International Gene Synthesis Consortium

Harmonized Screening Protocol v3.0

3 September, 2024

1 Preamble

This document outlines the standards and practices that International Gene Synthesis Consortium (IGSC) Provider and Manufacturer members apply to prevent the misuse of synthetic nucleic acids. By uniformly screening the sequences of ordered nucleic acids and vetting synthesis customers, IGSC members collaborate to reduce the risk of misuse of synthetic nucleic acids. IGSC members establish and continuously improve best practices, safeguard the many benefits of nucleic acid synthesis technology, and help ensure broad compliance with relevant regulatory frameworks, government guidance, and other international standards where available.

First established in 2009 as a trade organization, the IGSC was incorporated as a California-based not-for-profit 501c(3) corporation in 2015. The IGSC members together represent a majority of global commercial gene-length nucleic acid synthesis capacity.

2 Background

As gene-length synthesis technologies improved in the early 2000s, there was increasing awareness of the dual-use nature of gene-length synthetic DNA within industry, civil society, and governments. In 2006, the National Science Advisory Board for Biosecurity (NSABB) in the United States recommended[1] that the U.S. government provide guidance to the emerging industry as a way of helping build a culture of responsible synthesis without unduly holding back technological development. The following year, the J. Craig Venter Institute published a report[2] that laid out several options for reducing the risk of misuse while balancing technological advancement.

In 2009, many of the largest gene synthesis companies came together to form the International Gene Synthesis Consortium (IGSC) to provide a focal point for engagement on these issues and development and dissemination of best practices for reducing the risk of misuse of gene-length

[1] https://biosecurity.fas.org/resource/documents/NSABB%20guidelines%20synthetic%20bio.pdf
[2] https://www.jcvi.org/research/synthetic-genomics-options-governance

synthetic DNA. In 2010, the U.S. government published the *Screening Framework Guidance for Providers of Synthetic Double-stranded DNA*[3] that, for the first time, laid out in detail the importance of- and specific recommendations for both customer- and sequence screening. The IGSC responded by publishing the first version of its *Harmonized Screening Protocol* - a document intended to help IGSC members design and implement screening programs. The IGSC also created its Restricted Pathogen Database (RPD), a data set used by member companies for sequence screening.

Over the next 13 years, several developments have led to the need to update the Harmonized Screening Protocol:

- The U.S. government invested[4] research dollars to improve sequence screening tools, helping to create a new commercial market for such tools. Several screening tool vendors joined the IGSC.
- Several companies were created to build benchtop-scale DNA synthesis devices.
- In response to these and other developments, in 2023, the U.S. government published the *Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids*[5], an update and expansion of the 2010 guidance document.
- The Biden Administration in the U.S. in October of 2023 published Executive Order 14110[6] laying out, in part, a roadmap for improving nucleic acid synthesis screening to reduce future risks potentially posed by artificial intelligence.
- The Office of Science and Technology Policy in the U.S. published the *Framework for Nucleic Acid Synthesis Screening*[7], the first comprehensive government framework with specific requirements for adherence.

This v3.0 of the Harmonized Screening Protocol provides both an updated screening protocol as well as an increase in specificity and context around how to build and operate screening systems with the goal of increasing the uniformity and accuracy of screening systems in use by nucleic acid providers.

[3] https://aspr.hhs.gov/legal/synna/Pages/syndna.aspx
[4] https://www.iarpa.gov/research-programs/fun-gcat
[5] https://aspr.hhs.gov/legal/synna/Documents/SynNA-Guidance-2023.pdf
[6]https://www.whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/
[7]https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf

3 Terminology

Where possible, the following definitions align with terms defined in the 2023 U.S. government *Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids* (in bold below). The definitions presented here are meant to be easy to understand, rather than definitions specifically accepted by the many different communities that work across dual-use technologies.

