Office of the Gene Technology Regulator
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26th March 2018

Response to Regulation Impact Statement for Consultation

Seqirus welcomes the opportunity to provide feedback to the OGTR on the proposed updates to the Gene Technology Regulation in Australia. Technical advances over the past decade have resulted in changes to the gene technology (GT) landscapes that are poorly addressed in current GT regulatory framework. For this reason, Seqirus does not consider Option 1 (retain the current GT Regulations) as appropriate.

Whilst Seqirus is broadly supportive of the proposed amendments to the GT regulations, Seqirus supports option 3 (amend the GT Regulations with some but not all draft amendment proposals) as it believes that, subject to interpretation of the proposed GT Regulations, there is significant potential to change the way Seqirus approaches the generation of new influenza candidate vaccine viruses.

Whilst the proposed GT Regulations speak to the classification and use of new technologies for the modification of genetic sequences, Seqirus wishes to highlight that not all applications of GT will result in the generation of an organism with a genetic modification. Rather, there are many potential applications of GT to improve the efficiency of existing breeding methods, and to reduce the potential risk to human health and safety and the environment.

Reverse genetics (RG) is a technique in influenza laboratories for the generation and study of influenza viruses (Hoffmann et al. (2002) PNAS 99, 11411-11416). The method involves the co-transfection of cells with multiple plasmids, each encoding a separate viral gene segments, that when combined enable the generation of a replication competent virus. Whilst the technology has great potential to enable efficiency gains and safety improvements in the development of candidate vaccine viruses for seasonal strains, due to regulatory burden, this technology has otherwise been limited to the generation of pandemic vaccine candidates. For this reason, Seqirus seeks OGTR clarification of the proposed GT Regulations to understand their potential impact on Seqirus' approach to the generation of new influenza candidate vaccine viruses.

For the avoidance of doubt, Seqirus wishes to categorically state that all RG rescues of seasonal influenza viruses at Seqirus are conducted under a DNIR and that all progeny viruses are considered as GMO viruses.

Clarification request - New Technologies – SDN-1, SDN-2 and ODM

The Regulatory Impact Statement for Consultation (Consultation RIS) only considers the use of new technologies (SDN-1, SDN-2 and ODM) for their potential to introduce sequence

variations/modification in organisms. However, particularly with respect to viruses, this is not the only application of GT. There are numerous examples in the literature of viruses being rescued from plasmids where the virus sequence is no different from that of what exists in nature or that can be derived from conventional breeding. The classification of such rescued viruses is potentially open to interpretation as to their regulatory status under the proposed GT regulations.

An example of this is the RG rescue of a seasonal influenza virus that contained the same sequence as either the circulating wild type virus, or one otherwise derived through conventional breeding of a circulating wild type virus and a laboratory adapted parental virus (reassortment). For this application of gene technology:

a) The original naked plasmid DNA encoding individual genes, are in isolation, not considered GMOs (Schedule 1 Item 3).
b) The rescue of the seasonal influenza virus results in the generation of GMO cells. This activity could potentially be considered under an NLRD (Part 2 2.1(d)).
c) Progeny rescued virus could potentially be considered a non-GMO virus under the following criteria:
    I. Not meeting any of the criteria listed under Schedule 1B – Organisms that are genetically modified organisms.
    II. Schedule 1 – Organisms that are not genetically modified organisms, Item 8 (an organism descended from a genetically modified organism (the initial organism), but which has not inherited any traits that occurred in the initial organism because of gene technology.

Seqirus wishes to seek clarification from the OGTR that this interpretation of Schedule 1 Item 8 for seasonal influenza viruses is consistent with the intent of the proposed GT Regulations. Notably, under the above interpretation, pandemic influenza vaccine candidates generated by reverse genetics would continue to be classified as GMO viruses as the parental virus in these situations would satisfy the criteria for risk group 3 under AS/NZS 2243.3:2010. Subject to OGTR clarification, the proposed GT regulations would facilitate the use of reverse genetics technology for the generation of candidate vaccine viruses against seasonal influenza; technology that to date, due to the higher regulatory burden, has otherwise been limited to the generation of pandemic vaccine candidate viruses.

Amendment request – RNAi

The proposed GT Regulations specifies an update to Schedule 1A - Techniques that are not gene technology to include a new item covering the use of RNAi (item 11). Item 11 covers the Introduction of RNA into an organism, if:

a. the RNA cannot be translated into a polypeptide; and
b. the introduction of the RNA cannot result in an alteration of the organism's genome sequence; and
c. the introduction of the RNA cannot give rise to an infectious agent.

A potential application of RNAi is to utilize the technology to assist in the selection of desired genomes where conventional breeding techniques are used (in this case, reassortment of influenza viruses). This application of RNAi mimics the use of antisera to drive selection of viruses during reassortment and satisfies criteria listed in the RIS that the application of RNAi:

- should not result in the expression of new proteins.
- is transient (does not involve the use of templates and is not incorporated into the genome).
- is consistent with the intent of the exclusions to regulation from 2001, some of which were listed on the basis that they "give rise to organisms that can occur in nature and as such do not pose a particular biosafety risk to the environment or human health and safety".

Schedule 1A Item 11 (c) specifies that the introduction of the RNA cannot give rise to an infectious agent. However in relation to this particular amendment, the RIS states:

> *Finally, the measure would not apply if production of infectious agents is possible. Only RNAi techniques are the intended scope of this exclusion, not techniques involving infectious non-coding RNAs such as viroids.*

Seqirus' interpretation of the RIS text is that this amendment has been drafted to address concerns regarding the use of infectious non-coding RNAs such as viroids that are potentially long lived, rather than the applications of RNAi technology where the RNA only serves a transient role. Thus Seqirus proposes Schedule 1A be amended to the following:

11. Introduction of RNA into an organism, if:
    a. the RNA cannot be translated into a polypeptide; and
    b. the introduction of the RNA cannot result in an alteration of the organism's genome sequence; and
    c. the *introduced* RNA cannot *be persistant, or* give rise to ~~an~~ infectious ~~agent~~ *non-coding RNAs such as viroids*.

This amendment would consider the transient use of RNAi to aid conventional breeding techniques such as virus reassortment as a non-GMO activity whilst retaining the core intent of the GT Regulations on RNAi to restrict this technology in applications where the RNA being provided (or its derivatives) have the potential to persist in nature.

Cost and benefits of proposed GT Regulations

Subject to OGTR clarification of the points raised in this submission, the benefit of the proposed GT Regulations is to foster a regulatory environment that strikes the right balance in encouraging innovation with the need to protect against potential risks to human health and safety and the environment rather than specific costs. This would flow through to efficiency gains and safety improvements in the development of candidate vaccine viruses for seasonal strains as Seqirus expands the use of technologies that, due to regulatory burden, have otherwise been limited to the generation of pandemic vaccine candidates.

Please feel free to contact me should you have any further questions.

Sincerely,
Vicky Gakias

IBC Secretary
Seqirus Pty Ltd