THE CENTRE FOR
LONG-TERM RESILIENCE

Synthetic Nucleic Acid Screening

Overcoming challenges with implementation

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CONTEXT

In October 2023, The Centre for Long-Term Resilience (CLTR) brought together stakeholders across academia, policy and the private sector to run a workshop for the UK Government's Department of Science, Innovation and Technology (DSIT) on synthetic nucleic acid screening.

This report summarises the workshop's key findings, including the technical challenges associated with screening implementation and the development of related regulations. It concludes with experts' recommendations for how the UK Government can address these challenges and bolster its capacity to prevent malicious actors from acquiring potentially harmful biological material without compromising beneficial and legitimate use.

The workshop was held under Chatham House rule; therefore, this report does not include quotes, attributions, names or affiliations of participants. Certain details from the final version of this report have been intentionally omitted from the publicly accessible version.

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EXECUTIVE SUMMARY

Synthetic nucleic acid screening aims to ensure only those with a legitimate peaceful use have access to sequences with potentially harmful applications.

IMPORTANCE OF SYNTHETIC NUCLEIC ACID SCREENING

Experts identified three reasons why screening is crucially important:

(1) Safeguarding physical material: Ordering synthetic nucleic acid is one of a limited set of options for malicious actors to obtain potentially dangerous pathogens.

(2) Protecting bioeconomy growth: Nucleic acid synthesis is one of the biotechnologies that will underpin the UK bioeconomy. Any biological incident involving synthetic nucleic acid that led to harm could undermine public trust and stifle the sector's ability to grow.

(3) Readiness for an emerging threat landscape: Rapid evolution in artificial intelligence (AI) capabilities may help malicious actors overcome existing barriers to misuse, or expand what is possible in biological weapon design.

Industry stakeholders were largely in favour of the UK implementing screening requirements, arguing mandatory screening regimes can:

Level the industry playing field. The fraction of a given order cost attributable to screening is increasing. As long as screening is voluntary, Providers[1] who choose to screen may find it difficult to remain cost-competitive with those who do not.

Justify practices to Providers' customer base. Practices associated with robust customer and sequence screening, such as requesting information about proposed end-use, are easier to justify to customers when compliance is mandated.

Increase accessibility to screening resources. Many stakeholders expressed interest in sustaining robust screening practices but cited a lack of time, money and expertise as hurdles to establishing their own screening capabilities without additional support.

Experts acknowledged several challenges associated with synthetic nucleic acid screening implementation, including:

Evaluating customer legitimacy and proposed end-use. It is difficult to determine a customer's legitimacy and verify the proposed end-use with a high degree of confidence.

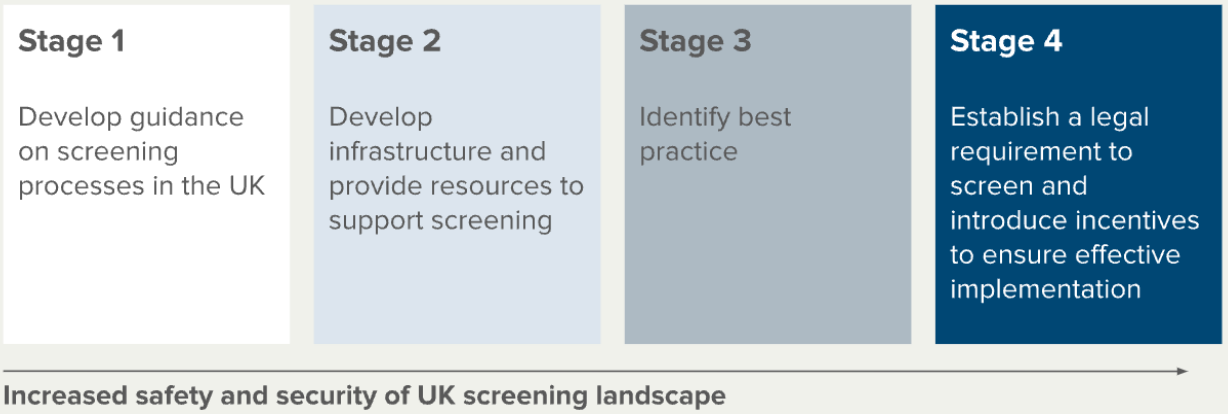
Lack of agreement on what constitutes a sequence of concern (SOC). There are various definitions of what constitutes a potentially harmful sequence, that differ in their stringency and feasibility of use.

Need for harmonisation across different countries' screening requirements. Ensuring compliance with divergent national standards or regulations could significantly burden Providers and adversely impact the market.

[1] A **provider** refers to any organisation, company, or entity that synthesises and distributes synthetic nucleic acids to **customers**, which can include individuals or organisations in academic laboratories, biotechnology firms, and commercial companies.

RECOMMENDATIONS FOR GOVERNMENT

Following expert discussion on the UK Government's role in addressing these challenges and bolstering the UK's screening landscape, we recommend the following **four-stage step-wise process.**



Adoption of these proposals **aligns with the UK's responsible innovation commitments** outlined in the 2023 Biological Security Strategy and would **enable robust customer and sequence screening without significantly disrupting the UK's existing and prospective bioeconomy**.

(1) Develop guidance on screening processes in the UK: Establishing baseline standards for current customer and sequence screening, and clarifying processes for reporting suspicious orders could enhance the security of the UK's screening landscape.

(2) Develop infrastructure and provide resources to support screening: Government provision of resources to support screening implementation, including screening databases and suspicious order reporting databases, would alleviate the burden on Providers, minimising market impact.

(3) Identify best practice: The UK Government can incentivise work to develop screening tool performance standards and test sets, and establish red teaming exercises, all of which facilitate the identification of best practices for customer and sequence screening.

(4) Establish a legal requirement to screen and introduce incentives to ensure effective implementation: With the appropriate infrastructure and evidence base for screening best practices established, the UK Government will be well-positioned to compel robust and nationwide screening, through mandating screening practices and introducing financial incentives to facilitate compliance.

1.0 DEFINING SYNTHETIC NUCLEIC ACID SCREENING

Screening synthetic nucleic acid orders can ensure that only those with a legitimate peaceful use case can acquire sequences with potentially harmful applications, referred to as 'sequences of concern' (SOCs).[2] Robust screening involves two components:

Customer screening allows Providers to know who their customers are and determine whether they have a legitimate use for SOCs.

Sequence screening allows Providers to establish what is being ordered and determine whether an order contains any SOCs.

1.1 Sequence Screening

Sequence screening typically involves the comparison of the sequences in a customer's order to a curated database of known sequences, some of which are designated as SOCs. Orders are 'flagged' if they contain SOCs or unfamiliar sequences.