Term	Definition
Customer	The individual or entity (such as an institution) that orders or requests synthetic nucleic acids from a Provider, or that purchases synthesis equipment from a Manufacturer.
Principal user	The individual who originates an order or request for synthetic nucleic acids or synthesizes nucleic acids and oversees the use of ordered or synthesized nucleic acids in the laboratory. The Principal User may also be the End User.
Synthetic nucleic acid	A single- or double-stranded DNA or RNA fragment produced by nucleic acid synthesis technology.
End user	The individual who possesses and uses synthetic nucleic acids that they have received from a Customer, Principal User, or another End User.
Provider	The entity that synthesizes and distributes synthetic nucleic acids to a Customer. A Provider is understood to be synthesizing nucleic acids as a transactional service, rather than a research scientist collaborating with a colleague.
Third-party vendor	An entity that orders synthetic nucleic acids from Providers and sells them or their constructs, with or without reformulation, or resells benchtop equipment for synthesizing nucleic acids.
Manufacturer	An entity that produces and sells benchtop equipment for synthesizing nucleic acids. Manufacturers may provide equipment to individuals, entities, Principal Users, or Third-Party Vendors.
Benchtop nucleic acid synthesis equipment	Benchtop nucleic acid synthesis equipment sold by Manufacturers that is intended to be used to synthesize nucleic acids for use within a research laboratory or within an institution. While this nucleic acid synthesis equipment may not be small enough to be placed on a benchtop (e.g., it sits on the laboratory floor), it is still considered benchtop equipment if it is sold with the intent that it will be used by researchers individually or in a core facility in an institution.
Oligonucleotides	Short, single- or double-stranded DNA or RNA fragments.

Dual-use	Technology or material that has both beneficial as well as potential harmful uses.
Restricted Pathogen or Toxin	A viral, bacterial or fungal species present on one or more lists of pathogens or toxins subject to some form of regulatory control.
Sequence of Concern (SOC)	A broad term often used to capture the ideal not just of sequences currently subject to formal regulatory control but any sequence that could be misused to cause significant harm. The 2023 updated U.S. government Guidance defines SoCs to include "*sequences known to contribute to pathogenicity or toxicity, even when not derived from or encoding regulated biological agents*" without further elaboration. Importantly, *there is currently no agreed-upon list of such sequences* but there are many ongoing discussions around the value of creation of such a list. Should such a list one day exist, the IGSC will evaluate its utility in synthesis screening and update this Protocol accordingly.
Sequence similarity	Any measurement used to determine whether a given sequence is likely to be a sequence of concern by comparison of that sequence with other sequences. Note that there are a wide variety of methods for computing sequence similarity, including edit distance, sequence homology, exact k-mer matches, presence of conserved residues, and neural network embeddings, and a wide variety of ways to apply these methods.
Best match	A database record with the highest sequence similarity (regardless of the degree of that similarity or the type of similarity measurement used) for any unique start & stop location on a query sequence in a sequence alignment.
Export license	A license, granted by a government to an exporter, allowing the export of specific controlled material from one country to another.
Venue shopping	Attempting to acquire controlled material from multiple different Providers in order to find a Provider willing to sell the material without further screening or licensing.

4 Regulatory Frameworks and Government Guidance

At the time of this publication, no country in the world *requires* Providers or Manufacturers to screen the sequences they are asked to synthesize. However, some of these sequences may still be subject to control under domestic- or export control regulatory frameworks. If a Provider or Manufacturer chooses not to screen orders, there is no way to remain compliant with these regulatory frameworks, opening the Provider or Manufacturer up to potential legal liability.

4.1 Domestic Regulatory Frameworks

Providers and Manufacturers should ensure they are aware of any regulatory requirements or necessary licenses for possession or sale of specific nucleic acid sequences from controlled organisms, viruses or toxins within their local jurisdictions. These include the Federal Select Agent Program in the United States, Schedule 5 in the United Kingdom and others.

4.1.1 Example: U.S. FSAP

In the United States, for example, the Federal Select Agent Program (FSAP)[8] controls access to some nucleic acid sequences, requiring licensing for possession. The FSAP program has provided a regulatory interpretation[9] specific to synthetic nucleic acids which can be helpful for U.S.-based Providers and Manufacturers to understand when a nucleic acid sequence may be subject to FSAP control.

