Australian Government
Department of Health
Therapeutic Goods Administration

Potential regulatory options for ‘export only’ biologicals

Consultation paper

Version 1.0, November, 2021

TGA Health Safety Regulation

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Purpose and scope

The Therapeutic Goods Administration (TGA) is considering regulatory options for biological therapeutic goods (biologicals) which are manufactured in Australia not for domestic supply, but for export only. Biologicals include human cell and tissue (HCT) therapies and viable animal cell therapies. This consultation paper outlines potential options for a pathway to allow biologicals for export only to be included in the Australian Register of Therapeutic Goods (ARTG). Since the creation of a new regulatory pathway would require changes to the *Therapeutic Goods Act 1989* (the Act), the decision is subject to passage of legislation by the parliament.

Therapeutic goods legislation provides a dedicated approval pathway for 'export only' medicines and medical devices. However, such a pathway is not currently provided for biologicals which are for 'export only'. This is largely because exported human cell and tissue (HCT) products were not envisioned during the development of the regulatory mechanism that governs biologicals, which is known as the biologicals framework.

Under current legislation, biologicals included in the ARTG are permitted to be exported; however, they are not permitted to vary from the product on the ARTG. This means that 'export only' biologicals cannot have different indications, release specifications, or labelling to that approved by the TGA, even if the importing country has assessed and approved the product independently.

The TGA recognises that countries importing Australian manufactured biologicals may have different standards to Australia. The imposition of current Australian regulatory requirements on export only biologicals may be onerous or inappropriate and inhibit local biological export industries. As such, the TGA is preparing recommendations for the Australian Government on the development of an export only pathway for biologicals. The aim is to provide more flexibility to export only biological manufacturers while still maintaining an appropriate level of regulatory oversight.

The purpose of this consultation paper is to give an opportunity for consumers, healthcare professionals and the biologicals industry to provide input on whether an export only pathway should be established for biologicals and, if so, in what form. Specifically, this consultation paper is requesting feedback on:

- potential options for the creation of a new regulatory pathway for export only biologicals
- suitability of current standards and Good Manufacturing Practice (GMP) requirements for biologicals for export only.

The TGA will then work to develop business processes and guidance documents to support the implementation of an export only pathway.

Background

Biologicals framework

The regulatory framework for biologicals provides the legislative basis for the regulation of HCT-derived products and live animal cells or tissues which are supplied in, or exported from, Australia. The biologicals legislation commenced on 31 May 2011 following a recommendation from Commonwealth, state and territory health ministers to improve the regulation of HCT-based therapies. All products within the scope of the framework need to comply with the requirements made under the legislation.

The biologicals framework applies different levels of regulation to products based on the risks associated with their use.

Class 1 biologicals are considered the lowest risk biologicals. These are specified in Schedule 16 of the Therapeutic Goods Regulations 1990 (Regulations), and the only products currently listed are some Faecal Microbiota Transplant (FMT) products. Under the Class 1 pathway there is no pre-market assessment by the TGA or a requirement for compliance with the Australian Code of Good Manufacturing Practice (GMP). For inclusion in the ARTG, sponsors of Class 1 biologicals must certify, among other things, that the product is safe and complies with applicable Therapeutic Goods Orders (TGOs). Sponsors are required to hold evidence of compliance and the TGA can assess compliance post-market.

The higher risk biologicals include Class 2 and 3, which are classified based on their method of preparation and intended use, and the highest risk products, Class 4, are mentioned in Schedule 16 of the Regulations. Regulatory requirements for these classes of biologicals are evaluated in the pre-market phase by the TGA, which includes assessment of compliance with general and product-specific TGOs and manufacture under GMP.

Importantly**,** unless exempt or supplied as an unapproved good, **biologicals must be included in the ARTG to be supplied in Australia or exported overseas**.

Regulatory options for export only biologicals

The current classification system for biologicals, which determines the evidence required to satisfy the TGA of safety, quality and efficacy, is not considered suitable for export only biologicals.

The objectives of the proposed export only regulatory scheme for biologicals are:

- to minimise regulatory burden on biologicals that are for export only
- to bring the biologicals framework into alignment with how other export only therapeutic products are regulated by the TGA.

Due to the high-risk nature of biologicals, which contain material of human origin and represent infectious disease risks, all proposed options include compliance with the same standards and GMP requirements which apply to domestically supplied biologicals. Specific information on applicable standards and GMP requirements has been included in this paper and for your information when considering the proposals.

