

Australia Group Recommendations Summary

Proposal #1: Control unique enzymes for toxin biosynthesis

Genetic Elements and Genetically-modified Organisms §3.a; add clause:

Any enzymes necessary for and specific to the synthesis of listed toxins or their sub-units.

Rationale

- Some Australia Group toxins are not directly produced as proteins, but can be biologically synthesised.
- There is evidence that some enzymes are **uniquely used** to synthesize certain toxins, including but are not limited to:
 - **sxtT** converts beta-saxitoxinol to saxitoxin
 - **sxtX** is necessary for the production of neosaxitoxin
 - **sxtSUL** is sufficient to produce gonyautoxins
- These enzymes would likely only be used to **facilitate toxin production**, and should be explicitly controlled as genetic elements.

Proposal #2: Exempt 2A and IRES sequences from control

Genetic Elements and Genetically-modified Organisms §1; add footnote:

These controls do not apply to nucleic acid sequences encoding multi-cistronic expression elements, such as 2A self-cleaving peptides and internal ribosome entry sites (IRES), that do not in themselves or through their transcribed or translated products, contribute to pathogenicity.

Rationale

- Both 2A and IRES sequences are **widely used in synthetic constructs with minimal biosecurity concerns**, and have been well studied given their useful biotechnology applications.
- All *Picornaviridae*, even non-controlled species, contain a class of short self-cleaving peptides known as “**2A sequences**”. *Picornaviridae* is a diverse family of 147 species, **most of which are not notable pathogens** e.g. the common cold.
- Similarly, the **IRES sequences** of *Picornaviridae* and *Flaviviridae* are found in a wide range of viral species, many of which are not controlled.
- Due to the minimal risk associated with these sequences and wide use, **these sequences should be exempt through a footnote**, similar to shiga-toxin-producing *E. coli* strains.

Proposal #3: Add virulence factors from non-controlled pathogens with childhood vaccines on warning list

We recommend appending **genes from *Morbillivirus hominis* (measles), as well as *Streptococcus pneumoniae*, and *Neisseria meningitidis*, in particular their virulence factors, to the Warning List. This is the closest equivalent for the current **track** designation given to their virulence factors within the SBRC.**

Rationale

- The SBRC has begun to investigate non-controlled pathogens for potential sequences of concern.
 - We assessed pathogens with childhood vaccines, some of which have a historically high burden of disease and still cause significant mortality and morbidity, for potential weaponization.
 - These pathogens were assessed based on factors including transmission, disease severity, manipulability, potential for immune evasion, and vaccine efficacy and coverage.
- We identified concerns from genes from ***Morbillivirus hominis* (measles)** and virulence factors from ***Streptococcus pneumoniae*** and ***Neisseria meningitidis*** due to:
 - ***Morbillivirus hominis* (measles)**: Extremely high transmission rates, decreasing vaccination rates, ability to cause severe disease (e.g. encephalitis) and immune suppression
 - ***Streptococcus pneumoniae***: Species has many subtypes, causes pneumonia and meningitis in susceptible populations, with relatively high case fatality rates. The global vaccine coverage is increasing, but remains too low to prevent transmission.
 - ***Neisseria meningitidis***: Causes meningitis with high mortality, and often long-term neurological effects, with relatively low vaccine coverage.
- Within the SBRC, these sequences are now **tracked**, meaning that screening systems should identify them in orders, but synthesis providers are not recommended to conduct follow-up screening for every order.
- Within the Australia Group, the closest equivalent identified to the **“tracked”** status designated for these genetic elements seems to be the **Warning List**.
 - The Warning List does not currently include any viruses, nor does it include Genetic Elements. More significant modifications than simply adding the three species names may be needed to more accurately reflect this risk assessment.
 - We recommend including Genetic Elements explicitly in the Warning List.