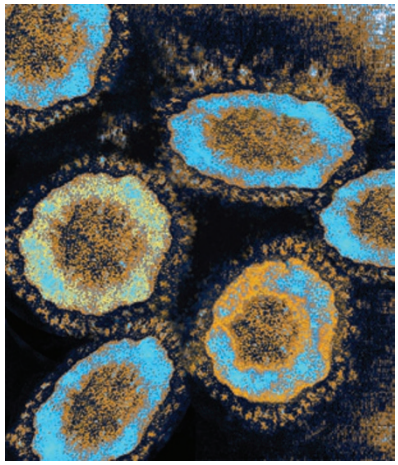
Synthetic DNA firms embrace hazardous agents guidance but remain wary of automated 'best-match'

After more than four years of public and private discussion and review, the US government has officially issued its *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (http://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf), a set of voluntary guidelines intended to help gene synthesis companies intercept unauthorized purchases of genetic components from human or agricultural pathogens. Many are relieved that standardized guidelines have finally been established, enabling the industry to harmonize practices and provide reassurance to large corporate clients that represent their bread and butter.

"Overall it's not a bad framework, and I think it's been designed with a lot of expertise," says Markus Fischer, director and cofounder of Entelechon in Regensburg, Germany, a gene synthesis provider, also part of the International Association Synthetic Biology (IASB), one of two major industry groups representing gene synthesis companies. In the absence of clear government guidance, the IASB and its counterpart, the International Gene Synthesis Consortium (IGSC), each developed their own 'best practices' for screening both DNA orders and the customers that place them. To draw up its official guideline, the US Department of Health and Human Services (HHS), in Washington, DC, received comments from 22 organizations and individuals since publishing its draft Guidance in November 2009 (**Table 1**). The final version—released in October—includes only a few notable changes, such as the elimination of a size cut-off for screening decisions on double-stranded segments.

Although the Guidance structurally resembles preexisting protocols, critics such as Stephen Maurer of the University of California at Berkeley are concerned that its recommendations are weaker than what is needed and may encourage companies to cut corners in the future. "Industry had embraced a higher standard, and now the government is going to lead us to a lower standard," he says. Chief among his concerns is the proposed mechanism for screening sequences.

The government proposes a 'best match' strategy, in which orders are compared against GenBank in 200-bp segments, based on both nucleotide and all six possible peptide sequences. If the top 'hit' is from a pathogen on the government's list of select agents and toxins (http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List.html) or, for international orders, the 'Commerce Control List' (http://www.gpo.gov/bis/ear/pdf/ccl1.pdf), it should be considered a 'sequence of concern' for further expert analysis, in conjunction with a careful assessment of the ordering customer's credentials.



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The select agents list omits many known human pathogens, such as the SARS coronavirus.

Maurer suggests that by not expressly calling for human review of database matches—regardless of whether or not they are on the select agents list—this strategy is inherently less effective than the 'top homology' method already in use at several companies, including Entelechon, in which all GenBank results are manually assessed. "We mandate that one of our employees reviews the complete list of hits, and not just the ones that have been automatically flagged," says Fischer. "A fully automated screening system leaves significant biosecurity questions unanswered."

According to Theresa Lawrence, a senior science advisor with HHS, top homology was rejected in the interest of applying a consistent standard for distinguishing potential threats based on analysis of an established data source. "There was concern with the top homology approach that we would have to designate an arbitrary threshold," she says, "and this approach needs human screeners, which can represent an inconsistent mechanism from provider to provider."

Although GenBank represents a rich resource for genetic data and is therefore a powerful foundation for such screens, it is nevertheless a product of community curation and potential 'sequences of concern' may be inconsistently designated. "GenBank is just a repository," says Sean Eddy, a computational biologist at the Howard Hughes Medical Institute's Janelia Farm Research Campus in Loudon County, Virginia.

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IN brief

DNA not patentable

In a spine-chilling announcement, the US Department of Justice in October said unmodified human DNA should not be eligible for patent. The department's stance conflicts with the body of case law on the matter and a longstanding position held by the US Patent and Trademark Office, which has issued more than 10,000 of these patents. The Justice Department announced its position in response to a lawsuit involving patents on breast cancer genes *BRCA1* and *BRCA2*. A US district court in March declared the patents invalid, saying that the genes are products of nature rather than human-made inventions. Patent holders University of Utah and Myriad Genetics, based in Salt Lake City, appealed in June. In an amicus brief filed with the Federal Circuit Court of Appeals the Justice Department agreed that identifying and isolating DNA without further manipulation is not an invention, or patent eligible. How the agency's declaration will influence justices and the patent office worries biotech companies. But the patent office isn't easily swayed, says Thomas Kowalski, an attorney with Vedder Price in New York. "The patent office is not going to change what it's doing in view of what the Department of Justice says," he says. Besides, international agreements between the American, European and Japanese patent offices, known as Trilateral Co-operation, have concluded that unmodified DNA is patentable. *Emily Waltz*