None of the current pathways for inclusion of Class 1-4 biologicals in the ARTG were considered appropriate options for export only biologicals. Class 1 biologicals are exempt from GMP and do not undergo a pre-market assessment by TGA prior to inclusion in the ARTG. However, for

export only biologicals GMP compliance is considered important for appropriate oversight of manufacturing steps conducted in Australia and overseas.

Class 2-4 biologicals are assessed, under section 32DE of the Act, prior to inclusion in the ARTG and must comply with GMP requirements. The assessment on Class 2-4 biologicals requires a full dossier assessment in which quality, safety and efficacy is evaluated to ensure the product meets Australian requirements. These requirements are considered too high for export only biologicals.

When developing options for a pathway for export only biologicals, we considered the current risk-based framework and the export only pathways in place for medicines and medical devices (Appendix A). Broadly, the new legislative pathway for export only biological products would require that:

- it is safe for the purposes for which it is to be used
- it conforms with any relevant mandatory standards, such as: Therapeutic Goods Orders applicable to Biologicals (e.g. TGO 105, 107, 108 & 109)
- it complies with all prescribed quality or safety criteria
- the presentation of the goods is acceptable
- it does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*
- it is manufactured in GMP accredited facilities.

The options and their key features are outlined below and summarised in Figure 1:

- **Option 1: Automatic inclusion of export only biologicals for sponsors with a 'parent product' included in the ARTG.** If the Sponsor has an existing product included in the ARTG, with the same active ingredient and principal manufacturing site, they can certify compliance against specific requirements, with automatic inclusion in the ARTG. This option is designed to give flexibility to current sponsors of biologicals included in the ARTG.
- **Option 2: Abridged pre-market assessment of export only biologicals**. Submission of documentation addressing specific requirements for an abridged premarket assessment by TGA prior to inclusion on the ARTG. This option does not require an existing similar product to be included on the ARTG and caters for sponsors who do not have an entry on the ARTG.
- **Option 3 Status Quo.** The current requirement for biologicals, based on product classification, including GMP and premarket assessment.

Please note that options 1 and 2 are not mutually exclusive and, depending on stakeholder feedback, features of both options could be implemented to allow greater flexibility.