4.2 Export Control

Export control regimes, where nucleic acids are concerned, are designed to reduce the risk of misuse. These programs generally require Providers or Manufacturers to apply for- and receive export licenses from governments allowing shipment of specific materials outside of the country in which the material is produced. Licenses are usually very specific, allowing a Provider or Manufacturer to ship a specific controlled nucleic acid sequence to a specific Customer at a specific physical address. The same Customer requesting shipment of a different controlled material may trigger a requirement on the part of the Provider or Manufacturer to apply for- and receive a new export license before shipment can take place.

4.2.1 The Australia Group

As the broader biotech community is very international in nature, export controls are most effective if they are uniform across as many countries as possible. This uniformity helps prevent ‘venue shopping’ - the idea that a Customer intent on misuse could attempt to order material from multiple Providers until they find a Provider that does not require an export license before shipment can occur.

[8] https://www.selectagents.gov/sat/list.htm
[9] https://www.selectagents.gov/regulations/interpretations/dna.htm

The Australia Group[10] (AG) is a multilateral arrangement created in 1984. The AG, "*through the harmonization of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons.*" The 43 groups or nations[11] that currently participate in the Australia Group process all agree to, at minimum, use the Australia Group common control lists in their national export control programs. That is, if a material is controlled for export in one AG country, it is generally also controlled for export from any other AG country.

It is the responsibility of each individual Provider to ensure they understand when and if a given nucleic acid sequence requires an export license prior to shipment but, in general, in each Australia Group participant nation:

- Nucleic acid sequences that are a 'best match' to organisms *not* listed under either the Human and Animal Pathogens & Toxins list or the Plant Pathogens list generally do not require a license for shipment to most destinations.
- Nucleic acid sequences that are a 'best match' to *bacteria or fungi* listed on either of the AG common control lists will require an export license only if the gene's function 'endows or enhances pathogenicity'.
- Nucleic acid sequences that are a 'best match' to *viruses* listed on either of the AG common control lists will generally *always* require an export license.

4.2.2 Example: U.S. EAR

In the United States, export control is governed by the Export Administration Regulations (EAR). As part of the EAR, the United States maintains its Commerce Control List which describes all of the Export Control Classification Numbers (ECCNs). ECCNs 1C351 and 1C354 list controlled bacteria, fungi, viruses and toxins. ECCN 1C353 defines the conditions under which a 'genetic element' (which includes DNA and RNA) would require an export license.

The AG Human and Animal Pathogens & Toxins list appears in the EAR as ECCN 1C351. The AG Plant Pathogens list appears in the EAR as ECCN 1C354. The 'genetic elements' definition that is part of both AG lists appears in the EAR as ECCN 1C353.

As of 8 December, 2023, the United States Department of Commerce amended the EAR such that DNA or RNA sequences that fall under ECCN 1C353 (with the exception of genetic elements of items controlled by 1C351.d.14 and .15) *no longer require an export license* for shipment to other countries that are part of the Australia Group process. While an export license may no longer be required, verification of legitimacy as recommended in the 2023 Guidance is still recommended for all IGSC members for orders of sequences that would be controlled under ECCN 1C353.

[10] https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/index.html
[11] https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/participants.html

4.2.3 Example: U.S. ITAR

The U.S. Department of State operates a licensing regime around the International Traffic in Arms Regulations, controlling the export of specific 'defense-related articles.' These articles are listed in the United States Munitions List (USML)[12] which does include, in Category XIVb, control over some 'biological agents and biologically derived substances and genetic elements thereof.' Note 2 to paragraph (b), however, states that ITAR does not control genetic elements that are '*unable to produce or direct the biosynthesis of infectious or functional forms of the biological agents or biologically derived substances*.'

4.2.4 Export Control Classification

Some governments may offer an export control classification service, allowing companies to file a request for formal classification of a specific request from a Customer. This process can be especially useful for synthetic DNA orders as the export control status of genes from controlled bacteria and fungi can be difficult to determine if there is no literature supporting whether a gene can 'endow or enhance' pathogenicity or not. As an example, classification requests for the U.S. Commerce Department can be filed using the SNAP-R system[13].

4.3 Applicable Government Publications

Thus far, only the government of the United States has produced documents specifically intended to provide guidance or specific screening requirements to the nucleic acid synthesis industry on biosecurity best practices.