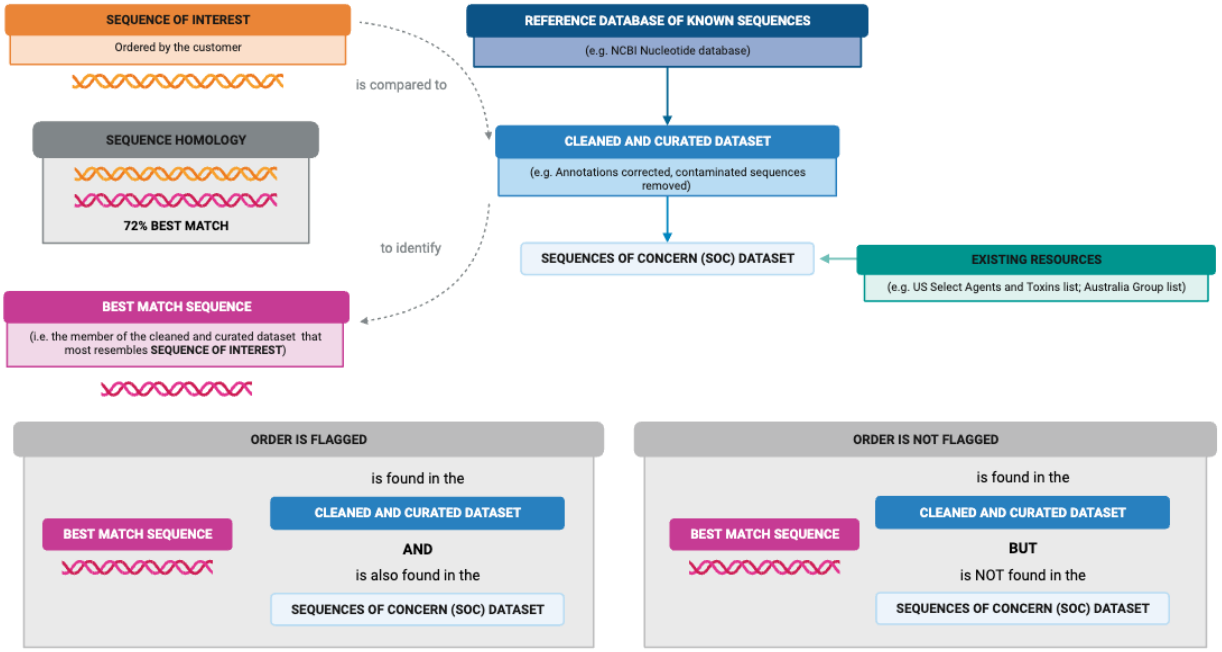


Figure 1 | Sequence screening workflow using 'best match' screening.

Screening tool providers possess their own proprietary databases, as do synthetic nucleic acid Providers who perform in-house screening. Although there is substantial overlap in the list of sequences designated as SOCs (e.g. sequences that match agents on the US Federal Select Agent Program, or the Australia Group List), there can also be significant variation, impacting the overall sensitivity and efficacy of a given tool. As a result, one tool may recommend fulfilling an order that another would refuse due to the hazardous nature of a given sequence.

[2] Specifically, the 2023 US HHS Screening Guidance defines SOCs as "A nucleotide sequence that is a Best Match to a sequence of federally regulated agents... except when the sequence is also found in an unregulated organism or toxin." The Guidance suggests this definition should be expanded to include "sequences known to contribute to pathogenicity or toxicity, even when not derived from or encoding regulated biological agents", as soon as is practical. For more, see US Department of Health and Human Services (HHS) Administration for Strategic Preparedness and Response (ASPR). 2023. "Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids."

1.2 Customer Screening

Customer screening is often conducted in two stages: **verifying customer identity** and **verifying customer legitimacy**.

(1) **Verifying customer identity**: Authenticating that someone is who they say they are and not impersonating others. This could involve reviewing the customer's company name, address and online presence (e.g. trade directory listing[3]). Some companies also evaluate basic legitimacy at this stage (e.g. refusing shipments to residential addresses).

(2) **Verifying customer legitimacy:** Authenticating that customers ordering SOCs are legitimate members of the scientific community with a legitimate, peaceful proposed end-use. Recommended checks include reviewing information such as users' publication history or research identifiers (e.g. ORCID), the proposed end-use of the order, institutional approvals and registration with relevant[4] authorities.

Two-stage customer screening is efficient because it ensures that only flagged orders are subjected to the more burdensome component of customer screening: the process of verifying customers' legitimacy.

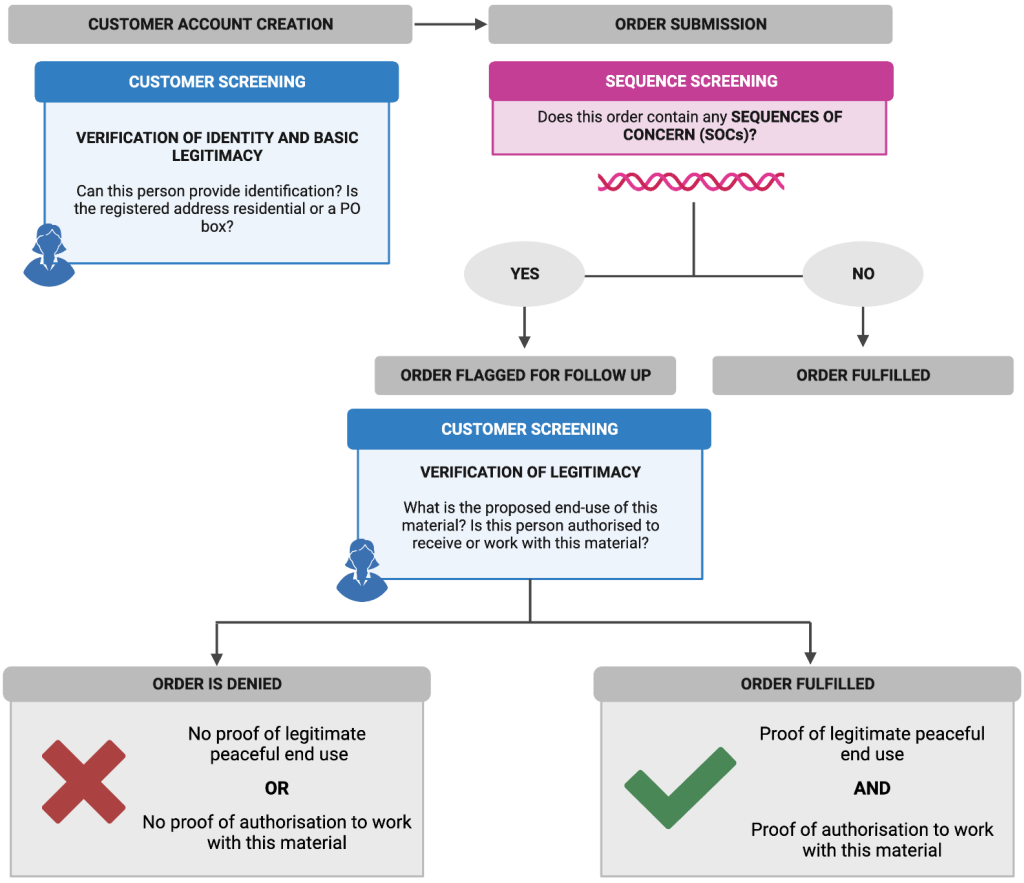


Figure 2 | An example synthetic nucleic acid procurement workflow with customer and sequence screening integrated