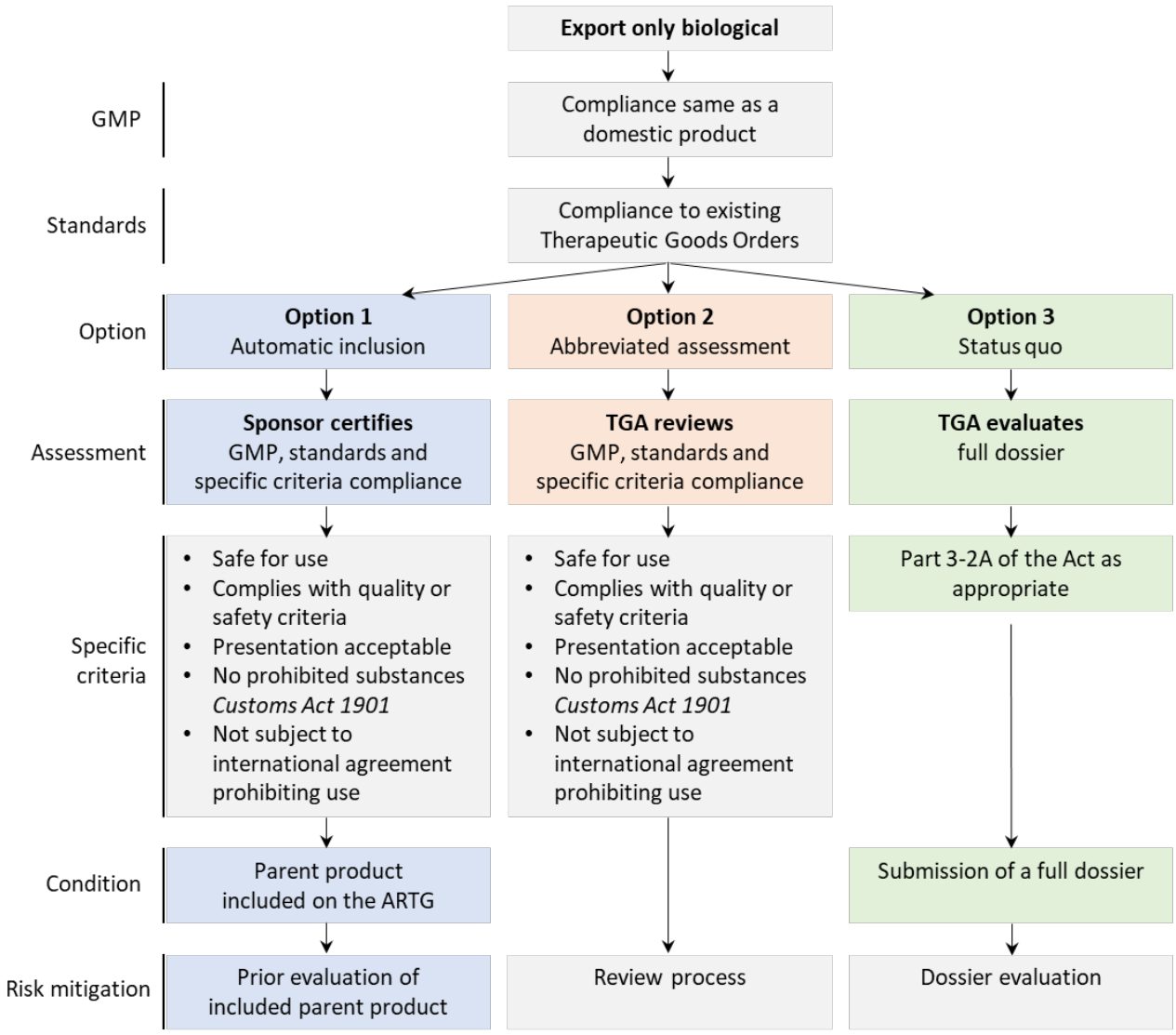

Figure 1: Proposed options for export only biologicals

Standards for export only biologicals

Biologicals present a unique challenge to regulators as there is a lack of international default standards (i.e. monographs) which can be universally adopted to ensure quality and safety is globally consistent. Therefore, we seek your feedback on the applicability of current standards for biologicals and whether they are fit for purpose for export only goods.

At present, biologicals that are included in the ARTG must comply with all relevant standards, including the following TGOs:

- Therapeutic Goods (Standard for Faecal Microbiota Transplant Products) (TGO 105) Order 2020
- Therapeutic Goods (Standard for Biologicals—Labelling Requirements) (TGO 107) Order 2021
- Therapeutic Goods (Standard for Human Cell and Tissue Products—Donor Screening Requirements) (TGO 108) Order 2021
- Therapeutic Goods (Standards for Biologicals—General and Specific Requirements) (TGO 109) Order 2021

The TGOs represent Australian requirements for biologicals, but these Australian requirements may differ from other international regulators, especially donor selection, testing and labelling requirements.

We recognise that this may present a challenge for sponsors who also need to comply with the importing country's requirements. However, recent updates to the above TGOs include changes which may make compliance for export only products easier, these include:

- excluding biologicals for export from the prescriptive labelling requirements set out in TGO 107, but the requirements for donor traceability still apply.
- excluding autologous biologicals from the donor selection and testing requirements set out in TGO 108.

The TGOs represent current best practice and were developed to align with other international standards. Using the current TGOs as standards applicable to export only biologicals would ensure that a minimum standard for quality and safety is met. However, where different requirements are approved by the importing country, exemptions to supply a product which does not comply with the TGA standard may be requested under section 14(s14) of the Act. It may also be appropriate to make potential amendments to current TGOs to allow for greater flexibility, or develop a stand-alone TGO for export only biologicals.

We recognise that stakeholders may have specific requirements which need to be met for the importing country and seek feedback from the sector on whether the application of the standards is appropriate, or where flexibility should be considered.

Question 1: Do you agree that all the requirements set out in the current TGOs for biologicals should apply to export only biologicals? If not, please highlight any clauses in the current TGOs that you believe should not apply or should be more flexible for export only biologicals and why.

GMP requirements

The Australian Code of Good Manufacturing Practice (cGMP) for Blood and Blood Components, Human Tissues and Human Cellular Therapy Products applies to Blood, Human Tissues and Human Cellular Therapy Products manufacturers that undertake the collection, processing, testing, storage, release for supply, and quality assurance of Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.

Manufacturing Licensing requirements are set out in Part 3-3 of the Act and include requirements to comply with both general and specific conditions of licence. It is a condition of licence that Blood, Tissue and Cellular Therapy products manufacturers observe the Manufacturing Principles determined under Section 36 of the Act. The Manufacturing Principles require these manufacturers to demonstrate that manufacturing practices comply with the cGMP.

