Australian Government
Department of Health
Therapeutic Goods Administration

Changes affecting TGA issued conformity assessment certificates

Guidelines for notifying the TGA about "substantial changes" to, or transfers of, conformity assessment certificates

Version 2.0, February 2020

TGA Health Safety Regulation

The purpose of this guidance is two-fold:

(1) to assist manufacturers in assessing whether proposed changes to a conformity assessment certificate amount to "substantial changes", and, if so, what the manufacturers' obligations are for the purposes of meeting the automatic conditions on a conformity assessment certificate; and

(2) set out events that trigger a transfer of a conformity assessment certificate, and its associated responsibilities, to a new entity (i.e. a new manufacturer)

This is a guide only. Sponsors and manufacturers are encouraged to seek independent professional advice to ensure they comply with their legislative and regulatory requirements under the therapeutic goods legislation. This document will evolve over time. Updates and clarifications will be included as required. Feedback on the guidance is always welcome.

Contents

1. Compliance with "substantial changes" condition

A TGA issued conformity assessment certificate is subject to a number of automatic conditions imposed under section 41EJ of the *Therapeutic Goods Act 1989* (the Act). One of these conditions requires that the person in respect of whom the certificate is issued (i.e. the manufacturer) will notify in writing the Secretary of the Department of Health of any plan for substantial changes to:

a. quality management systems; or

b. the product range covered by those systems; or

c. the product design of kinds of medical devices

in respect of which the certificate is issued.[1]

The purpose of this guidance is to assist a person in respect of whom a conformity assessment certificate has been issued in assessing whether their proposed changes require notification to the TGA in accordance with the Act. This guidance also clarifies that notification of a planned substantial change in and of itself does not result in a change to the existing conformity assessment certificate. Rather, for the planned substantial change to come into effect, it is necessary for a new conformity assessment certificate to be issued.

To that end, manufacturers apply for a "**Substantial change notification and application**" conformity assessment application through their TGA Business Services (TBS) portal, which serves the dual purpose of evidencing the manufacturer's compliance with their notification obligation under the Act, and an application for a new conformity assessment certificate for approval to implement the proposed change.

Urgent changes that are vital to public health and safety should be implemented immediately.

A labelling change that adds a **contraindication, warning or precaution** vital to public health and safety should be implemented *immediately*, with relevant change documentation maintained under the manufacturer's QMS. These types of changes - including the notification to the TGA - should be carried out in accordance with the Uniform Recall Procedure for Therapeutic Goods (URPTG).

However, the manufacturer is required to notify the TGA of the change as part of their application for recertification. Documentation supporting any change must be made available to the TGA at any time, and upon request.

2. What is considered a substantial change?

A substantial change is considered to be a change to the manufacturer's QMS or medical devices, including IVD medical devices, that is expected to impact the quality, safety and performance of the devices.

[1] See subsection 41EJ(3) of the Act.

The concept of a substantial change is linked to the principles of safety and effectiveness in the context of a risk-based regulatory framework to control the risk of medical devices, including IVD medical devices.

Manufacturers are required to comply with conditions imposed automatically on the TGA issued conformity assessment certificate under the Act that they notify the TGA in writing of any plan for substantial changes to the following matters:

- Quality Management System (QMS)
- the product range covered by those systems
- the product design of the kinds of medical devices

Examples on what the TGA considers to be "substantial changes" and "not substantial changes" are provided in Section 4 and Section 5 respectively.

3. What is the effect of a notification of a planned substantial change?

Notification of a planned substantial change has the effect that, under the Act, the manufacturer in respect of whom the existing conformity assessment certificate has been issued remains compliant with the conditions imposed on the certificate. **Notification of a planned substantial change does not result in the conformity assessment certificate being changed.**

For a planned substantial change to be given effect, it is necessary for the manufacturer to make an application for a new conformity assessment certificate as set out in section 41EB of the Act which, subject to the Secretary's decision, may result in a new certificate being issued with regards to the substantially changed medical device.