[3] The UK Government Digital Service has extensive guidance on measures to prove and verify someone's identity. See UK Government Digital Service's Good Practice Guide (GPG) 45.
[4] In the United States, for example, this would include registration with the Federal Select Agent Program.

Experts highlighted three reasons why the implementation of synthetic nucleic acid screening is valuable and critically important, including:

- **Safeguarding physical material.** There are multiple steps in the biological weapon development process at which Government or industry can intervene to mitigate risk.[5] Intervening at the point of material acquisition is attractive, as this serves as one of only a few avenues to obtain potentially dangerous pathogens (with others being, for example, environmental collection)—a step which the majority of malicious actors are likely to need to proceed.

- **Growth of the bioeconomy.** Nucleic acid synthesis is part of a wider array of biotechnologies that will underpin the UK bioeconomy. A biological incident involving synthetic nucleic acid that led to harm (even one of comparatively small scale) could undermine public trust. A lack of public trust could seriously stifle the biotechnology sector's ability to grow, making the economic case for screening strong.

- **Shifting threat landscape.** Rapid evolution in artificial intelligence (AI) capabilities and the intersection of AI with the life sciences may have significant implications for the biological threat landscape. Specifically, AI-enabled tools could help malicious actors overcome existing barriers to misuse, or expand what is possible with regards to biological weapon design (e.g. enable countermeasure evasion).[6]

[5] For example, an actor needs to design and acquire an agent, as well as a delivery system. For further discussion of these steps, see Sophie Rose and Cassidy Nelson, 2023. "Understanding AI-Facilitated Biological Weapon Development." The Centre for Long-Term Resilience.
[6] Sophie Rose and Cassidy Nelson, 2023. "Understanding AI-Facilitated Biological Weapon Development." The Centre for Long-Term Resilience.

2.0 CURRENT SCREENING LANDSCAPE

2.1 Major initiative

The most significant public initiative by a national government on synthetic nucleic acid screening is the recent ***US Executive Order* on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence,** which requires US Government agencies to:

- Develop standards for security and access controls for managing SOC databases.
- Restrict those in receipt of life sciences funding from federal agencies to procure nucleic acid only through Providers that adhere to screening standards.
- 'Stress test' screening systems and report annually on their findings to US national security officials and other relevant agencies.

2.2 Existing guidance

There are also two publicly available sets of voluntary synthetic nucleic acid screening guidance:

(1) **International Gene Synthesis Consortium (IGSC):** The IGSC is a trade industry organisation formed by several large DNA synthesis companies for the purposes of harmonising their approach to screening.[7] The IGSC Harmonized Screening Protocol outlines the screening standards and practices expected of IGSC members, and was last updated in November 2017.

(2) **US Department of Health and Human Services (HHS):** The US HHS' Administration for Strategic Preparedness and Response (ASPR) released updated screening guidance, Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids, in October 2023. It was accompanied by a Companion Guide to assist with the implementation of the guidance, which includes case studies to assist companies with verifying customer legitimacy.

Experts widely appreciated the revisions to the HHS Guidance, particularly noting the following additions:

- **Establishing a baseline for best practices for all entities involved in screening, with a view to incrementally phase-in improvements.** For example, the Guidance suggested the length for screening be decreased from 200 to 50 nucleotides within three years of its publication.
- **Comprehensive actor definitions.** The Guidance supplies detailed definitions for distinguishing between Providers, customers, principal users, and end users and clarifying their relationships with third-party vendors.
- **Expansion of SOC definition.** The scope now includes *all* sequences and sequence fragments that could contribute to pathogenicity or toxicity, whether from regulated or unregulated agents, including completely novel sequences.

[7] See James Diggans and Emily Leproust, 2019. "Next Steps for Access to Safe, Secure DNA Synthesis." Frontiers in Bioengineering and Biotechnology, Volume 7.

Experts' primary criticisms of the HHS Guidance were:

- **Lack of a definition of legitimate use.** Industry stakeholders highlighted the challenge in discerning the legitimacy of a customer's use and emphasised the ease with which a malicious actor could provide the detail needed to masquerade legitimacy. Some noted the value of a clear definition for customer clarity.
- **Voluntary in nature.** Compliance with the Guidance is still voluntary, which all experts strongly regarded as insufficient.
- **Insufficient for future threat landscape.** Experts noted that even robust implementation of the current gold-standard screening measures would be inadequate in the face of sophisticated attacks and future threats.

The International Organization for Standardization (ISO) is also in the final stages of reviewing proposed requirements "for the production and quality control of synthesised double-stranded DNA" (ISO/FDIS 20688-2), unpublished as of October 2023.[8]

3.0 INDUSTRY PERSPECTIVE

A variety of industry stakeholders, including those from companies with large market caps and smaller, more specialised companies, were largely **in favour of the UK implementing mandatory screening requirements.**

Industry representatives specifically identified mandatory screening regimes as valuable for several reasons, including:

- **Mandatory screening levels the industry playing field:** Given the falling cost of synthesis per nucleotide and increasing labour costs[9], the fraction of a given order market price attributable to screening is increasing. This makes it difficult for companies—especially smaller companies—who do screen to remain cost-competitive with those who do not. If all companies were required to screen, no company would be at a cost disadvantage.
- **Justification to customer base:** Companies aim to make their customers happy and retain their business. However, voluntary screening guidance, such as those from the IGSC and HHS, ask companies to scrutinise customers and their orders. Multiple industry stakeholders identified this misalignment as a key 'stumbling block.' This is reinforced by the aforementioned red teaming results, where customer service representatives allowed orders to be delivered to residential addresses.
    - Providers identified concerns such as being worried about introducing friction to customers, due to the need to request extra information and worries about privacy and IP.