4.3.1 2010 US Government Guidance

The U.S. government engaged with the DNA synthesis industry in a series of meetings meant to help the government understand the industry, its capabilities, its rate of growth and the degree to which companies competed internationally for business. In October of 2010, the Assistant Secretary for Preparedness and Response (ASPR[14]) published[15] the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (the 'Guidance').

This document established the initial set of best practices and recommendations for Providers:

1. Screen all Customers to ensure Customers have a legitimate use for the sequences they are ordering
2. Screen sequences over 200 bp to ensure the Provider understands the nature of the biological component they have been asked to synthesize

[12] https://www.ecfr.gov/current/title-22/chapter-I/subchapter-M/part-121
[13] https://snapr.bis.doc.gov/snapr/
[14] ASPR was elevated to an operating division within HHS and renamed the Administration for Strategic Preparedness and Response on 22 July, 2022.
[15]https://www.federalregister.gov/documents/2010/10/13/2010-25728/screening-framework-guidance-for-providers-of-synthetic-double-stranded-dna

3. Retain all records of Customer- and sequence screening for at least 8 years (a length of time designed to align with the statute of limitations for use of a weapon of mass destruction under U.S. law).

While the IGSC had formed in 2009 (during the ongoing series of discussions between industry and the U.S. government that led to the Guidance), in 2010 in response to the Guidance the IGSC published the first version of its Harmonized Screening Protocol, intended to embrace and extend the practices called for under the Guidance.

4.3.2 2023 US Government Guidance

On 13 October of 2023, ASPR released[16] an updated version of the guidance, the product of an extensive interagency process. This updated guidance document:

- Formalized definitions for various players in the synthetic DNA market
- Extended the Guidance to cover benchtop nucleic acid synthesis devices and Manufacturers
- Lowered the length threshold for sequence screening from 200 to 50 bp (within 3 years of the date of publication of the Guidance)
- Expanded the definition of Sequences of Concern beyond regulated pathogens and toxins.
- Created a companion guide[17] providing more detail on verifying legitimacy along with example use cases and suggested responses

4.3.3 Executive Order on Artificial Intelligence

On 30 October 2023, the United States released the Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence[18], also known as EO 14110 or 'the AI EO'. While the majority of this EO was directed at improving safety and security practices around artificial intelligence systems, the EO also recognizes that AI-assisted biological design tools pose novel risks that existing approaches to evaluating AI systems for safety do not address. As a result, two pages of the EO were devoted to nucleic acid synthesis screening, recognizing nucleic acid synthesis as an important point at which to reduce the risk of misuse of AI-designed nucleic acid constructs.

[16] https://www.govinfo.gov/app/details/FR-2023-10-13/2023-22540
[17] https://aspr.hhs.gov/legal/synna/Documents/SynNA-Companion-Guide-508.pdf
[18]https://www.whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/

The EO in particular directed the following:

- Directed a broad governmental effort, led by the Office of Science and Technology Policy (OSTP) in the White House, to "establish a framework, incorporating, as appropriate, existing United States Government guidance, to encourage providers of synthetic nucleic acid sequences to implement comprehensive, scalable, and verifiable synthetic nucleic acid procurement screening mechanisms"

- Directed a second broad effort, taking place after publication of the Framework and led by the National Institute of Standards and Technologies (NIST), to 'develop and refine':
    - specifications for effective nucleic acid synthesis procurement screening
    - best practices, including security and access controls, for managing sequence-of-concern databases to support such screening;
    - technical implementation guides for effective screening; and
    - conformity-assessment best practices and mechanisms.

- Directed all government funding agencies, 180 days after publication of the Framework, to "establish that, as a requirement of funding, synthetic nucleic acid procurement is conducted through providers or manufacturers that adhere to the framework, such as through an attestation from the provider or manufacturer."

- Directed the Department of Homeland Security (DHS), within 180 days of the establishment of the Framework, to "develop a framework to conduct structured evaluation and stress testing of nucleic acid synthesis procurement screening"

4.3.4 Framework for Nucleic Acid Synthesis Screening

On April 30, 2024, OSTP published its Framework for Nucleic Acid Synthesis Screening[19] ('the Framework'). The Framework was created in response to the requirement laid out in EO 14110 and, for the first time globally, laid out 'a unified process for screening purchases of synthetic nucleic acids and benchtop nucleic acid synthesis equipment'.