It is proposed that export only biologicals would be required to be manufactured in GMP accredited facilities to ensure that there is consistency with the applicable standards and manufacturing principles across the sector. These are the same requirements applying to all biologicals included in the ARTG. This approach is consistent with requirements for export only medicines (Export of medicines from Australia guidance) and ensures that products meet the appropriate standards which are accepted and required internationally.

This requirement means that any Australian manufacturing sites would require a TGA-issued GMP licence and any overseas manufacturing and/or testing facilities would be required to obtain a TGA-issued GMP certificate. For more information on the GMP requirements for biologicals and how to obtain GMP licences and certificates please see the manufacturing biologicals webpage.

Question 2: Do you agree with the proposed approach to GMP requirements, including that overseas manufacturing and testing facilities should be required to obtain a TGA-issued GMP certificate? If not, please explain why and tell us how manufacturing quality could be ensured.

Question 3: Are there any steps of manufacturing where GMP certification should not be required for export only biologicals? If so, please explain which steps and why.

Option 1: Automatic inclusion of export only biologicals for sponsors with a 'parent product' included in the ARTG

This option aims to provide flexibility to sponsors of existing ARTG entries. Sponsors who have a biological on the ARTG that is similar to the one they wish to export could apply for automatic inclusion of their biological for export only. Certain characteristics of the export only product would not be allowed to differ from the Australian supplied 'parent product'.

The export only product must not differ from the Australian supplied product in the following:

- active ingredient
- principle manufacturing site
- sponsor
- dosage form
- formulation or composition.

This may allow the export only product to differ from the Australian supplied product in:

- clinical indication
- specifications
- containers/ critical materials
- label
- shelf life.

The export only biological would undergo automatic inclusion in the ARTG following a declaration certifying compliance with specific requirements which would require that, among other conditions, the biological:

- Is safe for the purposes for which it is to be used.
- Conforms with any relevant mandatory standards, such as:
  - Therapeutic Goods Orders applicable to biologicals (TGO 105, 107, 108 & 109)
- Complies with all prescribed quality or safety criteria.
- The presentation of the goods is acceptable.
- Does not contain substances that are prohibited imports for the purposes of the Customs Act 1901.

A full set of proposed requirements can be found in Appendix B and is proposed to be incorporated in a new section of the Act.

Sponsors would be required to hold evidence of how they comply with the requirements set out under the relevant section of the Act. This includes, but is not limited to, evidence supporting the indication and shelf life. The sponsor should also hold evidence that the importing country has accepted the product for use.