[8] See 2023, "Nucleic Acid Synthesis - Part 2: Requirements for the Production and Quality Control of Synthesized Gene Fragments, Genes, and Genomes (ISO/FDIS 20688-2)" International Standards Organization for updates relating to these standards.
[9] A 2015 report found that approximately 5% of synthetic nucleic acid orders are flagged for review. Flagged orders can take several hours (and often require bioinformatics expertise) to resolve (Sarah R Carter and Robert M Friedman, 2015. "DNA SYNTHESIS AND BIOSECURITY: Lessons Learned and Options for the Future." J. Craig Venter Institute).

Many noted screening practices are hard to justify to customers when compliance is voluntary, not mandated.

- **Increased accessibility to screening resources:** Industry stakeholders broadly expressed their desire to integrate biosecurity practices and conduct their synthesis responsibly. However, many expressed they felt they lacked the time, money or expertise to build and maintain robust, up-to-date in-house screening capabilities themselves (e.g. the development of a screening tool, hiring and training staff for resolving flagged orders, deciding on a screening methodology).
- **Confers legitimacy:** One industry stakeholder noted that early-stage companies have a desire to be seen as legitimate and professional, and hypothesised that small additional costs to them as a result of screening may be worth it if it builds trust with customers.
- **Minimisation of reputational risk:** Companies who can verify that they were compliant with government regulations or industry best practice may be able to minimise reputational risk in the case of an incident involving one of their products.
- **Employee health and safety:** One industry stakeholder noted that screening positively contributed to the broader health and safety of laboratory employees, and welcomed more specific guidance on screening best practice.
    - **Personal liability:** One industry stakeholder noted that Directors of UK companies have a personal responsibility to ensure a safe and healthy work environment, and suggested that verified compliance with a mandatory screening regime could, in theory, minimise Directors' exposure to that personal liability.

Industry stakeholders did not express concern about the impact screening regulation may have on the ability to attract investment or hinder Providers from operating in the UK.

Some justified their position by noting that the Providers with the largest market shares globally are able to maintain their market share in spite of screening. Others noted that government interventions such as regulatory sandboxes are viewed as an attractive solution to barrier-to-market-entry issues in other highly regulated sectors, such as the financial services industry.[10]

However, these stakeholders represent only a sample of UK-based companies. We believe further solicitation of industry perspectives, particularly early-stage companies or those who are not currently IGSC members, is needed. Understanding the most significant barriers to Provider screening can better inform the structure and incentives of future regulatory regimes.

[10] The UK's Financial Conduct Authority allows financial services firms to apply for regulatory sandboxes. In late October 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) also announced AI-Airlock, a new regulatory sandbox for AI developers working on AI-enabled healthcare software or medical devices.

4.0 KEY CHALLENGES IDENTIFIED

Evaluating customer legitimacy. The majority of experts identified difficulties with understanding "who should be allowed to order what?" as a significant hurdle for Providers, which they cited as arising from the lack of guidance on what constitutes a 'legitimate customer'. This is particularly burdensome given that approximately 5% of flagged orders require this additional component of customer screening to resolve. Whilst experts acknowledged that the recently updated HHS Guidance offered a good starting point, there was broad agreement that additional clarification would be valuable (See Recommendation 1A).

Lack of agreement on what constitutes an SOC. Experts broadly agreed that clarification from the Government on what constitutes an SOC, given the variety of definitions that could be used and, therefore, differences in what should be provided only to select customers (See Recommendation 1B). For example:

- **Regulated pathogen lists:** A minimal approach to defining SOCs could draw solely from existing lists of regulated pathogens, such as the UK's Schedule 5 Pathogens list, the United States' Select Agent and Toxins list and the Australia Group list. The two significant limitations of this approach identified by experts were: (i) the inherent inadequacy of relying *solely* on taxonomic lists[11] and (ii) concerns about the speed with which these lists can be updated following the identification of novel threats.
- **Function-based:** Function-based screening aims to identify components of a sequence that have been identified as presenting a dangerous function[12] (e.g. it contributes to the suppression of host immune signalling), in addition to taxonomies identified on regulated pathogen lists. The US HHS has specified that they intend to expand the definition of SOCs to include "sequences known to contribute to pathogenicity or toxicity" as soon as is practical.[13]

Need for harmonisation across different countries' screening requirements. The primary concern identified by industry stakeholders was the additional burden Providers may face in needing to understand how to comply with different regulatory requirements across different jurisdictions. Defaulting to complying with the 'strictest' regulations may pose a challenge, as refusing to fulfil an order without a legal obligation to do so in a Provider's jurisdiction may be difficult to justify to customers, and thus disadvantage Providers. (See Recommendation 4C)

For a more comprehensive overview of existing challenges with the implementation of synthetic nucleic acid screening, see the Appendix.

[11] For further discussion, see Piers Millett et al., 2023. "Beyond Biosecurity by Taxonomic Lists: Lessons, Challenges, and Opportunities." Health Security, online ahead of print.
[12] For an example of a function-based approach to identifying mechanisms of pathogenesis, see Gene D Godbold et al., 2022. "Categorizing Sequences of Concern by Function To Better Assess Mechanisms of Microbial Pathogenesis." Infection and Immunity, Volume 90, Number 5.
[13] US Department of Health and Human Services (HHS) Administration for Strategic Preparedness and Response (ASPR), 2023. "Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids."

5.0 RECOMMENDATIONS FOR GOVERNMENT

The following recommendations represent a **step-wise process** for achieving robust customer and sequence screening of synthetic nucleic acid orders, whilst **minimising adverse effects on the UK's current and future bioeconomy**.

The process consists of four stages:

STAGE 1 | Develop guidance on screening processes in the UK

Establishing guidance for current customer and sequence screening ensures that Providers who voluntarily screen are implementing high-quality screening. Guidance can serve as an interim mechanism for enhancing the security of the UK's broader screening landscape whilst understanding of best practices evolve and an array of regulatory approaches are explored.

STAGE 2 | Develop infrastructure and provide resources to support screening

Government provision of resources to support screening implementation can alleviate the burden on Providers, increasing the likelihood of voluntary compliance and minimising the adverse impact of future regulation on the market.

STAGE 3 | Identify best practice

Whilst identifying a current baseline approach to screening is a useful first step, the UK Government is also in a position to catalyse the implementation of more robust practices by incentivising research to identify gold standard practices for customer and sequence screening.

STAGE 4 | Establish a legal requirement to screen and introduce incentives to ensure effective implementation

As the infrastructure to support Providers and the evidence base for screening best practices grow, the UK Government will be well-positioned to compel screening, through mandating screening and introducing financial incentives to facilitate compliance.

