drug. The clone, the production technology and the clinical data will be donated to the WHO-associated Utrecht Centre of Excellence for affordable biopharmaceuticals (UCAB) to be used for the local production in the developing world.

The process for the pilot bedside production is being developed by a company with experience in high cell density perfusion culture systems. This company will also do the technology transfer to the hospital pharmacy, including the training of the local staff. As most pharmacies of academic medical centers in the Netherlands, the pharmacy has a GMP-licensed facility, where the production will be in standard equipment for small-scale production in disposable cell culture systems. The total investment needed for the equipment is ~€100,000 ($108,000).

The products will be made according to specifications of monographs to be requested from the Royal Dutch Pharmaceutical Society (KNMP). In magistral production, the pharmacist will be responsible for the release of the product for administration to the patient.

If the pilot proves successful and the model is seen as attractive, the question arises of how to introduce bedside production to other hospitals. The main challenges will be infrastructure and personnel. Most hospital pharmacies will lack GMP or comparable facilities and trained staff. Therefore, the savings expected through local production will be invested in the development not only of other new personalized biologics but also in hardware that will enable efficient production of biologics in any hospital pharmacy. The goal is to create a closed, integrated, easy-to-operate, small machine capable of producing grams of biopharmaceuticals of high and reproducible quality. It will be based on perfusion bioreactor technology, supporting the growth of producer cells at high densities in prefilled disposable cassettes.

When the number of products and pharmacies involved in bedside production starts to grow (**Table 1**), the principle of magistral production for individual patients may come under pressure. Ultimately, producing all products in all pharmacies is an unlikely scenario and exchange of products between cooperating pharmacies may prove more efficient. This will bring bedside production outside the scope of magistral production and uncharted regulatory territory. New regulations will then be needed, that need to be smart, open and flexible to avoid the technological lock-in caused by the current guidelines and legislation of the current pharmacological development paradigm.

produce the great majority of products needed as individualized medicines for patients. Doses of biologics vary from µg/kg up to 20 mg/kg. To be able to provide bedside production of such biologic products, the production capacity should therefore be in the gram scale (5–20 g) and preferably with a mobile production unit with a small footprint that can be readily implemented in standard cleanroom facilities of hospital pharmacies. This limits the production volume to 30–50 liters. Production at this size is common practice in the pharma industry during the discovery and early-development phase of biopharmaceuticals and enables the use of disposable bioreactors to standardize and speed up production.

Sixth, new technology is coming on line that supports local, small-scale drug production systems, which are becoming more automated. The development of new methods for the genetic modification and selection of host cells and new chemically defined culture media and feeding strategies have dramatically increased volumetric productivity over the past few years. The introduction of high-cell density and perfusion technologies has made production levels of up to 8 g/L possible. Moreover, recent advances in transient gene expression now make it possible to produce grams of antibodies in fewer than 14 days. Some systems for transient expression allow the selection of cell lines for continuous production in cases when the patient needs prolonged treatment[20]. Fast production is important for individualized medicine to keep the interval between diagnosis and treatment as short as possible.

Seventh, small-scale production can also facilitate downstream processing. Small volumes of a drug enable the use of alternative methods for concentration and purification such as flocculation, precipitation and aqueous two-phase extraction systems, which are cheaper and, more importantly, faster than the classic chromatographic techniques used in bulk biopharma manufacturing facilities. Moreover, advances in the development of self-cleaving fusion tags for affinity purification would in the future enable standardization of the purification of a wide range of biologics[21].

A final advantage of magistral production may be in the provision of combinations of drugs. At the moment, the commercial barriers and proprietary nature of programs at competing manufacturers **[AU:OK?]** often stand in the way of providing the right combination of drugs tailored to address all the targets in an individual patient. The magistral production approach, again, would sidestep this issue.

Given the above, we contend that bedside production of biopharmaceuticals in a hospital pharmacy setting is technically feasible and an intriguing alternative to bulk-scale drug production. Indeed, there are already documented cases where such magistral production has been achieved (**Fig. 1**). All of the above technologies can ultimately be combined in a closed, easy-to-operate, tabletop-sized machine with integrated production and purification that could be used in standard cleanroom facilities of a hospital pharmacy (**Box 1**).

On the basis of current large-scale facilities based on disposable units where production costs are estimated at ~€20 ($22) per gram of protein, magistral drug manufacture in a hospital pharmacy setting would be estimated at ~€2,000 ($2,200) per gram (if a continuously**[AU:OK?]** producing cell line were used). Overall, from design to production in a transient system, we estimate a cost of between €5,000 ($5,400) and €10,000

($10,800) per gram. As the prices of current biopharmaceuticals can range up to €500,000 ($540,000) per gram, magistral production seems economically viable.