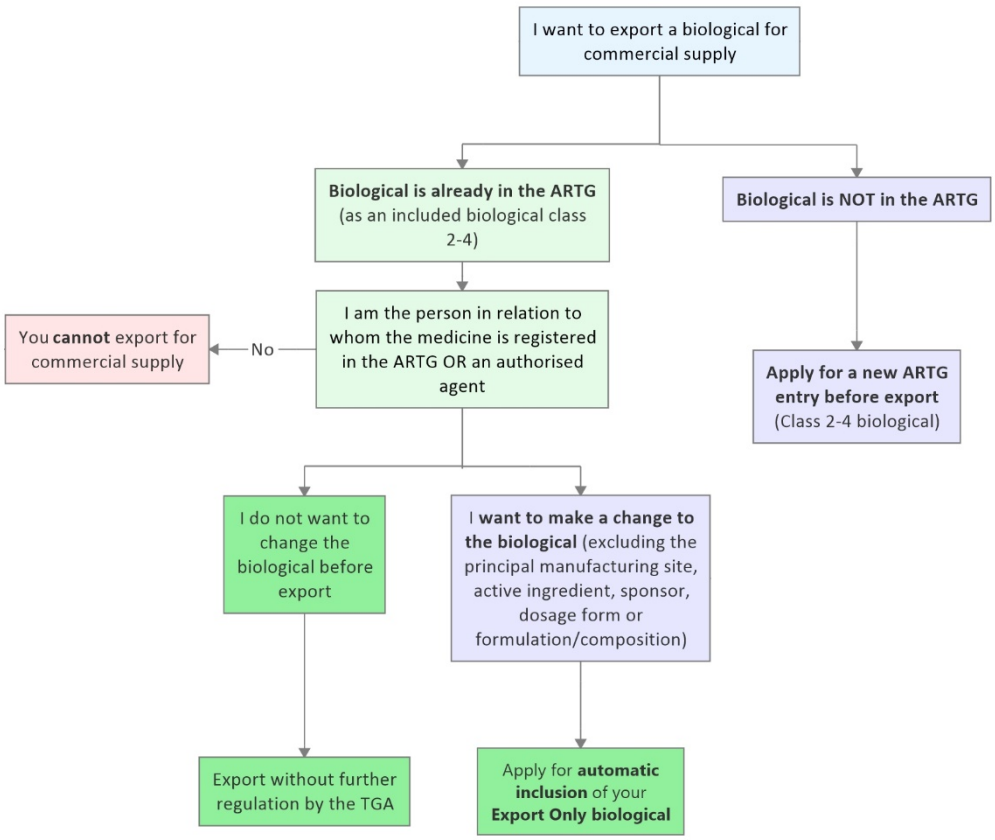

Figure 2: Overview of the export only pathways available under Option 1, utilising an automatic inclusion pathway, with parent product requirements

Features

This option has been designed to allow current sponsors flexibility over their similar export only biological. Overseas regulators can have confidence that biologicals exported from Australia meet a minimum level of quality and safety despite the lack of international pharmacopeia and monographs.

This pathway would facilitate expansion of Australian manufactured biologicals into overseas markets, with minimal regulatory assessment by the TGA. The automatic inclusion process would also ensure timely inclusion of products on the ARTG and ultimately supply.

Considerations

This option is limited to those sponsors that have a current ARTG entry and there are restrictions on which aspects of the export only product can differ from the parent product. If a sponsor wants to change the primary manufacturing site, sponsor, active ingredient, dosage form or formulation/composition of their registered product then this is no longer considered to be related to the 'parent product. They would need to apply for a new ARTG entry (Class 2-4), requiring submission of a dossier for evaluation. This is the current approach to all biologicals in the ARTG whereby any of these changes create a separate and distinct good.

Whilst there is no pre-market evaluation, sponsors would have to sign a declaration stating compliance to the relevant standards and conditions imposed and would be required to hold evidence of compliance. For this option, post-market compliance checks would occur and sponsors failing to produce evidence of compliance could have their product cancelled.

Question 4: Does Option 1 provide sponsors with enough flexibility to export their biologicals, whilst still ensuring quality & safety of the goods? Please explain your answer.

Question 5: Do you agree Option 1 should be restricted to export only biologicals linked to a current ARTG parent product? If not, please explain why.

Question 6: If Option 1 is restricted to goods linked to a parent product, is the list of characteristics that must not differ between the domestically supplied and export only product appropriate? If not, please tell us why and which characteristics you think should be allowed to be different from the 'parent product' to provide flexibility to sponsors whilst still ensuring the quality and safety of the goods.

Option 2: Abridged pre-market review

In this option the TGA proposes to regulate export only biologicals via an abridged pre-market review process, consistent with the approach for export only medicines.

The export only biological would be reviewed against a proposed new section of the Act which would require that, among other conditions, the biological:

- Is safe for the purposes for which it is to be used.
- Conforms with any relevant mandatory standards, such as:
  - Therapeutic Goods Orders applicable to biologicals (TGOs 105, 107, 108 & 109)

- Complies with all prescribed quality or safety criteria.
- The presentation of the goods is acceptable.
- Does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*.

A full set of proposed requirements can be found in Appendix B.

The level of evidence needed by the sponsor to demonstrate compliance to the requirements outlined above would be communicated through export only specific guidance. Mandatory documentation would include:

- Declaration of compliance to relevant standards.
- The finished product specification (including formulation).
- The label, including any package inserts and the Product Information (PI) if applicable.
- Evidence of valid TGA issued GMP licenses and certificates for manufacturing sites (as applicable).

The TGA would review the above documentation in the application against the listed criteria, including the acceptability of the medicine's safety for the intended purpose of use, and the acceptability of the presentation of the medicine. Should further information be required, it would be requested under section 32JA of the Act. An overview of the process can be seen in Figure 3.