The pursuit of these stages can be viewed as contributing to the **fulfilment of the UK's 'Responsible Innovation' commitments outlined in the 2023 Biological Security Strategy**. The subcomponents of each stage are explored in more detail below.

STAGE 1 | Develop guidance on screening processes in the UK

Producing guidance on current best practice for customer and sequence screening supports Providers who voluntarily screen and enables them to implement high-quality screening. Bolstering the existing practices of UK companies now can also serve as the groundwork for a future transition into a regulatory regime, as Providers will have had an opportunity to implement and enhance screening components.

Crucially, the development of this guidance does not depend on the existence of regulations mandating screening. The guidance can serve as a stop-gap measure to enhance the security of the UK landscape whilst decision-making on regulatory options is ongoing.

This guidance should include current best practices for customer and sequence screening, as well as the process Providers should follow to report potentially suspicious orders.

(1A) Task DSIT with producing public-facing guidance on current best practices for customer screening.

Customer screening in this context involves verifying a customer's identity and, where they are ordering SOCs, their legitimacy.

'Know Your Customer' (KYC) responsibilities are already common across many sectors. In the UK, KYC checks are mandatory for banks and financial institutions, cryptocurrency exchanges, real estate services, iGaming, e-commerce, and financial services firms.[14]

There is existing UK Government guidance on best practices for verifying customer identity[15]—which serve as a starting point for clarifying best practices for verifying customer legitimacy in the context of synthetic nucleic acid orders. This could draw on the recommendations relating to customer screening in the updated HHS Guidance, as well as the scenarios outlined in the Companion Guide—though, as previously noted, it would be valuable to expand beyond what is listed in these publications.

Developing guidance on KYC practices in the synthetic nucleic acid landscape may also serve as a test pilot for the integration of security practices in the life sciences sector more broadly, which may be necessary as other capabilities advance (e.g. AI-enabled biological tools, cloud laboratories).

(1B) Task DSIT with producing public-facing guidance on current best practices for sequence screening

Experts expressed that it would be helpful for clarification on what the UK Government sees as best practices when it comes to sequence screening, including specifying what is considered an SOC and suggesting methodologies for screening. In the absence of government-issued guidance, Providers make their own judgement calls, leading to variation in what material customers are able to obtain.

[14] For example, 2017. "The Money Laundering, Terrorist Financing and Transfer of Funds (Information on the Payer) Regulations 2017." UK Statutory Instruments, Number 692.
[15] 2023. "Guidance: How to prove and verify someone's identity." Cabinet Office and Government Digital Service.

Experts acknowledged that there remain open questions about what should be classified as an SOC. They suggested starting with a broadly agreed upon 'fundamental' set of SOCs and expanding the SOC list over time as additional decisions were made. These decisions could be informed by the UK's Advisory Committee on Dangerous Pathogens (ACDP), Health and Safety Executive (HSE), National Protective Security Authority (NPSA), Department for Business and Trade Export Controls Joint Unit (ECJU) and the UK's Biosecurity Leadership Council, as relevant.

This screening guidance could draw on the expert advice elicited in this workshop and the updated US HHS Guidance, the scope of which was expanded to include recommendations on:

- Broadening the definition of SOCs to include sequences with known pathogenic or toxic functions, when it becomes practical to do so
- Best practices for all parties involved in synthesis, use and transfer (including Providers and customers, as well as third-party vendors)
- Screening orders at a smaller length (i.e. 50 nucleotides)
- Screening all types of synthetic nucleic acids (i.e. single- and double-stranded DNA and RNA)

(1C) Task DSIT with producing public-facing guidance on the process Providers should follow to alert UK Government in the case of suspicious orders

Experts agreed it would be valuable for governments to develop guidance on the process Providers should follow if they receive what they believe to be a suspicious order. This process is necessary for ensuring that the Government can be rapidly notified of, and investigate, potential malicious activity. This guidance should also clarify who Providers should contact if they are uncertain as to whether a flagged sequence constitutes an SOC.

This could be modelled after the UK Government Home Office guidance on precursor chemical reporting, or the existing CSAR system to NCA for suspicious chemical orders. The United States also has analogous public-facing guidance on this process.[16]

As part of the development of this guidance, experts encouraged the Government to consider:

- **Resourcing the teams designated to provide advice on 'grey area' orders:** Several experts noted that mechanisms for resolving uncertainties as to whether a sequence constitutes an SOC will be difficult to design and uphold in practice. This is due to the need for the designated entity (e.g. an expert working group or export control team) to be able to provide quick turnaround advice, given the rapid turnaround time standard in industry (orders are typically fulfilled within 4 - 10 days). These teams will also need the time and resources to be able to absorb additional requests for clarification in the face of regulatory adoption.
- **Reporting thresholds:** Some experts noted that the existing threshold of reporting suspicious nucleic acid orders to the United States FBI is too high. One expert noted that a system analogous to Suspicious Activity Reports (SARs) obligations in the financial sector may be more appropriate.[17] The role of SARs is to bring suspicions to the attention of the NCA so they can be further investigated, which allows for a greater degree of government oversight and could enable patterns of illicit activity to be identified.

[16] See Page 2 of the US HHS Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids
[17] In the UK, it is explicitly stated that the threshold for suspicion needed to initiate reporting is low. See UK Financial Intelligence Unit (UKFIU), 2021. "Introduction to Suspicious Activity Reports (SARs)." National Crime Agency.

STAGE 2 | Develop infrastructure and provide resources that support screening implementation

Government provision of resources to support screening implementation can enhance the security of the screening landscape whilst alleviating the burden on Providers, which:

- increases the likelihood of voluntary compliance with screening guidelines; and
- minimises the impact of future regulation on the market

Components of this infrastructure offer a mechanism for greater government oversight, which can also inform the design—and assist in the implementation—of future regulatory regimes.

(2A) Establish an SOC database to be housed within the relevant UK Government department or agency.

Experts and industry stakeholders strongly encouraged the UK Government to develop an SOC database. Sequence screening requires access to an annotated, curated dataset of known sequences that includes those classified as SOCs. This dataset impacts tools' overall sensitivity and efficacy: variation means different tools can make inconsistent recommendations about whether orders contain an SOC.

Experts acknowledged the creation of this database could pose significant national security risks, which has historically prevented the pursuit of its creation by US and UK Governments. However, the majority noted that such a database is ultimately necessary for informing a robust synthetic nucleic acid screening regime and that failing to do so only undermines our already limited defensive capabilities.

Furthermore, the United States' recent *Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence*, requires their National Institute of Standards and Technology (NIST) to develop "best practices, including security and access controls, for managing sequence-of-concern databases" in the next 180 days to support screening, indicating that they are considering establishing their own SOC database.