To notify the TGA of a substantial change and apply for a new conformity assessment certificate, please go to TBS and select "**Substantial change notification and application".**

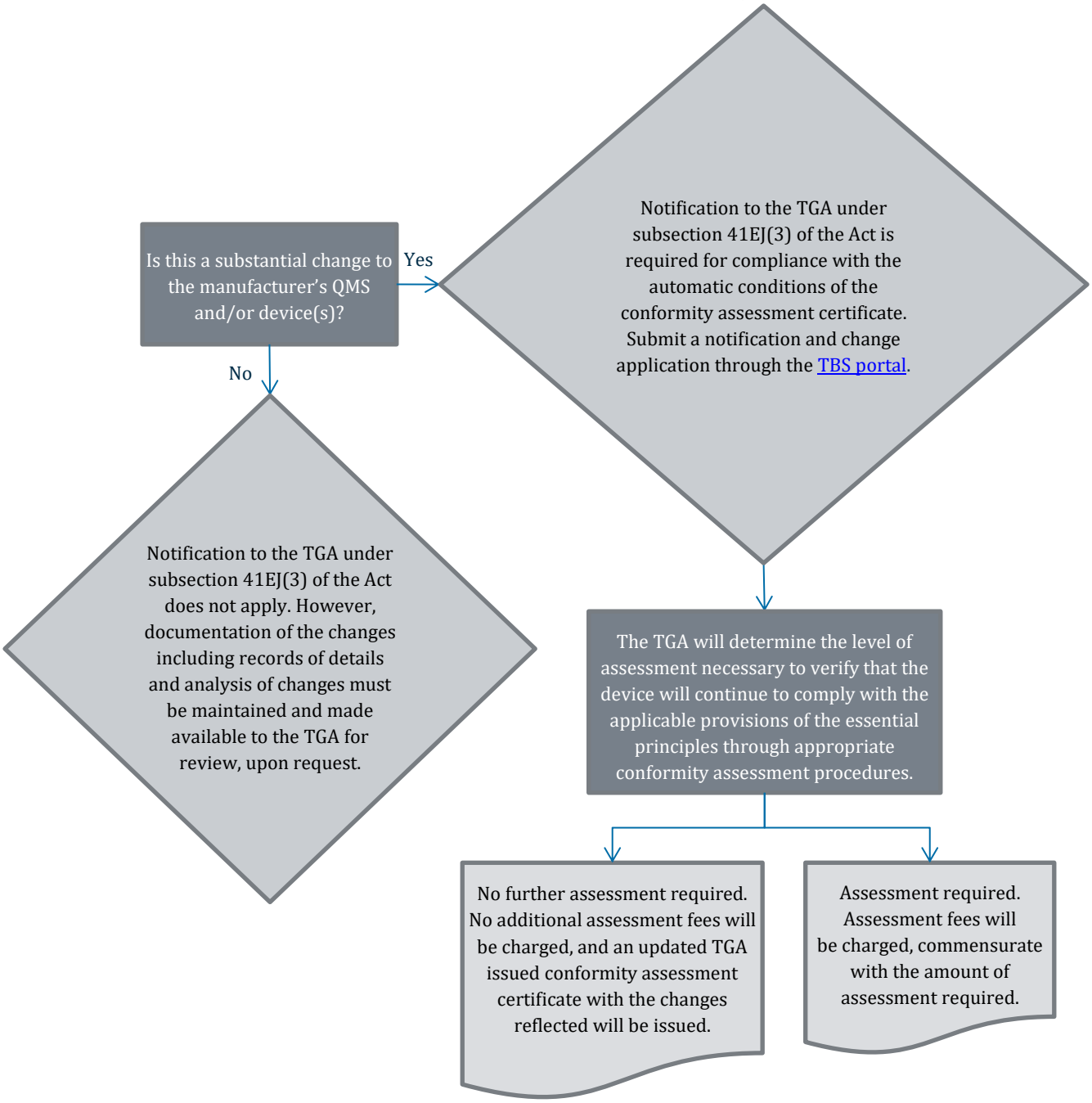
Following receipt of an effective application[2] the TGA will determine the level of assessment necessary to verify that the device will continue to comply with the applicable provisions of the essential principles through the appropriate conformity assessment procedures, and issue a new conformity assessment certificate if the supporting evidence is considered acceptable (see Flowchart 1).