We recently concluded a pilot study to get some idea about the economics of bedside production. We set up local production of recombinant human α-glucosidase (rhGAA) from scratch, starting with the construction of high-producer cell lines and developing the heterologously produced protein up to formulation in a pharmaceutical form. Although the system was not optimized for efficiency, the cost of production of rhGAA was $1.491/gram, taking in account all costs: cell-line generation, reagents, materials, labor, infrastructure and other.**[AU: how does price compare to bulk production?]**

Regulatory oversight of magistral production

The industrial production of pharmaceuticals started in Germany at the end of the nineteenth century. Nevertheless, 80% of all prescriptions were still compounded by a local pharmacy in the 1950s. Currently, >90% of all prescriptions concern products manufactured in bulk by the biopharma industry. The development, production and marketing of this industry's products are heavily regulated. All these regulations were initiated by incidental, but serious, cases of malpractice, fraud and a lack of proper evaluation of manufacturing safety and quality.

The 1960s thalidomide tragedy,**[AU: 'incident' is too understated; if 'tragedy' seems overstated, reword as desired]** in which the sedative was prescribed off-label to pregnant mothers, resulted in 10,000 severely malformed babies in Europe, 5,000 of whom died. This prompted the United States to pass the Kefauver–Harris Drug Amendments in 1962, which required manufacturers to prove safety and efficacy in return for market registration. More recently, the debacle in the early 2000s in which 28,000 deaths were attributed to off-label marketing of Merck's (Kenilworth, NJ, USA) cyclooxygenase 2 (COX2) painkiller Vioxx also prompted a clamp down on industry and a greater emphasis on drug safety[22]. Thus, commercial drug manufacture is subject to stringent and standardized regulatory oversight from federal authorities, such as the FDA, the European Medicines Agency and the Pharmaceutical and Medical Devices Agency (Tokyo).

In contrast to mass-production of drugs, magistral drug production falls under the umbrella of drug compounding. Compounding occurs in two different forms: the official formula and the magistral formula[23]. The official formula for a drug is one that can be found in an official text (e.g., the British Pharmacopeia or the European Pharmacopeia). Products compounded as official formula are for storage and for delivery to patients with a prescription from their doctor. In the magistral form, the medicinal product is instead produced for an individual 'named' patient on the basis of a prescription written by the attending physician.

In both the United States and Europe, compounding is exempted from marketing authorization or manufacturing regulations like GMP. Compounding in the European Union (Brussels) is regulated by both national pharmacopeias and guidelines from international organizations, such as the World Health Organization (Geneva) or Pharmaceutical Inspection Conventions. In the United States, compounding used to be regulated at the state level, but in 2013, new federal legislation was introduced to move the oversight to the FDA[24]. The reason for this was a major incident that occurred at the New England Compounding Center in 2012. Fungal contamination in three lots of methylprednisolone used for epidural (spinal) steroid injections and distributed to 75 medical facilities in 23 states and administered to about 14,000 patients caused 48 fatalities and 720 persistent fungal infections needing treatment.

Safety issues for magistral drugs

The above incident has been cited as proof of the risks of compounding (**Box 2**). It is also held up as an example that proves that the type of magistral individualized drug production we propose in this article is untenable. We contend, however, that the scale of manufacture and wide (bulk) distribution of the New England Compounding Center lots can hardly be considered compounding for an individual patient. It should instead be held up as an example of the dangers of bulk, industrial production. It also illustrates the risks of the different types of compounding. The 2012 event pertained to compounding to an official formula and distribution on a wide scale. This is a very different prospect from compounding to a magistral formula that is destined for one patient.

Risk is not only defined by the probability of an event happening but also by its consequences. In compounding, the risks are smaller than those of industrial production of pharmaceuticals. In a magistral formula, the link between patient, prescriber and pharmacist is direct, and any problem with the product is completely traceable, can be acted upon immediately and is thus restricted to one individual.

The risk posed by a faulty mass-produced product of the biopharma or compounding industry distributed worldwide is much higher than for a magistral product produced for an individual patient. Thus, the thalidomide and Vioxx incidents discussed above took many years and many victims to discover and correct. To take an example of a mass-produced biologic rather than the aforementioned small molecules, the mass-produced biopharmaceutical Eprex (epoetin alfa) was associated with pure red cell aplasia (PRCA) after a formulation change in 1998 (ref. 25). The formulation increased the immunogenicity of the product and induced antibodies that cross-neutralized endogenous erythropoietin in patients, leading to severe anemia. Although the first publication revealing the problem came out in 2002, it took another year before use of subcutaneous Eprex was banned. In these 5 years, at least 275 patients developed PRCA. In **Box 1**, we discuss the safety issues related to biologic manufacture of relevance to magistral production for individual patients.

The risk of compounding is also minimal compared with industrial production because the medicine is produced by a pharmacist or by a technician under his direct supervision. The GMP regimen by pharmaceutical industries for large-scale production was designed to enable production by operators without any pharmaceutical background. In addition, the magistral product is used within a short time after manufacture, thus avoiding degradation and deterioration and shelf-life issues, a source of side effects especially for biologics. Finally, the equipment used for magistral compounding is small and relatively simple to operate compared with the equipment used for large-scale production of biologics, again minimizing the probability of defects or malfunction.

In the magistral situation and unlike industrial pharmaceutical production, a limited number of health professionals are responsible for both the production and the safe administration of the drug to a named patient. In our view, this would ensure optimal and direct surveillance of magistral production of precision drugs.