(2B) Establish a database for industry to facilitate sharing of information that could prevent malicious circumvention of screening practices.

Venue shopping is a strategy for obtaining hazardous sequences by placing smaller, 'broken-up' orders split across multiple providers or from a single provider over a prolonged time period.[18] Experts agreed that mechanisms allowing Providers to share information from orders containing an SOC would be valuable for mitigating the risk of bad actors circumventing screening in this way.

Experts and industry stakeholders distinguished the burden of proof or threshold that needed to be met for notifying government agencies (e.g. when reporting an attempt to order an SOC order

[18] For a more detailed discussion, see Engineering Biology Research Consortium (EBRC) Security Working Group, 2022. "Security Screening in Synthetic DNA Synthesis." EBRC.

or a query about whether a sequence constituted an SOC) and notifying competitors about potentially suspicious orders or attempts to order SOCs.

They noted that a database for industry use should involve submitting sequence information to inform others of new SOC identified and to shape a database of SOC order attempts. Industry stakeholders repeatedly expressed that it was preferable that this did not include customer information due to concerns regarding violations of privacy or intellectual property (as their orders may contain proprietary information). This was cited as part of the reason an analogous database established by the IGSC is severely underutilised (the other reason being the burdensome nature of filling out the long form).

(2C) Establish a regulatory sandbox for synthetic nucleic acid screening implementation via DSIT's Engineering Biology Regulators Network.

A regulatory sandbox for synthetic nucleic acid screening requirements provides the UK Government an opportunity to ensure any regulatory decisions balance innovation and bioeconomy growth considerations with the UK's responsible innovation commitments under the 2023 Biological Security Strategy.

The sandbox could be beneficial in six key ways:

(1) Signals openness to innovation and sector growth
(2) Allows for monitoring of the regulatory effect on the market
(3) Facilitates market entry of new companies
(4) Serves as an evidence base for future regulation
(5) Builds regulatory capacity in the UK Government
(6) Identifies remaining regulatory gaps that can be addressed

Other UK Government agencies have established similar mechanisms, including the Medical and Healthcare products Regulatory Agency (MHRA)'s recently announced AI Airlock for AI developers working on AI-enabled healthcare software or medical devices, and the Financial Conduct Authority (FCA)'s regulatory sandbox for financial services firms.

The UK Regulatory Horizons Council has previously recommended regulatory sandboxes be established for analogous technologies as a mechanism for assessing the impact of different regulatory approaches on smaller companies.[19]

[19] UK Regulatory Horizons Council. (2022). "Regulatory Horizons Council Report on Genetic Technologies."

STAGE 3 | Identify best practice

Multiple experts expressed that further work on identifying best practice for both customer and sequence screening would be both necessary and welcome. The UK Government has the opportunity to incentivise this work to inform the evidence base for best practice, and build its capacity for verifying compliance with best practice.

(3A) Incentivise the development of nucleic acid screening tool performance standards and the test sets needed to evaluate these.

Experts identified that the development of a test set to quantitatively evaluate synthetic nucleic acid screening tool performance would be valuable for five distinct reasons:

(1) Required by all screening systems. All screening systems require a test set to evaluate whether their tool accurately flags SOCs and does not flag known, benign sequences.

(2) Avoids duplicative effort. Curating a bespoke test set of sequences with consensus-based designations (e.g. flag, no flag, optional) is both time- and resource-intensive. This is exacerbated by data quality issues such as poorly annotated sequence databases. A common test set would alleviate the burden on Providers and tool developers. It would particularly alleviate barriers to small companies' market entry and participation, which has positive implications for bioeconomy growth.

(3) Confers legitimacy to order fulfilment decisions. Shared definitions for what sequences should be flagged make it easier to defend decision-making to customers and governments (i.e. "other tools make the same decisions.")

(4) Offers a way of measuring efficacy and comparing tools. Allows Providers and tool developers to evaluate their tools' performance. Allows government stakeholders to measure and compare the screening efficacy of different tools.

(5) Offers a way to verify compliance. Performance on test sets could later serve as a way of verifying compliance with screening tool performance standards or screening requirements.

There are multiple open questions that would need to be addressed in the process of standards development, including:

- **What is an acceptable process for resolving flagged sequences that are 'undetermined'?** (i.e. sequences for which there is uncertainty around the role of a gene)
- **Does the UK Government have the capacity to support a significant increase in export control queries or the capability to assess novel materials?**

Resolving these will require coordination between DSIT and the UK Department for Business and Trade (DBT)'s Export Control Joint Unit (ECJU). Engaging with other relevant regulators (such as the Australia Group) would also be valuable.

Following the identification of screening tool performance standards, the UK Government should conduct an assessment to understand whether existing tools are fit-for-purpose or whether the landscape would benefit from the injection of a financial incentive to support the development or integration of free-to-use screening tools.

(3B) Task the National Protective Security Authority with establishing biannual red teaming exercises to audit UK-based nucleic acid Providers.

Red teaming exercises are an effective way to highlight vulnerabilities in systems and are commonly undertaken in the cybersecurity community to identify security flaws. The extensive vulnerabilities highlighted by historical red teaming of Providers' customer and sequence screening practices emphasise the need for regular auditing of screening capabilities.

Regular red teaming exercises would offer the UK Government the ability to:

- **Monitor and accurately assess the threat landscape.** Results of red teaming can inform likelihood estimates of adversaries acquiring or being in possession of harmful material.
- **Identify and responsibly disclose vulnerabilities.** Responsible disclosure[20] of vulnerabilities to Providers allows them to develop mitigation or fixes, minimising the likelihood the vulnerability is exploited by malicious actors. Experts noted that vulnerability disclosure to IGSC would also be valuable, in so far as this informs best practice, but disagreed on whether additional public "naming-and-shaming" of affected companies would be useful.
- **Iterate and improve upon best practices for screening.** Knowledge of vulnerabilities can inform the refinement of the UK's own guidelines or standards for customer and sequence screening, ensuring they remain resilient and up-to-date. This could benefit all Providers by updating practices across the board on discovering a vulnerability.
- **Verify compliance.** If a mandatory screening regime is pursued, red teaming offers an opportunity to assess compliance with screening requirements.

Some experts noted that independent, non-governmental bodies could also perform red-teaming, the results of which—in the absence of mandatory screening requirements— could inform accreditation programs. Providing an avenue for accreditation or similar (i.e. certification or licensing indicating compliance with guidance or standards) also offers an opportunity to both showcase Provider legitimacy and reassure public safety.

[20] 'Responsible disclosure' best practice involves first disclosing vulnerabilities to affected companies so that they can patch or fix vulnerabilities ahead of public disclosure, minimising the likelihood the vulnerability is exploited.