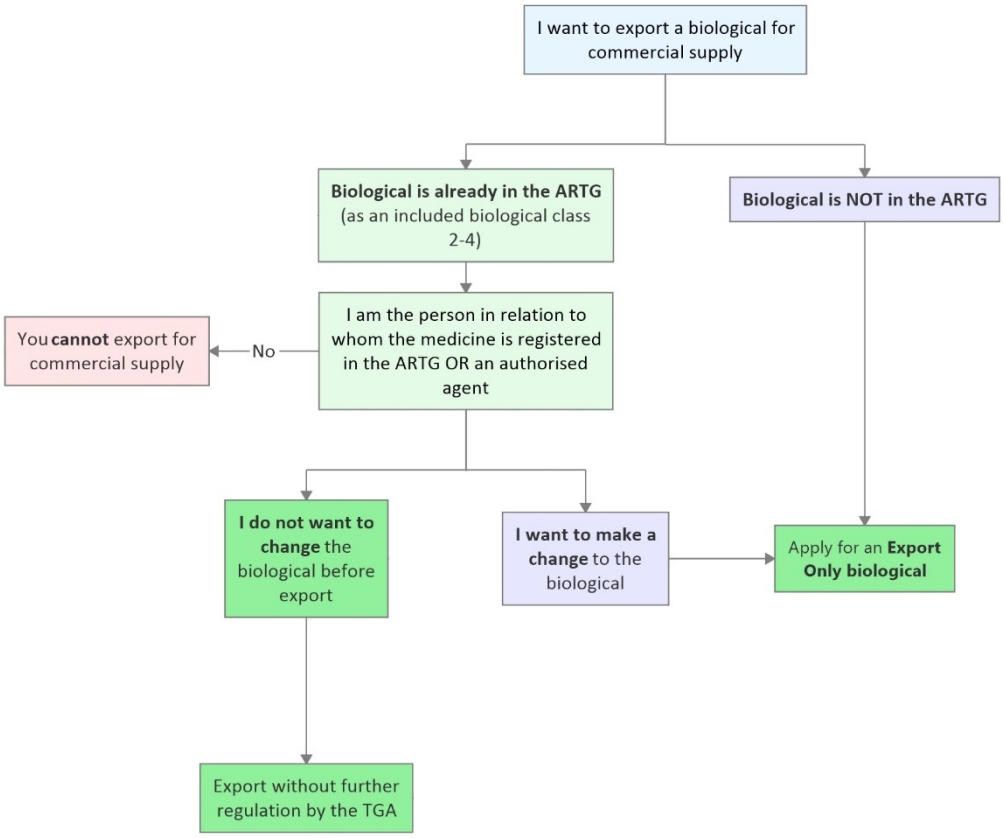

Figure 3: Overview of the export only pathways available under Option 2 pre-market review.

Features

This pathway would be developed specifically to support export only biologicals and provides a legislative framework for a pre-market review, compared with the current assessment requirements for Class 2-4 biologicals.

This option ensures that there is adequate review of the product to ensure that it meets the requirements set out in the Act prior to allowing inclusion of the biological on the ARTG. This gives overseas regulators confidence that the biologicals which are exported from Australia meet a minimum level of quality and safety.

Considerations

This option provides a flexible pathway for sponsors who wish to export products not already included in the ARTG. Sponsors would need to supply certain critical information to provide some assurance that they have met quality and safety requirements prior to inclusion in the ARTG to allow for export. The proposed target timeframe for assessment would be 30 working days, consistent with the target timeframe for export only medicines. Post-market compliance checks could be undertaken for aspects not subject to pre-market evaluation and sponsors failing to produce evidence of compliance could have their product cancelled.

Question 7: Does Option 2 provide sponsors with enough flexibility to export their biologicals, whilst still ensuring quality & safety of the goods? Please explain your answer.

Question 8: Do you agree with the proposed target timeframe of 30 days for assessment? If not, please explain why.

Option 3: Status Quo

The current legislative framework does not provide a specific pathway for the regulation of export only biologicals. To export biologicals for commercial supply sponsors must have an ARTG entry for their biological and be authorised to supply in Australia.

Whilst sponsors of existing ARTG entries can export their product for commercial supply to any overseas country, the product is not permitted to vary from the Australian supplied product. If the importing country requires changes to the product, for example, to use different specifications, a different shelf-life, or a different indication, the sponsor would be required to either:

- apply to the TGA for a variation to their current Australian supplied ARTG entry, noting that for example, multiple versions of specifications or shelf lives cannot be maintained for a single product
- apply to the TGA for a new registration of a biological (this would require a full dossier submission and maintenance of the ARTG entry)
- apply to the TGA for a section 14 '*Consent to import, supply or export therapeutic goods that do not comply with standards - information for industry'* if the sponsor could not comply to the current standards.

See Figure 4 for an overview of the process.