The Framework 'incorporates and supplements' the 2023 HHS/ASPR guidance, using many of that document's definitions and recommendations while formally defining both a) a list of criteria providers and benchtop manufacturers must attest to to adhere to the Framework as well as b) directing federal funding agencies to procure synthetic nucleic acids only from 'Providers or Manufacturers that adhere to the framework'.

[19] https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf

The Framework requires the following 6 items from synthesis providers and benchtop manufacturers to be considered 'in adherence' to the Framework (quoting directly from the document given the importance of these items):

1. *Attest to implementing this screening framework through a statement that either is posted on a public website or provided to both the federally funded customer and federal funding agency;*
2. *Screen purchase orders for synthetic nucleic acids to identify SOCs;*
3. *Screen customers submitting purchase orders of synthetic nucleic acids with SOCs, and purchase orders of benchtop nucleic acid synthesis equipment, to verify legitimacy;*
4. *Report potentially illegitimate purchase orders of synthetic nucleic acids involving SOCs or of benchtop nucleic acid synthesis equipment;*
5. *Retain records relating to purchase orders for synthetic nucleic acids and benchtop nucleic acid synthesis equipment; and*
6. *Take steps to ensure cybersecurity and information security.*

As of the publication date of this version of the Harmonized Screening Protocol, NIST is developing a form by which synthesis providers and benchtop manufacturers will be able to attest to their adherence to the Framework and thereby qualify for receipt of federal funds for synthetic nucleic acids.

5 Assessing Risk and Legitimate Use

The U.S. Guidance indicates that Providers should ensure that Customers have a 'legitimate, bona fide and peaceful purpose' for purchased synthetic nucleic acids that contain Sequences of Concern. There is, however, no agreed-upon framework (within any country, much less internationally) against which Providers could measure a Customer's stated use to determine its legitimacy. There is also no framework available for consistently categorizing specific biological risk posed by a given construct.

Given this lack of formal frameworks for understanding and recording risk, Providers should ensure that in discussions with Customers, the stated intended use for ordered Sequence of Concern nucleic acids is a) self-consistent (in that the Customer appears to have sufficient expertise to understand the planned use for ordered sequences) and b) consistent with the nature of the ordered sequence(s).

This series of judgments by the Provider generally requires significant scientific expertise on the part of the individual representing the Provider in these conversations. It is common for these individuals to have doctoral degrees and significant experimental experience. It is additionally valuable for these individuals to have a background or training in the history of biological weapons and an understanding of agents and toxins traditionally considered weaponizable. Such a background will maximize the potential for Providers to detect potential misuse of a Sequence of Concern.

Individuals with insufficient expertise will be less likely to detect when the provided intended use makes little sense or is contradicted by the nature of the ordered sequence(s).

6 Screening Data Resources

Modern biosecurity screening can be implemented by determining the 'best match' sequence similarity for each functional region in each sequence in an order from among a large database of reference sequences. The species identity of these 'best match' findings can then be compared against lists of species subject to regulatory control. If a sequence has a region that is a 'best match' to a regulated pathogen or toxin, the Provider should carry out a more detailed analysis of the sequence to determine if the sequence is subject to formal regulatory control and whether detailed follow-up with the Customer should be carried out.

Providers should maximize the size of the reference database used to ensure that 'best match' determinations are as accurate as possible. If Providers use small reference databases in their screening, they run the risk of either a) missing the 'best match' to controlled species (false negatives) or b) finding the 'best match' to controlled species when, in a larger database, the 'best match' would be to a species not subject to regulatory control (false positives). Care must also be taken to ensure that the reference database does not contain mis-categorized, chimeric, or otherwise ambiguous material that can cause an incorrect assessment of control status (false positives or false negatives).[20]

6.1 State-Specific Lists of Entities

Many national governments maintain lists of people or institutions with whom there may be limitations on engaging in business transactions. Governments may maintain multiple lists, each with a different reason for inclusion on the list. Some lists focus on entities formally sanctioned by a country, some on entities with higher risk of illegal diversion of shipped materials.