USPTO's do-good vouchers

Patent owners may soon be able to cut the time needed to have a patent reexamined by up to two-thirds if they can demonstrate a humanitarian use. The US Patent & Trademark Office (USPTO) is proposing a system that would offer fast-track reexamination vouchers as an incentive to stimulate "creation or licensing that addresses humanitarian needs." Because patents under reexamination are often the most valuable commercially, a fast-track procedure would let patent owners "more readily and less expensively affirm the validity of their patents," according to the *Federal Register* notice. The USPTO currently takes 19 to 20 months for such reexaminations, whereas the expedited review promises a six-month turnaround. The system is modeled on the US Food & Drug Administration's priority review vouchers given to entities that develop drugs to treat neglected tropical diseases. In this case, patent holders who receive the fast-track reexamination voucher could use it on any other patent they own or transfer it to the open market. Although the intent is worthy, there are too many unanswered questions, worries Thomas Kowalski of Vedder Price. "What will the USPTO do to ensure that those in the developing world as well as the poor in the developed world can gain access to the technology? Also, the voucher should be tied specifically to the technology with the humanitarian use instead of being independent and transferable." *Michael Francisco*

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Table 1 Timeline of events leading up to the synthetic DNA guidance

December 2006	The US government's National Science Advisory Board for Biosecurity issues a report recommending the establishment of "uniform and standardized screening practices among providers of synthetic DNA."
June 2007	The US Government convenes an interagency working group on synthetic nucleic acid screening.
November 3, 2009	Companies of the International Association Synthetic Biology (Entelechon, ATG:biosynthetics, Biomax, febit and Sloning Biotechnology) present their "Code of Conduct" for the screening of gene orders and customers.
November 19, 2009	Companies of the International Gene Synthesis Consortium (Blue Heron Biotechnology, DNA2.0, GENEART, GenScript and Integrated DNA Technologies) release a similar set of 'best practices' guidelines, the "Harmonized Screening Protocol."
November 29, 2009	The US Department of Health and Human Services releases a draft version of its *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* for public comment.
January 11, 2010	The American Association for the Advancement of Science (AAAS) hosts a meeting for policy specialists and scientists from academia and industry on "Minimizing the Risks of Synthetic DNA: Scientists' Views on the U.S. Government's Guidance on Synthetic Genomics."
January 26, 2010	Public comment period ends on the draft guidance.
October 13, 2010	HHS publishes its final version of the *Screening Framework Guidance*.

He adds, "The annotation is as provided by the person that deposited the sequence." Screening effectiveness could also be constrained by biases in the database contents, according to James Diggans, a researcher at MITRE, a not-for-profit national technology resource that focuses on security issues, located in Bedford, Massachusetts and McLean, Virginia. "There are far more harmless sequences in these databases than there are sequences that could be used to harm human health."

For other scientists, the reliance on the select agents list is also problematic. Eighty-two items currently listed represent known risks to human, plant or animal health, and are unambiguously regulated by federal law. But many known human pathogens, such as severe acute respiratory syndrome virus, are omitted, and others worry about the problems that could be posed by the yet-unknown sequence variants. "If you synthesize a genome without creating the actual organism it encodes—and where now you aren't even limited to the variability found in nature—how do you taxonomically classify that genome sequence?" says Eddy.

Eddy and other scientists recently partnered with the US National Research Council in an effort to bring some clarity to the characterization of high-risk genes. The resulting report, *Sequence-Based Classification of Select Agents: A Brighter Line* (http://www.nap.edu/catalog/12970.html), concludes that although it is presently impossible to reliably predict gene function based on sequence, it should nevertheless be within reach to develop mechanisms that can help categorize sequences as belonging to predefined 'hazardous' or 'safe' classes of genes, an effort that could greatly improve the future efficiency of synthetic gene order screening.

Several parallel efforts are also underway to develop more sophisticated and comprehensive pathogen databases. Fischer and Maurer are collaborating on Virulence Factor Information Repository (VIREP), a repository for annotated information about known virulence genes, based at UC, Berkeley. The IGSC has also stated its intention to develop an extensive regulated pathogens database, which could offer a broadly useful community resource. However, both groups are waiting on government support to help move these projects forward.

For now, the member companies of the IGSC, which are predominantly based in the US, are moving to adapt their standards to comply with the HHS recommendations. However, the guidance also invites companies to apply their own "equivalent or superior" screening standards and several companies indicate that they will continue to err on the side of caution in their screening procedures. "If we get a gene in, we screen it," says Robert Dawson, director of bioinformatics at Coralville, Iowa–based Integrated DNA Technologies. "There's never a case where we would have a gene go right into production without a human being having looked at both the sequence and the prospective customer." HHS has also made it clear that these are minimum screening recommendations and not the final word, and discussions are ongoing.

Given the early stage of the field, when the risk from synthetic biology is still seen as relatively low—to date, no IGSC member company reports having received an order for a 'sequence of concern' that also came from a dubious customer—some hope that there will be sufficient opportunity for these guidelines to grow into a more effective monitoring strategy. "It's a line in the sand drawn by the US government that now serves as something to be improved over time," says Diggans. "All of these things make a direct contribution to maintaining near-term biosecurity, but it will need to evolve quickly—the technology is moving ever faster."

Michael Eisenstein, *Philadelphia*