Clinical aspects of magistral production

Classic clinical development of a biopharmaceutical involves three phases, with one or more double-blind, comparative clinical trials in hundreds of patients as the ultimate proof of the efficacy of the new drug. In individualized medicine, where $n = 1$, such an approach is not possible and other approaches to test the safety and efficacy are necessary[26]. What is required is a novel, robust system of evaluation that ensures patient safety and allows early and accurate assessment of efficacy. Currently, authorization of products by regulatory authorities for orphan disorders is frequently followed by requirements to collect additional safety and effectiveness data. The reason for

this is that surrogate or intermediate endpoints are used, and outcomes on clinically meaningful endpoints remain uncertain. However, these registries **[AU: which registries?]** have severe limitations, including a striking paucity of high-quality data, as well as a lack of independent analysis of outcomes[27]. Systems for collaborative, independent analysis of data are currently being advocated. For magistral production of precision biopharmaceuticals, a similar approach could be envisioned for small groups of patients, including the set-up of international independent registries. In such a system, patients would be adequately informed and involved in all decisions. The close interaction between dedicated physicians, pharmacists and patients would accelerate the evaluation of effectiveness and safety, and it might also enable fine-tuning of the biologic to the individual needs of the patient.

Conclusions

We have outlined a proposal for magistral production of protein therapies. Clearly, magistral drug production would not substitute for pre-existing commercial models of drug discovery and development. What we put forward here is a drug manufacture model that complements, but does not supersede, them. And it promises to turn the dream of individualized medicine into a reality for the first time.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Olfson, M. & Marcus, S.C. *Health Aff. (Millwood)* **32**, 1116–1125 (2013).
2. Le Tourneau, C. *et al. Lancet Oncol.* **16**, 1324–1334 (2015).
3. Pirmohamed, M. *et al. Br. Med. J.* **329**, 15–19 (2004).
4. Jameson, J. & Longo, D.L. *N. Engl. J. Med.* **372**, 2229–2234 (2015).
5. Faulkner, E. *et al. Value Health* **15**, 1162–1171 (2012).
6. Carrera, P.M. & Ormond, M. *Maturitas* **82**, 94–99 (2015).
7. Cohen, J.P. *Nat. Biotechnol.* **29**, 751–756 (2012).
8. de Bono, J.S. & Ashworth, A. *Nature* **467**, 543–549 (2010).
9. Damkier, P. *Int. J. Clin. Pharm.* **37**, 669–670 (2015).
10. Collins, F.S. & Varmus, H. *N. Engl. J. Med.* **372**, 793–795 (2015).
11. Okie, S. *N. Engl. J. Med.* **361**, 737–740 (2009).
12. Avorn, J. *N. Engl. J. Med.* **367**, 193–197 (2012).
13. Frueh, F.W. *Value Health* **16** Suppl, S27–S31 (2013).
14. Fleck, L.M. *Urol. Oncol.* **32**, 202–206 (2014).
15. Slater, J. *et al. Healthc Manage Forum* Oct 19 2015. **[AU: please provide more information: has the work been published? Which journal or in a Proceedings? Was this a talk?]**
16. Moors, E.H., Cohen, A.F. & Schellekens, H. *Drug Discov. Today* **19**, 1711–1720 (2014).
17. European Public Assessment Report Glybera (EMA Website)
18. Aronson, N. *Ann. NY Acad. Sci.* **1346**, 81–89 (2015).
19. Abernethy, A. *et al. Clin. Cancer Res.* **20**, 1081–1086 (2014).
20. Steger, K. *et al. J. Biomol. Screen.* **20**, 545–551 (2015).
21. Ge, X. *et al. J. Am. Chem. Soc.* **127**, 11228–11229 (2005).
22. Topol, E.J. *N. Engl. J. Med.* **351**, 1707–1709 (2004).
23. Minghetti, P., Pantano, D., Gennari, C.G. & Casiraghi, A. *Health Policy* **117**, 328–333 (2014).
24. Qureshi, N., Wesolowicz, L., Stievater, T. & Lin, A.T. *J. Manag. Care Spec. Pharm.* **20**, 1183–1191 (2014).
25. McKoy, J.M. *et al. Transfusion* **48**, 1754–1762 (2008).
26. Kooijman, M., van Meer, P.J., Moors, E.H. & Schellekens, H. *Expert Opin. Drug Saf.* **11**, 797–801 (2012).
27. van Meer, P.J. *et al. MAbs* **5**, 810–816 (2013).
28. Schneider, C.K. & Kalinke, U. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **50**, 1213–1220 (2007).
29. Patten, P.A. & Schellekens, H. *Dev. Biol.* **112**, 81–97 (2003).
30. Bach, P.B., Conti, R.M., Muller, R.J., Schnorr, G.C. & Saltz, L.B. *Br. Med. J.* **352**, i788 (2016).
31. Ciriminna, R. *et al. Nanoscale* **6**, 6293–6300 (2014).
32. Gising, J., Odell, L.R. & Larhed, M. *Org. Biomol. Chem.* **10**, 2713–2729 (2012).
33. Szymkuć, S. *et al. Angew. Chem. Int. Edn Engl.* **55**, 5904–5937 (2016).