Example lists include:

- The U.S. Treasury Office of Foreign Asset Control Sanctions List[21]
- The U.S. Commerce Department Entity List[22]
- The U.S. Commerce Department Denied Persons List[23]
- The EU Consolidated list of persons, groups and entities subject to EU financial sanctions[24]

Screening of customers against such lists can also be implemented through the use of "Know Your Customer" services, commonly used in the financial industry.

[20] See, for example: https://doi.org/10.1038/s41598-023-32481-z
[21] https://sanctionssearch.ofac.treas.gov/
[22] https://www.bis.doc.gov/index.php/policy-guidance/lists-of-parties-of-concern/entity-list
[23] https://www.bis.doc.gov/index.php/policy-guidance/lists-of-parties-of-concern/denied-persons-list
[24] https://data.europa.eu/data/datasets/consolidated-list-of-persons-groups-and-entities-subject-to-eu-financial-sanctions?locale=en

6.2 INSDC Sequence Databases

The International Nucleotide Sequence Database Collaboration (INSDC) brings together the operators of the three largest global sequence repositories, Japan's DDBJ[25], the EMBL-EBI[26] in Europe and the U.S. NCBI[27].

Each of these organizations publishes large collections of protein- and nucleotide sequences. For sequence screening purposes, Providers should prefer using the 'non-redundant' version of these databases[28] - these contain only one instance of each unique sequence submitted to the database. In this way, Providers maximize the total number of unique sequences searched for 'best match' similarity while minimizing the total number of sequence records searched.

6.3 IGSC Restricted Pathogen Database

Many nations maintain lists of named pathogens and toxins subject to some form of regulatory control in those nations (either for domestic possession, for export outside of the country, or both). Providers must ensure they are aware of the nature and extent of such controls for each country in which they manufacture synthetic nucleic acids.

Examples of such lists include:

- The Australia Group Common Control Lists
- U.S. Select Agents and Toxins
- U.S. Commerce Control List (search the file for 1C351, 1C353 and 1C354)
- U.S. Munitions List
- EU List of Dual-Use Items (search the file for 1C351, 1C353 and 1C354)
- UK Schedule 5

The IGSC Restricted Pathogen Database (RPD) attempts to collate all of these global lists into a unified set of species and sequence records subject to some form of regulatory control. The RPD consists of two collections of record types:

1. A list of NCBI taxonomy record IDs - each ID points to a specific location in the 'tree of life', uniquely identifying a biological species subject to some form of regulatory control.
2. A list of GenBank sequence record identifiers, each pointing to a GenBank record for a sequence from a controlled toxin.

The RPD is managed by the IGSC in a GitHub repository. Any change made by governments to regulatory controls or change made to the taxonomy or specific GenBank records results in a GitHub pull request reflecting the change. These are reviewed and approved by at least 2 IGSC

[25] https://www.ddbj.nig.ac.jp/index-e.html
[26] https://www.ebi.ac.uk/
[27] https://www.ncbi.nlm.nih.gov/
[28] https://www.nlm.nih.gov/ncbi/workshops/2023-08_BLAST_evol/databases.html

Provider or Manufacturer companies before being merged. After each change is merged, a new version of the RPD is released and announced to the IGSC membership.

