International Gene Synthesis Consortium

http://www.genesynthesisconsortium.org

Harmonized Screening Protocol© v2.0

Gene Sequence & Customer Screening to Promote Biosecurity

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1. Preamble

This document outlines the standards and practices that the International Gene Synthesis Consortium (IGSC) gene synthesis members apply to prevent the misuse of synthetic genes. By uniformly screening the sequences of ordered genes and vetting gene synthesis customers, IGSC members collaborate to establish and continuously improve best practices, safeguard the many benefits of gene synthesis technology while minimizing risk, and help ensure broad compliance with HHS Guidance for Double-Stranded DNA Providers and other international standards.

First established in 2009 as a trade organization, the IGSC was incorporated as a California-based not-for-profit corporation in 2015. The ICGS members together represent approximately 80% of global commercial gene synthesis capacity.

2. Gene Sequence Screening

2.1. IGSC members screen synthetic gene orders to identify regulated pathogen sequences and other potentially dangerous sequences.

2.2. IGSC members screen the complete DNA sequence of every synthetic gene order against the DNA 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). The IGSC has assembled and curated the RPD to include data from all organisms on the Select Agent list, the Australia Group List, and other national lists of regulated pathogens. This database is shared and deployed amongst IGSC members where members frequently supplement their biosecurity systems with additional sequence data. As a baseline, IGSC companies screen against all pathogen and toxin genes as specified in the US Select Agents and Toxins List, the US Commerce Control List, and the EU list of dual-use items.

2.3. IGSC companies translate all six reading frames of each synthetic gene ordered and/or requested 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 homology screening as a filter to identify pathogen and toxin DNA sequences. When automated screening identifies a potential pathogen or toxin sequence, the order 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.

3. Customer Screening

3.1. IGSC members require identification data from all potential customers for synthetic genes, including at a minimum a shipping address, institution name, country, telephone number, and email address. We do not ship to PO Boxes.

3.2. Potential customers are screened against OFAC's SDN List, the Department of State's Debarred List, and BIS's Denied Persons, Entity, and Unverified lists, or the HADDEX list, and/or any other list required by applicable national regulations.

3.3. IGSC members require additional customer screening before accepting orders for DNA sequences from regulated pathogens or toxins. Although the U.S. Select Agent Regulations and the European Commission regulations do not restrict access to all Select Agent genes, IGSC members supply genes from regulated pathogens only to researchers in *bona fide* government laboratories, universities, non-profit research institutions, or industrial laboratories demonstrably engaged in legitimate research. Customers ordering Select Agent or Australia Group DNA fragments must provide a written description of the intended use of the synthetic product; we 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.

3.4. IGSC members use the current recommendations from the U.S. CDC and/or the Department of Agriculture and/or the European Commission (CR42) to determine which DNA sequences are Select Agents as recombinant DNA fragments. We supply genes with such sequences only if the supplier and the customer are able to comply with all Select Agent regulations applicable to that gene.

3.5. In general, IGSC members only sell DNA or fragments of regulated pathogens to *bone fide* end-users. We do not sell or ship such material to distributers or other resellers, unless those companies identify the end-user receiving the products and demonstrate their compliance with every requirement otherwise applicable to that end-user.

4. Record keeping

4.1. 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.

4.2. Sequence Screen Results: IGSC members retain records of every gene sequence screening result for at least 8 years.

5. Order Refusal & Reporting

5.1. IGSC members reserve the right to refuse to fill any order and to notify other IGSC members and/or authorities upon identifying potentially problematic orders.

5.2. IGSC members have established relationships with local and national law enforcement and intelligence authorities with whom we can share information to report and to prevent the potential misuse of synthetic genes.

5.3. 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 2.

6. Regulatory Compliance

6.1. IGSC members comply with all applicable laws and regulations governing the synthesis, possession, transport, export, and import of gene synthesis and other products.

6.2. IGSC members will not synthesize gene sequences unique to and derived from Variola virus DNA.

7. Consortium Collaborative Activities

IGSC members collaborate to:

7.1. Update annually the IGSC Regulated Pathogen Database to include all gene sequences identified as potentially hazardous by authoritative groups such as the CDC, the Australia Group, and the U.S. and European governments.

7.2. Ensure that we use the best and most effective algorithms to screen gene sequences against the Regulated Pathogen Database.

7.3. Engage with our respective national governments in support of effective oversight of gene synthesis technology and encourage international coordination.

7.4. Incorporate recommendations from the regulatory, scientific and public interest communities into our screening and other biosecurity processes.

8. Revisions to the Harmonized Screening Protocol

8.1. This document represents the current best efforts by a group of companies and other member institutions committed to the responsible use of gene synthesis technology. IGSC members welcome comments and suggestions to improve the Harmonized Screening Protocol from scientists, regulators and other interested parties. This document will be revised periodically in response to these suggestions and to changes in the scientific, technical, or regulatory environment.

9. Terminology

9.1. Gene Synthesis – The production of double-stranded, recombinant DNA fragments from oligonucleotides. Synthetic genes are typically provided in plasmid vectors or as pools of largely homogenous double-stranded DNA fragments.

9.2. Oligonucleotides – Chemically-synthesized, single-stranded DNA fragments.

9.3. Synthetic Gene – A gene or other DNA fragment produced by Gene Synthesis, typically greater than 200 base pairs in length.

10. Related Links for Sequence Screening

10.1. Australia Group Listed Source Organisms
http://www.australiagroup.net/en/human_animal_pathogens.html
http://www.australiagroup.net/en/plants.html

10.2. WHO Recommendations concerning the distribution, handling and synthesis of Variola virus DNA
http://www.who.int/entity/csr/disease/smallpox/handling-synthesis-variola-DNA.pdf

10.3. 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

10.4. German Export Control for dual-use goods - HADDEX
http://www.bafa.de/DE/Aussenwirtschaft/Ausfuhrkontrolle/Arbeitshilfen/arbeitshilfen_node.html

10.5. US HHS Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA
https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx

10.6. US Consolidated Select Agents and Toxins List
https://www.selectagents.gov/selectagentsandtoxinslist.html

10.7. 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

10.8. US CDC Current Recommendations for Synthetic Nucleic Acids
https://www.selectagents.gov/na-guidance.html

11. Related Links for Customer Screening

11.1. US Treasury Dept. Specially Designated Nationals and Blocked Persons List
https://www.treasury.gov/resource-center/sanctions/SDN-List/Pages/default.aspx

11.2. US State Dept. List of Statutorily Debarred Parties
http://www.pmddtc.state.gov/compliance/debar.html

11.3. US Commerce Dept. BIS Lists of Parties of Concern
https://www.bis.doc.gov/index.php/policy-guidance/lists-of-parties-of-concern