U.S. Department of Health & Human Services
Assistant Secretary for Preparedness & Response

Frequently Asked Questions
Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

What is synthetic double-stranded DNA (dsDNA)?

Synthetic dsDNA is chemically manufactured dsDNA, which encodes genetic information. It is distinct from naturally occurring dsDNA, which is isolated directly from an organism. The ability to make dsDNA, based on a genetic sequence, allows a researcher to request custom dsDNA from a provider who will synthesize the order and ship it to the researcher.

Does *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* impose new regulations on providers of synthetic dsDNA or customers?

No, this document does not establish new regulations. Adherence is voluntary. The document recommends baseline standards for the gene and genome synthesis industry and other providers of synthetic dsDNA products regarding the screening of orders. Some specific recommendations serve to remind providers of their obligations under existing regulations, but no new regulations are imposed.

Why is guidance needed for dsDNA synthesis?

The chemical synthesis of dsDNA potentially allows for the generation and modification of some viruses and bacteria. More specifically, dsDNA synthesis could enable individuals not authorized to possess Select Agents or Toxins (or, for international orders, items listed on the Commerce Control List or CCL) to obtain them using dsDNA ordered from providers of synthetic dsDNA. As a result, guidance to address such synthetic dsDNA is needed.

Many synthetic dsDNA providers are eager for the U.S. government to provide them with guidance regarding best practices in mitigating biosecurity risks.

Why take a voluntary rather than a regulatory approach to screening synthetic dsDNA orders?

The U.S. government supports taking a voluntary rather than a regulatory approach to screening synthetic dsDNA orders at this time. The commercial DNA industry has acted responsibly in reaching out to the U.S. government to seek guidance. Providers and the U.S. government share the goal of reducing the chances that a Select Agent or Toxin (or a CCL item for international orders) could fall into the wrong hands.

Regulations already cover some types of synthetic orders of dsDNA. The U.S. Department of Health and Human Services and the U.S. Department of Agriculture, under the National Select Agent Program, already regulate nucleic acids that can produce infectious forms of Select Agent viruses and nucleic acids that encode the active forms of Select Agent toxins. Orders of synthetic dsDNA that fall into either category must comply with existing regulations (www.selectagents.gov).

Additionally, the field of synthetic genomics presents a novel challenge, and regulations may not provide the flexibility to address this challenge. The relationship between dsDNA sequence and pathogenicity (the ability of an organism to cause disease) is not currently understood well enough to be fully codified in regulation. While there is a body of knowledge on the mechanisms of disease, microbial physiology is controlled by an intricate balance of gene expression and regulation. Therefore, gene presence and structure do not necessarily predict an organism's characteristics. Double-stranded DNA itself is not dangerous. Only when dsDNA is engineered to reconstitute an organism would safety, security, and regulatory concerns arise.

Regulations take time to develop and may need to be modified to keep pace with science. The field of synthetic genomics is evolving very quickly. A voluntary approach is one way to deal with many uncertainties about the future of the field. Initial screening recommendations have been outlined in the document, but these may need to be adjusted in practice. The approaches taken in the document will be evaluated on an ongoing basis.

Finally, if U.S. regulations were developed, they would only cover U.S. dsDNA providers, whereas providers exist all over the world. Voluntary guidance may provide a better opportunity to establish a baseline that is relevant internationally.

Will implementing the recommendations unduly burden industry?

The U.S. government has consulted with representatives of synthetic dsDNA providers to understand their current practices and help ensure that these recommendations will not cause undue burden. The vast majority of synthetic dsDNA providers are already conducting similar sequence and customer screening.

Will implementing the recommendations unduly burden customers?

Because major synthetic dsDNA providers already conduct similar screening, the implementation of the recommendations in *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* is unlikely to add an additional burden to customers.

Will individual scientists sharing synthetic dsDNA or synthetic dsDNA products with colleagues or other scientists be considered providers in the context of the guidance?

In this context, a provider is an entity synthesizing dsDNA for and distributing dsDNA to a customer, not a research scientist collaborating with a colleague.

Why was dsDNA derived from or encoding Select Agents and Toxins (and items on the CCL, for international orders) selected as the focus?