7 IGSC Harmonized Screening Protocol

7.1 Customer Screening

Requirement	Description
1.1	IGSC members require identification data from all potential Customers for synthetic nucleic acids, including at a minimum a shipping address, institution name, country, telephone number, and email address. We do not ship to residential addresses or to PO Boxes.
1.2	Potential Customers are subject to restricted party screening against any relevant lists of sanctions or denied party lists maintained by countries relevant to each Provider's base of operations. Relevant lists include the U.S. OFAC's SDN List, the U.S. Department of State Debarred List, and U.S. BIS's Denied Persons, Entity, and Unverified lists, or the German HADDEX list, and/or any other list required by applicable national regulations.
1.3	IGSC members require additional Customer screening before accepting orders for nucleic acid sequences from regulated pathogens or toxins. IGSC members supply nucleic acid sequences from regulated pathogens and toxins only to researchers in bona fide government laboratories, universities, non-profit research institutions, or industrial laboratories demonstrably engaged in legitimate research. Customers ordering significant portions of the genomes from regulated pathogens or toxins must provide a written description of the intended use of the synthetic product. IGSC companies should verify independently a) the identity of the potential Customer and purchasing organization, and b) that the described use is consistent with the activities of the purchasing organization.
1.4	IGSC members use the current recommendations from the U.S. CDC and/or the Department of Agriculture and/or the European Commission to determine which nucleic acid sequences are Select Agents as recombinant nucleic acid fragments. We supply such sequences only if the supplier and the Customer are able to comply with all Select Agent regulations applicable to that sequence.
1.5	In general, IGSC members only sell DNA or fragments of regulated pathogens to bona fide end-users. We do not sell or ship such material to distributors or other resellers, unless those companies agree to identify the end-user receiving the products and demonstrate their compliance with every requirement otherwise applicable to that end-user, or are themselves members of the IGSC that follow the Harmonized Screening Protocol.

7.2 Sequence Screening

Requirement	Description
2.1	IGSC members screen synthetic gene orders to identify regulated pathogen sequences and other sequences of concern.
2.2	IGSC members screen the complete nucleic acid sequence of every order 200 bp or longer against the sequences in a common Regulated Pathogen Database (RPD), and against all entries found in one or more of the internationally coordinated sequence reference databanks (i.e., NCBI/GenBank, EBI/EMBL, or DDBJ). Members are encouraged to decrease the minimal length of sequences screened to 50 bp as soon as reasonable. Members must transition to this shorter screening length threshold by October 24, 2026 at the latest to conform to the requirements of the U.S. OSTP Framework. The IGSC has assembled and curated the RPD to include data from all organisms on the U.S. Federal Select Agent list, the Australia Group Common Control Lists, and other national lists of regulated pathogens. This database is shared and deployed to IGSC members. Members frequently supplement their biosecurity systems with additional sequence data. As a baseline, IGSC companies screen against all genes encoding toxins, genes from listed viruses and genes that 'endow or enhance pathogenicity' from listed bacteria or fungi in the U.S. Federal Select Agents and Toxins List, the Australia Group Common Control Lists, and the EU list of dual-use items.
2.3	IGSC companies at minimum translate all six reading frames of each synthetic nucleic acid sequence ordered into an amino acid sequence. This sequence is screened against the protein sequences derived from the RPD database described above.
2.4	IGSC companies use automated sequence screening as a filter to identify 'best match' sequence similarity to controlled pathogens and toxins. When automated screening identifies a potential Sequence of Concern, the order and similarity data is reviewed by a human expert using common IGSC screening criteria and is either accepted, accepted with a requirement for additional Customer review, or rejected.
2.5	The IGSC recommends that pools of synthetic oligonucleotides be subject to biosecurity sequence screening as described in this Harmonized Screening Protocol.

7.3 Record Keeping & Retention

Requirement	Description
3.1	Product & Delivery Information: IGSC members retain records of every gene synthesized and delivered for a minimum of 8 years after shipping, including at least the following: (a) the synthetic DNA sequence; (b) the vector (if applicable); and (c) the recipient's identity and shipping address.
3.2	Sequence Screen Results: IGSC members retain records of every gene sequence screening result for at least 8 years.

7.4 Order Refusal and Reporting

Requirement	Description
4.1	IGSC members reserve the right to refuse to fill any order and to notify other IGSC members and/or law enforcement or other authorities upon identifying potentially problematic orders.
4.2	IGSC members have established relationships with local and national law enforcement and intelligence authorities with whom we can share information to prevent the potential misuse of synthetic nucleic acids.
4.3	IGSC members will report any request for a gene associated with the pathogenicity of an organism received from a suspicious potential Customer and/or potential Customer failing to establish their legitimacy in application of the practices set forth in section 7.1.