STAGE 4 | Establish a legal requirement to screen and introduce incentives to ensure effective implementation

Experts unambiguously pointed to mandatory screening as the recommended ultimate objective of any government's approach to nucleic acid screening.

The preceding three stages serve as a pragmatic way to incrementally move toward, and inform, legal screening requirements in line with evidence-based best practice.

The UK Government can complement this legal screening requirement with other incentives that make screening more financially viable for Providers. This could include linking domestic life sciences funding to procurement of screened nucleic acids or harmonising the UK's national screening regulations with those of the United States and other international partners.

(4A) Establish a legal requirement for Providers of synthetic nucleic acids to screen.

Experts made it clear that **implementing regulation that mandates customer and sequence screening of nucleic acid orders was the best option for preventing misuse** and felt strongly that this could be achieved without adversely impacting the UK's growing bioeconomy.

They saw this as preferable to the status quo, where:

- Responsible Providers are competitively disadvantaged by screening;
- Providers implement variable and inconsistent screening practices; and
- The broader market is vulnerable to requests made by malicious actors, allowing access to dangerous materials with potentially significant national security implications

A legal synthetic nucleic acid screening requirement could build upon the guidance established in **Stage 1**, supported by the infrastructure and resources developed in **Stage 2** and updated to reflect evidence-based best practice identified in **Stage 3**.

The UK Government could consider exploring how existing legislation, in particular, the Anti-Terrorism, Crime and Security Act 2001 (ATCSA) and the Biological Weapons Act 1974, may facilitate the introduction of screening requirements.

However, the implementation of synthetic nucleic acid screening requirements involves trade-offs that the Government should consider:

- Legal requirements may introduce longer delays when standards need updating, compared to amending voluntary guidelines;
- The perceived or actual effect of these regulations on the wider international landscape;
- The chance of other regions adopting screening under voluntary guidance (for instance, NIH Recombinant DNA Guidance) as opposed to a legal obligation; and
- The black market implications if Providers limit their clientele to simplify compliance.

Careful regulatory assessment and planning which addresses these factors will be crucial to ensure the effectiveness of a screening mandate while minimising adverse effects.

(4B) Require UK Research and Innovation (UKRI) and other government funding bodies to establish a funding requirement that all synthetic nucleic acid is purchased from Providers who adhere to UK screening requirements, or equivalent.

Government funding supports a significant portion of domestic research and development (R&D) activities involving synthetic nucleic acids carried out in many countries.[21] Requiring R&D efforts to source nucleic acid from companies that screen confers two major benefits:

- **Incentivises Providers participation in screening** so they are able to capture a significant portion of the synthetic nucleic acid market
- **Avoids circumvention of UK domestic screening requirements** by government-funded users, who could otherwise place an order from an overseas company located in a jurisdiction that does not require screening

An equivalent requirement has just been established in the United States via the *Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence*, and is due to come into effect within 180 days of identifying screening standards. This will cover procurement by actors in federally-funded academia and research, but will not impact procurement by industry stakeholders, such as pharmaceutical companies, who are privately funded.

(4C) Coordinate with the United States and other international partners to facilitate the harmonisation of national screening approaches.

As noted elsewhere in this briefing, a primary concern expressed by Providers relates to the burden of complying with different jurisdictional requirements and standards for screening.

Divergent national standards and regulations have historically negatively impacted the market via reduced profitability[22] in other industries, such as automobile manufacturing (due to the need to comply with differences in allowable emissions across the EU, United States and Japan). This ought to be avoided.

As no country currently requires screening, leading on national implementation and global coordination could give the UK an outsized opportunity to shape the global screening approach and position them as a global leader in responsible innovation, reflecting commitments laid out in the UK's 2023 Biological Security Strategy.

This effort should initially prioritise bilateral coordination with the United States, given their progress on screening via the updated HHS Screening Guidance and White House Executive Order on AI. This would honour the commitments made in The Atlantic Declaration on demonstrating US-UK leadership and cooperation on issues related to synthetic biology and security.

The G7 commitment to an AI Code of Conduct and set of International Guiding Principles may also serve as a forum through which the UK can advocate for their preferred approach to screening among a core group of international partners, given the potential for screening to serve as an intervention that reduces the risks from AI-enabled biological tools.

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[21]2023. "Synthetic Biology Market – Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2023-2032." Precedence Research.
[22] Center for Automotive Research, 2016. "Potential Cost Savings and Additional Benefits of Convergence of Safety Regulations between the United States and the European Union."

APPENDIX - Challenges with implementing synthetic nucleic acid screening

A.1 CUSTOMER SCREENING

Verifying scientific legitimacy of customers: Providers cite that understanding "who should be allowed to order what?" is a significant hurdle for robust screening implementation. This arises from a lack of formal guidance on what constitutes a 'legitimate customer.' This is particularly burdensome given that approximately 5% of flagged orders require this additional component of customer screening to resolve (Carter and Friedman 2015). Whilst experts acknowledged that the 2023 US HHS Screening Framework Guidance and its Companion Guide serve as a good starting point, there was broad agreement that additional clarification would be valuable (US Department of Health and Human Services 2023a; US Department of Health and Human Services 2023b).

Verifying proposed end-use: Despite the verification of a customer's proposed end-use of a sequence being recommended by both the IGSC and US HHS, there are no guidelines or formal definitions for what constitutes a legitimate end-use (International Gene Synthesis Consortium 2017; US Department of Health and Human Services 2023a). Verification may also require substantial subject matter expertise to verify, which can be financially burdensome for Providers.

Verifying international customers: Industry stakeholders have flagged that they experience difficulties in verifying international customer documentation (e.g. identity documents, institutional biosafety forms), which come in a variety of formats and languages.

Identifying the true 'end-user': Common practices among academic and industry researchers make it challenging to ensure that synthetic nucleic acids are only used by approved end users. Research laboratories and academic groups often have a single purchasing account with multiple users and commonly share genetic material informally, particularly within their own institutions (Kahl et al. 2018).

Accounting for third-party purchasing: Third-party vendors who order sequences on behalf of an end user can complicate customer screening approaches. They may be hesitant to disclose their client's identity or provide information about orders to other Providers for commercial reasons (Engineering Biology Research Consortium (EBRC) 2022). The 2023 US HHS Screening Framework Guidance assigns the same responsibilities to third-party vendors as it does to Providers of synthetic nucleic acids (US Department of Health and Human Services 2023a).

Functionality and scalability of the screening system in a crisis: During a crisis, such as the 2014 Ebola outbreak or the COVID-19 pandemic, there is often a significant increase in the number of scientists interested in working with an agent to develop medical countermeasures and diagnostic tests. It may be important for screening mechanisms to be able to rapidly verify scientists during such events so as not to undermine beneficial research efforts.

