**curation, including the Human Genome Mutation Database, the Human Variome Project, the Leiden Open Variation Database and ClinVar, as we believe the only way to achieve community consensus is through broad collaborations.**

**In conclusion, we recognize the hard work of the thousands of research and clinical geneticists who have been actively working in this community, and it is our mission to build upon the many achievements already accomplished in this field. We actively seek to work with all other organizations to achieve the best possible understanding of human variation and to enable the most effective care of patients affected with genetic disease.**

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The authors declare no competing financial interests.

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# Why an abbreviated FDA pathway for biosimilars is overhyped

**To the Editor:**

This journal has highlighted the debate about the likelihood that the US Food and Drug Administration (FDA) will require clinical data for its proposed pathway for biosimilars, or biogenerics—copies of innovator biologics. The head of FDA's drug center, Janet Woodcock, has acknowledged in congressional testimony (http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm) the scientific and technical challenges posed by biosimilars. She said that in asking for new data, the agency "will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product." That demonstration will certainly involve sophisticated analytical chemistry and possibly animal studies. And she emphasized the importance of possible immunogenicity—the ability to stimulate an immune response—of a follow-on version of a biological drug. Woodcock observed that "The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited," and concluded that "Therefore, some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed."

Additional indications of the FDA's view of biosimilars are provided in two publications, one of them from last month. In the *Federal Register* last October[1], the agency acknowledged that the Biologics Price Competition and Innovation Act of 2009 is intended to align with "appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing." But it also acknowledges that "The implementation of an abbreviated approval pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger and often more complex structure of biological products...."

The detail in the FDA's statement is revealing. It describes two levels of similarity. To meet the lower, more lenient standard, a product would be considered biosimilar to the reference product if it "is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and if *there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency*" [emphasis added]. This finding, when accepted by the FDA, would substitute for a demonstration of the subject product's efficacy, which would have been established by the reference product. It is hard to imagine how one could demonstrate the absence of "clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" without new clinical data.

The report goes on to say that "To meet the higher standard of interchangeability, a product must demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

The second publication, in the *New England Journal of Medicine* by four senior FDA officials[2], provides additional confirmation of the earlier statements: First, "Generally, therapeutic proteins must have a specific set of structural features (e.g., amino acid sequence, glycosylation, protein folding) essential to their intended effect, and slight modifications can affect their performance in humans"; second, "inadvertent chemical modifications can affect their immunogenicity"; third, "additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future"; fourth, before regulators can even advise on required animal and human studies, "the FDA should already have completed an in-depth review of comparative analytic characterization and *in vitro* data"; and fifth, "[t]he FDA process for biosimilars must include product-specific safety monitoring" because "pharmaceutical companies will make manufacturing-related changes to biologics periodically throughout their lifecycles, and even small changes could affect safety or efficacy."

Thus, it seems a foregone conclusion that clinical trials—possibly large ones to achieve sufficient statistical power—will be required to demonstrate the efficacy and, especially, the safety of 'biosimilars' before the FDA approves them. The higher standard for interchangeability will be extremely difficult to meet.

If any further insight into the FDA's mindset is needed in addition to the clear statements by the agency's top drug regulator and the October 2010 *Federal Register* notice, there are the agency's approvals over many years of a small number of 'follow-on biologics'—biosimilars or generic biologicals by another name—all of which required a substantial amount of laboratory and clinical testing. This history and the agency's rationale for those approvals is summarized in a 2007 article by FDA officials[3].

Depending on where their self-interest lies, various interested parties, including insurance companies, healthcare providers, pharmaceutical companies and members of Congress have aggressively lobbied FDA to make policy toward biosimilars in a way that

favors the developer of either the original drug or the follow-on version—most often turning on how the agency defines terms like 'exclusivity' and 'bioequivalence'.