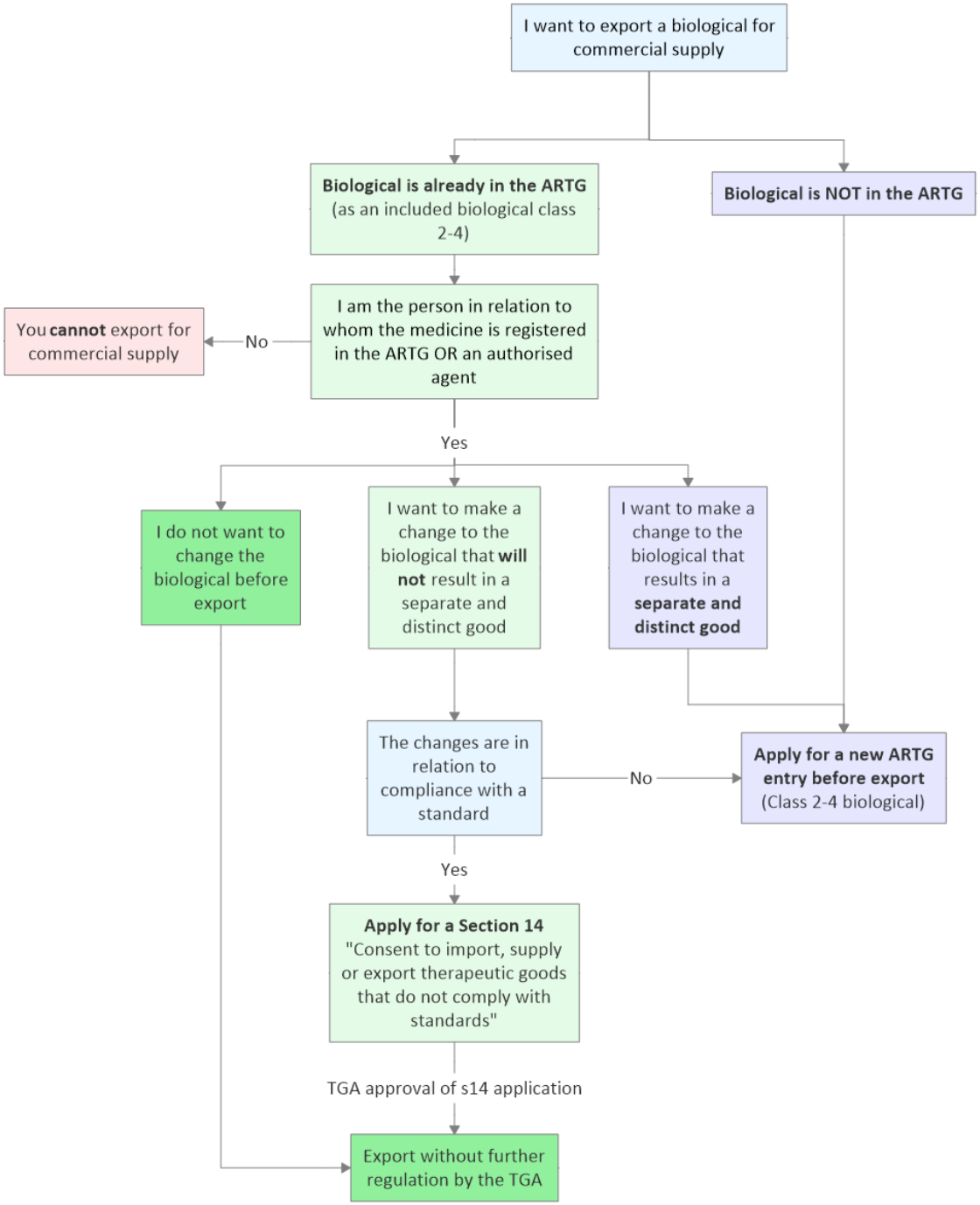

Figure 4: Overview of biological export pathways available under Option, 3 Status Quo

Features

This level of regulation ensures that all biologicals exported from Australia are manufactured to a high level of quality and safety and gives the highest level of confidence to importing countries that the product is of the same quality as that provided in Australia.

Considerations

This option is inflexible and does not address difficulties for sponsors when importing countries request differences for the imported product. This could impact a sponsor's ability to export biologicals which have been approved for use by other countries.

Fees and charges

Our existing processes for the registration of biologicals (including application and evaluation costs) are fully cost-recovered as fees from applicants.

It is proposed there would be a fee associated with the inclusion process for an export only biologicals. Fees reflect the TGA resources required to undertake the work.

Option 1: This proposed pathway mimics the current pathway utilised for Class 1 biologicals, with no pre-market assessment and an automatic inclusion process. Therefore, the proposed fee for **option 1** would be approximately the same as that which is in place for Class 1 biologicals, around $1,100.

Option 2: This proposed pathway requires minimal pre-market assessment, comparable with a self-assessable request (SAR) or minor variation in terms of time and effort. Therefore, the proposed fee for **option 2** is proposed to be around $2,100, to reflect the pre-market review that takes place.

