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Patient-centered drug manufacture

Bedside production of protein drugs could help payers by lowering drug prices. It may ultimately lead to individualized treatments.

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For the past 30 or so years, protein drug manufacture has been a bulk business. Centralized manufacturing facilities produce gobs of therapeutic proteins that are aliquoted and distributed to the masses. But it doesn't have to be this way; instead, drug production could be carried out on demand and at a small scale, providing just enough drug for a single patient. A Commentary on p. 507 from Schellekens *et al.* proposes just such a bedside-manufacturing model—also known as 'magistral' production. If proven feasible, the economics, speed and efficiency of this model would allow payers to exert downward pressure on the prices of protein drugs, streamlining production and bypassing bulk manufacturers, wholesalers, retailers and regulators. What's more, Schellekens *et al.* argue magistral production could open new possibilities for ultra-orphan drugs and ultimately individualized medicines—an idea industry dismisses as impractical.

Precision medicine today is not tailored to individual patients but to groups of patients who share a particular molecular marker within a disease (e.g., mutations in *ALK*, *HER2* or *BCR-ABL*). It has to be this way because only patient markets of a certain size support the economics of contemporary drug development—which requires a return on investment of >$1 billion over 12–15 years to support intellectual property protection, lengthy regulatory qualification and extensive manufacturing operations. What's more, only a handful of companies currently have the financial and intellectual muscle to negotiate both the drug and its accompanying diagnostic kit through regulatory oversight. This not only limits the rate of development of new precision drugs and diagnostics and the diseases amenable to treatment but also ensures such drugs are among the most expensive in the world.

Magistral drug production turns this model on its head. Regarded as a form of drug compounding, it traditionally has involved a licensed pharmacist producing sufficient drug for an individual 'named' patient on the basis of a prescription written by an attending physician. Because no drugs move over US state lines and treatment is specified only for an individual patient, products prescribed in this manner fall outside of US Food and Drug Administration rules for marketing authorization or GMP manufacturing.

The magistral approach may also sidestep intellectual property rules because US patent legislation contains an exemption for personal use. In any case, doctor–patient confidentiality may keep magistral production out of the public domain, making it difficult for patent holders to discover infringement.

Historically, the magistral approach has been the domain of small-molecule drugs. However, several technological advances bring closer to reality its adoption for therapeutic protein manufacture. The first is the development of small-scale (30- to 50-liter) mobile production units compatible with standard cleanroom facilities in hospital pharmacies. New increasingly automated technology is also coming on line to support pilot production units that could generate grams of protein in under two weeks.

The first candidates for magistral protein production will likely be follow-on versions of approved monoclonal antibodies and replacement proteins. But the magistral platform could also be used to produce replacement proteins in an ultra-orphan disease where protein function is missing or compromised, with prices undercutting those currently offered by commercial manufacturers. Of course, for many rare diseases, commercial drugmakers regard the patient population as too small to be profitable anyway; in such cases, magistral production will be the only game in town.

Ultimately, it may be possible to develop altered versions of existing drugs in the magistral context tailored to individual patients; for example, the CDR of an antibody might be altered to counter mutations emerging in a tumor that compromise a drug target. As yet, however, this remains a distant prospect. It is still unclear how such new molecular entities would be validated before introduction to a patient—and also how data on safety and efficacy would be gathered in an $n = 1$ patient trial.

The most serious concern, though, is how to assure the quality and integrity of magistrally produced therapeutic products that fall outside existing regulatory checks. Few academic medical centers have the requisite expertise and equipment for a magistral production facility. And if magistral manufacture were widely adopted, how would quality control operate to ensure products remained free from impurities, aggregates, protein cleavage/degradation/crosslinking, undesirable post-translational modifications and altered three-dimensional structure? One solution (at least for simple proteins) may be the emergence of completely automated platforms. At the moment, such instruments remain in prototypical form (e.g., Synthetic Genomics' BioXp benchtop instrument). But if they became sufficiently reliable and affordable, they could ensure greater product consistency by reducing the potential for human error and intervention.

In the meantime, this journal is in no doubt that existing commercial manufacturers—and all others bound by the chains of existing drug commerce and distribution—will hate this idea. Magistral protein production represents a disruptive threat to bulk manufacturers. It is likely that both the brand and generic industries will do everything in their power to thwart magistral manufacture through legislative and regulatory means. After all, this is what the brand industry did to biosimilars, delaying market entry by a decade. We anticipate Correspondence detailing a catalog of reasons why magistral production is unsafe and cannot work.

But to this journal, magistral production looks like a first step to actually achieving individualized, patient-centric medicine. In its present outline, there are many more questions than answers about how to assure quality and carry out safety and efficacy testing in individual patients. But unlike precision medicine, magistral production has an important ally: payers will find it very attractive. Just take a look at who is bankrolling the pilot study Schellekens is currently spearheading in the Netherlands.