The high costs involved in planning, conducting and analyzing the results of clinical trials will prevent a stampede to make biosimilars; in fact, several major drug companies are pursuing the development of biosimilars as though they were completely new and distinct from the original products and have expressed their intention to submit a new Biologics License Application to obtain marketing approval. Thus, the savings to federal entitlement programs, insurers and patients will surely be far less than some of the hyperbolic predictions made by politicians and others.

Eventually, the availability of biosimilars will spur competition and reduce prices. Because of advances in technology, some of the new products may even be better than the original, brand-name drugs. But for the time being, the new regulatory pathway for most biosimilars will not be significantly abbreviated nor will it significantly affect skyrocketing healthcare costs.

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# Stem cell funding in the Midwest

**To the Editor:**

We noticed that the news story "Stem cell funding resumes" by Laura DeFrancesco (*Nat. Biotechnol.* **29**, 468, 2011) contained the final sentence "…efforts continue in at least two states, Minnesota and Oklahoma, to prohibit hESC [human embryonic stem cell] research." This does not accurately describe the status of hESC research in Minnesota today.

There were unsuccessful legislative efforts in Minnesota this past session to prohibit and restrict funding for somatic cell nuclear transfer (SCNT) procedures for making new hESC lines. There were no efforts to restrict hESC research generally. This research is permissible under Minnesota law and continues to be performed at the University of Minnesota.

The SCNT legislation passed by the legislature was opposed by patient advocacy groups, the business community and both the University of Minnesota and the Mayo Clinic. Governor Dayton vetoed the legislation in a strongly worded statement. However, even if the legislation had been enacted, it would not have limited hESC research generally.

All states have a minority of their population who oppose research involving hESCs. However, we do not consider that efforts in Minnesota are any closer to success than elsewhere.

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# Comprehensive catalog of European biobanks

**To the Editor:**

Biobanks are well-organized resources comprising biological samples and associated information that are accessible to scientific investigation[1,2]. They have become a key element for research involving human genetic or genomic and proteomic information in conjunction with other personal or health data. There is consensus in the scientific community that progress in understanding disease will depend on the establishment, harmonization and broad use of this information[3–7].The large spectrum of existing biobanks has been considered as a specific strength of European research[4,6]. Their optimal use, however, is constrained by fragmentation, a lack of harmonization, incompleteness and a lack of overview of existing resources[1,3].

Planning of the European Biobanking and BioMolecular Resources Research Infrastructure (BBMRI) was initiated in 2008 (refs. 1,2). The following are among its goals: first, to make data and materials rapidly and widely available to researchers; second, to provide tools to improve the quality of biobanks on a broad scale; third, to provide an operational concept for a sustainable infrastructure; fourth, to deliver standard operating procedures; and fifth, to suggest codes of conduct.

An online catalog has been established for the collection and presentation of data describing the majority of European biobanks. Based on a format originally provided by The Public Population Project in Genomics (P3G) observatory (http://www.p3gobservatory.org/)[8], BBMRI developed a core questionnaire to collect essential information from European biobanks, such as objectives, number and type of samples, and specific strengths. The core questionnaire was supplemented with a total of six additional questionnaires covering the topics of (i) sample description, (ii) resources and methods, (iii) law and ethics, (iv) IT solutions, (v) research outcome and (vi) costs and funding (**Supplementary Table 1**). In 2008 and 2009, the questionnaires were sent to the representatives of institutions and biobanks who had expressed interest in contributing to this project. Plausibility checks were applied to the completed questionnaires. By March 2011, the catalog included data from 63 population-based and 219 clinical biobanks located in 27 countries (**Supplementary Fig. 1**), together representing more than 20 million samples (**Fig. 1** and **Supplementary Table 2**). We defined 'population-based' biobanks as large repositories of samples from volunteers in the general population, with and without disease, such as random cohorts or population isolates. 'Clinical' or 'disease-oriented' biobanks are derived from clinical individual-sample collections organized around a specific disease or disease group. We counted each biological specimen taken from a specific tissue at a particular date as a sample.

The catalog can be accessed via the BBMRI website (http://www.bbmri.eu/index.php/catalog-of-european-