The U.S. government identified Select Agents and Toxins (and, for international orders, those items listed on the CCL) as the most appropriate "agents of concern" because these well-defined lists comprise high consequence pathogens and toxins that have the potential to pose a severe threat to human, animal, or plant health or to animal or plant products. The possession, use, and transfer of the agents on the Select Agents and Toxins lists and CCL are managed through existing federal regulations.

It is appropriate to focus on dsDNA sequences from regulated agents because at this time, it is not possible to develop clear criteria that providers could use to robustly, comprehensively, and consistently identify non-Select Agent and Toxin or non-CCL "sequences of concern."

Nonetheless, the U.S. government recognizes that there are concerns that synthetic dsDNA sequences not unique to Select Agents or Toxins or CCL items may also pose a biosecurity concern. The U.S. government recognizes that many providers have already instituted measures to address these concerns. The ongoing development of best practices in this area is commendable and encouraged.

Why is suggested screening limited to synthetic dsDNA?

The synthetic dsDNA provider community is the focus of this document, rather than providers of single-stranded DNA (oligonucleotides) because generating or re-creating "agents of concern" using synthesized dsDNA pieces is technically less challenging than re-creating an organism with single-stranded oligonucleotides. Additionally, because of the high volume and rapid turnaround time for single-stranded DNA orders, a screening framework for single-stranded DNA is less practical and potentially much more burdensome to researchers and industry at this time. Given the rapid developments in DNA synthesis, the U.S. government will continue to examine this issue and may make amendments accordingly.

Why was the "Best Match" approach for screening against sequences in GenBank selected as the suggested sequence screening method?

Given existing capabilities, the "Best Match" approach was deemed more efficient and appropriate than a "Top Homology" or a customized sequence database approach. The "Best Match" approach involves a sequence screen against an existing, continuously updated database called GenBank to determine if the ordered sequence is the "best match" to a sequence from an "agent of concern." In the "Top Homology" approach, human screeners examine all sequences that exceed a certain threshold of homology to a dsDNA order after a GenBank screen to determine whether or not the matching sequences are derived from an "agent of concern." In the customized sequence database approach, an ordered sequence is screened against a curated, customized database of "sequences of concern."

New sequences are added to GenBank every day, and GenBank is the most comprehensive and updated database available. As a result, by screening against GenBank, the most recent sequence information is available.

The U.S. government carefully considered several sequence screening approaches, including "Top Homology" and customized sequence database approaches. Instituting a percent identity "cut-off" in the "Top Homology" approach would be arbitrary; the "Best Match" approach addresses the fundamental question: is this sequence more closely related to a sequence from a Select Agent or Toxin (or a CCL item, for international orders) than to any other sequence? The "Best Match" approach also helps to reduce the number of false positives caused by "housekeeping genes," which are genes that are required to maintain normal cellular physiology and that are shared among Select Agents and Toxins (or CCL items) and other organisms.

Creating a customized sequence database would require curation (development of a manually constructed database that links gene sequences to pathogenicity) and frequent oversight and would introduce the risk of omitting an important gene sequence from the database. The acquisition of knowledge about pathogenicity and virulence is progressing, but it is not possible at this time to provide a robust database that would identify all or even most dangerous sequences.

Is *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* consistent with current industry practices?

In developing *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*, the U.S. government consulted with representatives of synthetic dsDNA providers to understand their current practices. While there may be some differences in screening details between the U.S. government approach and that of individual providers, as well as differences from provider to provider, the overarching recommendations and intent are fairly consistent among industry and the U.S. government.

The proposed screening approach strikes a balance between mitigating biosecurity risks and minimizing any negative impacts on the conduct of research or business operations. A goal in developing the document was to ensure it would be feasible for small and large providers, as well as international providers. The document provides an acceptable baseline. One potential benefit of the proposed sequence screening method is consistency, because a hit for one company should register as a hit for other companies adhering to the guidance.

The guidance is not meant to be entirely prescriptive and does not explicitly delineate when manual and automatic screening should occur. The document emphasizes the importance of in-house, human bioinformatics expertise to follow-up on dubious hits.

Finally, the document acknowledges that the ongoing development of best practices by providers in this area is commendable and encouraged.

How will the U.S. government evaluate the effectiveness of the recommendations?

The U.S. government is developing an evaluation and monitoring strategy, recognizing that continued research and development may lead to new and improved screening methodologies. As new methods are developed, U.S. guidance may change accordingly.