7.5 Regulatory Compliance

Requirement	Description
5.1	IGSC members comply with all applicable laws and regulations governing the synthesis, possession, transport, export, and import of nucleic acid synthesis and other products.
5.2	IGSC members follow the 2016 World Health Organization Recommendations concerning the distribution, handling and synthesis of variola virus DNA[29].

[29] https://iris.who.int/bitstream/handle/10665/340578/WHO-OHE-PED-2016.3-eng.pdf?sequence=1

8 Revisions to the Harmonized Screening Protocol

Version	Release Date	Description of changes
v1.0	18 November 2009	Initial publication
v2.0	19 November 2017	Changed RPD update frequency to annual
v2.1	5 May 2020	Added recommendation for oligo pool screening.
v3.0	3 September 2024	Rewrite to align to 2023 revised U.S. government Guidance, EO 14110 and the OSTP Framework and to add significantly more context.

9 Appendix A: Additional Sources of Information

9.1 Customer Screening

US Treasury Dept. Specially Designated Nationals and Blocked Persons List

- https://www.treasury.gov/resource-center/sanctions/SDN-List/Pages/default.aspx

US State Dept. List of Statutorily Debarred Parties

- http://www.pmddtc.state.gov/compliance/debar.html

US Commerce Dept. BIS Lists of Parties of Concern & Entity List

- https://www.bis.doc.gov/index.php/policy-guidance/lists-of-parties-of-concern

9.2 Sequence Screening

Australia Group Listed Source Organisms

- https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/index.html
- https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/human_animal_pathogens.html
- https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/plants.html

World Health Organization Recommendations concerning the distribution, handling and synthesis of variola virus DNA
https://iris.who.int/bitstream/handle/10665/340578/WHO-OHE-PED-2016.3-eng.pdf

EU Council Regulation (EC) No 428/2009 of 5 May 2009 Community regime for the control of exports, transfer, brokering and transit of dual-use items

- http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R0428-20161116

German Export Control for dual-use goods - HADDEX

- http://www.bafa.de/DE/Aussenwirtschaft/Ausfuhrkontrolle/Arbeitshilfen/arbeitshilfen_node.html

US OSTP Framework for Nucleic Acid Screening

- https://www.whitehouse.gov/ostp/news-updates/2024/04/29/framework-for-nucleic-acid-synthesis-screening/

US HHS Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

- https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx

US Executive Order 14110

- https://www.whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/

US Consolidated Select Agents and Toxins List

- https://www.selectagents.gov/selectagentsandtoxinslist.html

US Commerce Control List - Category 1
1C351 Human and animal pathogens
1C353 Genetic elements and genetically modified organisms
1C354 Plant pathogens

- https://www.bis.doc.gov/index.php/regulations/export-administration-regulations-ear

US CDC Current Recommendations for Synthetic Nucleic Acids

- https://www.selectagents.gov/na-guidance.html

10 Appendix B: Customer Screening Tools

Vendor	Description
AEB Compliance Screening	https://www.aeb.com/en/trade-compliance-management-software.php
Dow Jones Risk & Compliance Solutions	https://www.dowjones.com/professional/risk/
Lexis Nexis Bridger Insight	https://risk.lexisnexis.com/products/bridger-insight-xg
SAP Global Trade Services (GTS)	https://www.sap.com/products/financial-management/global-trade-management.html
Trademo Sanctions Screener	https://www.trademo.com/global-trade-compliance/sanctions-screener

11 Appendix C: Sequence Screening Tools

Vendor: Tool	Description	Cost
NCBI: BLAST	https://blast.ncbi.nlm.nih.gov/	Free
Aclid	https://www.aclid.bio/	Commercial
Battelle: ThreatSeq / UltraSEQ	ThreatSEQ: https://www.battelle.org/markets/health/chemical-and-biological-countermeasures/biosecurity-pandemic-preparedness/threatseq UltraSEQ: https://pubmed.ncbi.nlm.nih.gov/37039637/	Commercial
RTX BBN: FAST-NA Scanner	https://fastna.myshopify.com/	Commercial
IBBIS: Common Mechanism	https://github.com/ibbis-screening/common-mechanism	Free
SecureDNA	https://securedna.org/	Free
SeqScreen	https://gitlab.com/treangenlab/seqscreen	Free