Option 3: This option utilises the current application pathways in place for biologicals. Therefore, the fees and charges are the same as what is currently in place. To see the current fees and charges for biologicals please see the TGA website.

Conclusion

Sponsors of biologicals have identified that there is a need to develop a unique pathway which can be used for the export of biologicals that differ from those supplied in Australia. Whilst biologicals can currently be exported if included on the ARTG, this option is restrictive and does not consider the different requirements of overseas regulators.

Question 9: Which option(s) would you use or prefer? You may select more than one option. Please explain why.

Question 10: Do you believe that your preferred option(s) provides confidence to overseas regulators that Australian made biologicals are of adequate quality and safety? Please explain why.

Question 11: Do you agree with the proposed fees for these options? If not, please explain why.

Providing feedback

We invite you to provide your feedback by completing our online survey on the TGA Consultation Hub.

All responses will be published on the TGA Consultation Hub, unless you specifically request that your response be kept confidential.

What happens next

We will review all feedback received in response to this consultation. Submissions received will be used to inform the Australian Government about which regulatory option should be supported. Feedback will also be used to inform the relevant standards which are applicable to export only biologicals and the manufacturing requirements for these products. There may be further consultations on the legislative options for export-only biologicals which will help inform further details, including fees and charges.

Appendix A: Current pathways for export only medicines and medical devices

Summary of current pathways for export only medicines and medical devices

	Medical devices	Medicines
Regulatory approach	Class 1 medical device	No Classes – Export only medicines are listed on the ARTG
Pre-market submission	Signed declaration of compliance under section 41FD of the Act	Documentation demonstrating compliance to standards, labels (and PI if applicable) and formulation for evaluation by the TGA
Must have an Australian supplied product in the ARTG	No - if applying for an export certificate. Yes - if applying for a certificate of free sale	No
GMP required	No	Yes
Subject to existing standards	No	No
Subject to an export only standard	No	Yes - Therapeutic Goods Order No. 70C - Standards for Export Only Medicine (TGO 70C)

Appendix B: Proposed new section of the Act for export only biologicals

The following outlines proposed text to specify specific requirements to certify against if Option 1 and/or Option 2 are implemented.

(1) A person may make an application to the Secretary to include an export only biological in the Register.

(2) An application must:
  (a) be made in accordance with a form that is approved, in writing, by the Secretary; and
  (b) be accompanied by a statement certifying the matters mentioned in subsection (3); and
  (c) be delivered to an office of the Department specified in the form; and
  (d) be accompanied by the prescribed application fee.

(3) The applicant must certify that:
  (a) the presentation of the goods is acceptable; and
  (b) the biological is safe for the purposes for which it is to be used; and
  (c) the biological conforms to every standard (if any) applicable to it; and
  (d) both of the following are complied with in relation to the biological:
    (i) the applicable provisions of the Therapeutic Goods Advertising Code;
    (ii) the other requirements (if any) relating to advertising applicable under Part 5-1 or under the regulations; and
  (e) the biological complies with all prescribed quality or safety criteria that are applicable to it; and
  (f) the biological does not contain substances that are prohibited imports for the purposes of the Customs Act 1901; and
  (g) if there are one or more absolute prohibitions in force for the purposes of subsection 9K(1) or (3):
    (i) if those prohibitions cover imports—any imports into Australia of the biological by, or on behalf of the applicant, will not contravene those prohibitions; and
    (ii) if those prohibitions cover exports—any exports from Australia of the biological by, or on behalf of the applicant, will not contravene those prohibitions; and
    (iii) if those prohibitions cover supplies—any supplies in Australia of the biological by, or on behalf of the applicant, will not contravene those prohibitions; and
  (h) if there are one or more prohibitions in force for the purposes of subsection 9K(1) or (3) that are subject to conditions:
    (i) if those prohibitions cover imports—any imports into Australia of the biological by, or on behalf of the applicant, will not contravene those conditions; and
    (ii) if those prohibitions cover exports—any exports from Australia of the biological by, or on behalf of the applicant, will not contravene those conditions; and
    (iii) if those prohibitions cover supplies—any supplies in Australia of the biological by, or on behalf of the applicant, will not contravene those conditions.

(4) An approval of a form may require or permit an application to be given in accordance with specified software requirements:
  (a) on a specified kind of data processing device; or
  (b) by way of a specified kind of electronic transmission.

Version history

Version	Description of change	Author	Effective date
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