A.2 SEQUENCE SCREENING

Defining SOCs: There is a lack of consensus around what constitutes an SOC, with possible scopes ranging from regulated pathogen lists (International Gene Synthesis Consortium 2017), to all 'sequences known to contribute to pathogenicity or toxicity' (US Department of Health and Human Services 2023a). Experts also disagree about the level of threat that screening should be interested in capturing. In the absence of a formal definition and ongoing advice, Providers set their own (widely varying) definitions, leading to differential access to potentially harmful sequences.

Designing screening methods robust to technological advances: Existing sequence screening protocols typically rely on measuring sequence similarity to the genomes of organisms on control lists, known as 'Best Match' screening (US Department of Health and Human Services 2023a). However, control lists are typically taxonomic in nature, meaning they do not fully capture the underlying biological functions of concern or newly-discovered threats or the novel harmful agents that may arise as a result of AI-enabled biological tools (Millett et al. 2023; Rose and Nelson 2023; Sandbrink 2023).

Lack of standards for assessing screening tool performance: Quantitative screening performance metrics and methods are needed to verify the capabilities of different screening tools, including their (i) baseline rates of false positives/negatives against test datasets and (ii) ability to detect modified or deliberately obfuscated sequences (Diggans and Leproust 2019).

Handling undetermined sequences: In addition to known benign and harmful sequences, there are sequences where screening tools disagree on whether to flag, or require further clarification before they can make a decision. In the absence of a clear SOC definition or database, it can be difficult for Providers to know where to direct such queries. The body responsible for this clarification must also be able to provide that advice quickly, given the typical industry turnaround time for fulfilling orders.

Disclosing information about flagged orders: The outcomes of sequence screening may need to be communicated to a range of stakeholders (e.g. Providers, Customers and legal authorities). It will be important to determine what information should be disclosed about SOCs identified in a flagged order, as providing precise details about the screening procedure and the flagged sequences could allow bad actors to identify SOCs or reverse-engineer and subvert screening.

Preventing 'venue shopping': There is a need to prevent the scenarios in which (i) a bad actor submits dangerous orders in an attempt to find a company that will fulfil the order, or where (ii) multiple sub-threshold orders are made to multiple companies, or a single company over a prolonged time period, with the customer intent on doing final SOC assembly themselves (Diggans and Leproust 2019).

Need for securitisation of dual-use information: Any database of hazardous sequences contributing to pathogenicity and toxicity in humans, animals and plants (i.e. SOCs) will require securitisation, including robust cybersecurity practices, to prevent unauthorised access or

exfiltration. Additionally, though a centralised SOC database has its advantages, companies may object to relying on a database associated with a government/outside of their control. Customers may have similar privacy or intellectual property concerns (DiEuliis et al. 2017).

Accounting for imperfect screening coverage: National screening regulations may only apply to Providers headquartered within that country—but this may only represent a fraction of synthetic nucleic acid being ordered (most major Providers will fulfil international orders). A robust approach must ensure domestic customers can't just order from foreign Providers (providing a security loophole and disadvantaging domestic Providers).

Quality of public sequence databases: Screening tools typically draw on sequences from public databases, such as the US National Institute of Health's GenBank, to evaluate 'best match' of a customer's sequence. As such, the underlying reference database significantly impacts which sequences are flagged, and can lead to large numbers of 'false positive' flags. Unfortunately, many public databases suffer from data quality issues, such as poorly annotated or contaminated sequences (Wheeler 2023). Additionally, the accessibility of these databases offers low-integrity actors the opportunity to deliberately 'poison' the database with inaccurate information.

Use of AI for defensive purposes such as sequence screening: Advances in artificial intelligence may improve our ability to predict function from sequences, which could significantly enhance functional screening practices. However, such a tool would also have dual-use implications.

A.3 COMMERCIAL IMPLICATIONS

Mandating screening without undue burden on existing Providers: Resolving flagged orders can be time and resource-intensive for Providers, as it requires (i) more thorough evaluation to determine if a sequence is a SOC and (ii) verifying the legitimacy of the customer placing the order (Carter and Friedman 2015). As labour costs rise and the costs of synthesis per nucleotide fall, the fraction of an order cost consumed by screening increases, which may make it difficult for Providers who screen to remain cost-competitive with those who do not.

Impact on the UK market and bioeconomy: Regulatory guidance will need to account for and align with existing business practices (e.g. existing protocols for verification of customer legitimacy and protection of customer privacy/IP), be implemented without unnecessary cost to providers or customers and should seek to minimise negative impacts on scientific research.

Protection of customer information and intellectual property: Many synthesis orders contain valuable intellectual property, as information about who is ordering what (or even the quantity being ordered) has significant economic value. Screening tools, data storage, and processes for passing information on to law enforcement will need to protect the data of legitimate customers and prevent corporate espionage.

Identifying the responsible/liable party for incidents arising from screening failures: With the exception of sequences covered by export controls, it is not necessarily clear who would be liable for a harmful biological event originating with synthetic nucleic acid. The provision of third-party

sequence and customer screening platforms could be less valuable if Providers possess all liability for events involving their products, since this degree of liability may encourage them to develop their own products to be able to verify third-party screening results

Avoiding disparate impact of regulation on smaller companies: Large firms will often operate with larger margins around their synthesis services and may be better positioned to absorb the additional time and resource requirements associated with aspects of a mandatory screening regime than smaller companies, who may have to pass these costs along to their customers therefore making them less competitive (Maurer et al. 2009).

A.4 OTHER REGULATORY CONSIDERATIONS

Delineating the role and responsibility of screening: To regulate nucleic acid synthesis, countries must assign responsibilities and grant authorisation to government entities for implementation and oversight. This will have particular implications for law enforcement, national security, non-proliferation and export control bodies.

Coordination or consistency of regulation at the international level: Providers may face an additional burden when determining how to comply with different regulatory requirements across different jurisdictions. Defaulting to complying with the 'strictest' regulations may pose a challenge, as refusing to fulfil an order without a legal obligation to do so in a Provider's jurisdiction may be difficult to justify to customers, thus disadvantaging Providers.

Regulatory overwhelm: Some experts expressed concern about whether export control bodies had the resources and capacity to regularly assess novel materials or provide advice on undetermined sequences.

Verifying compliance: A mandatory screening regime will require a mechanism and sustained resources for verifying Provider compliance with the requirements. Audits of compliance will likely need to be regular, in order to keep up with changes to requirements, and scaling Providers. Governments would also need to determine legally defensible penalties for non-compliance.