Note: The term "substantial changes" is not defined under the Act. The TGA therefore provides extensive guidance on what it considers to amount to a substantial change. Examples and flowcharts are set out at Section 4 and Appendix A of this guidance.

However, it is not possible to specify what would be considered a substantial change for each of the vast range of devices on the market. Manufacturers must have change control procedures in place that consider the impacts of the change and whether the change is "substantial" and requires notification to the TGA to comply with the automatic conditions of the TGA conformity assessment certificate.

[2] Under section 41EB of the Act, an application is not effective if the prescribed application fee has not been paid. The fee for an application for conformity assessment certificate is prescribed in Schedule 5, Item 1.1 of the *Therapeutic Goods (Medical Devices) Regulations 2002*

Flowchart 1: Process of notification of a substantial change



4. Tools to determine substantial changes

This section of the guidance document presents general principles and flowcharts to assist manufacturers to determine whether a change is considered substantial and requires notification to the TGA. Specific examples that detail common changes made to medical devices, including IVD medical devices, can be found in the Appendices.

4.1 Changes to Quality Management Systems

This section applies to changes to the manufacturer's QMS, including changes to manufacturing facilities or suppliers included on the TGA issued conformity assessment certificate, or their relevant scopes that are outlined in the certificate, or changes to validated processes performed at any of these sites. Flowchart 2 and Flowchart 3 detail questions to assist applicants and manufacturers in determining if a change to the manufacturer's QMS is considered to be substantial and therefore requires notification to the TGA. Specific examples are provided in Appendix A.

Changes to a manufacturing facility and/or relevant scope

For example, a change in:

- Name and/or address of the manufacturer
- Scope of existing manufacturing facilities, including manufacturing steps
- Addition or removal of a manufacturing facility along with associated activities

Note: Sometimes a name change may be the result of a certificate transfer due to the disposal of a business, its amalgamation with another manufacturer, the death or bankruptcy of the owner, or the winding up of a business. For these situations, please refer to Section 6.

Changes to manufacturing process

This includes any changes to the controls applied under a QMS for validated processes, in particular, changes to a process where the validation is required to mitigate the risks related to that process, or is required to ensure that the requirements that are essential for the safe and proper use of the device can be met. This is particularly important where the risks, if unmitigated, may adversely impact patients or users. For example, a change to:

- A drug coating process for a medical device
- The methods used for the verification of purchased products if those products are starting materials for a medical device that is intended to incorporate a medicinal substance or a material of animal origin
- A packaging process that may impact the sterile integrity of the medical device
- A manufacturing process for a medical device that might impact pre-sterilisation bioburden
- A sterilisation method (e.g. ethylene oxide (EO) to gamma, gamma to e-beam, etc.) for a medical device
- The replacement (e.g. as a result of decommissioning) or addition of sterilisation equipment for a medical device
- A viral inactivation process related to a medical device, including an IVD medical device
- The manufacturing quality control procedures for a medical device, including an IVD medical device (e.g. parametric release for sterilisation process, aeration or dwelling period for EO sterilisation, substantial change to batch release testing)

- The methods or controls for determining shelf life for a medical device, including an IVD medical device
- A manufacturing process affecting the concentration and composition (i.e. formulation) of reagents for an IVD medical device which may impact the active components in the assay, and hence the device performance and stability

Changes to a supplier identified in a TGA issued conformity assessment certificate and/or relevant scope in the certificate

For example, a change in:

- Name and/or address of a supplier identified in the certificate
- Scope of activities for a supplier already identified in the certificate including any manufacturing process or activity that is outsourced by the supplier (e.g. abattoir) that may impact the specification of the material/component provided by the supplier
- Addition of a new supplier to the certificate
- Removal of a supplier already identified in the certificate

Changes to the type of conformity assessment procedure

The conformity assessment procedure applied by the manufacturer appears on a TGA issued conformity assessment certificate. Therefore, changes to the conformity assessment procedure applied by the manufacturer, for example changing from a Schedule 3, Part 4 (Production Quality Assurance Procedures) system to a Schedule 3, Part 1 (Full Quality Assurance Procedures) system, requires notification to the TGA.

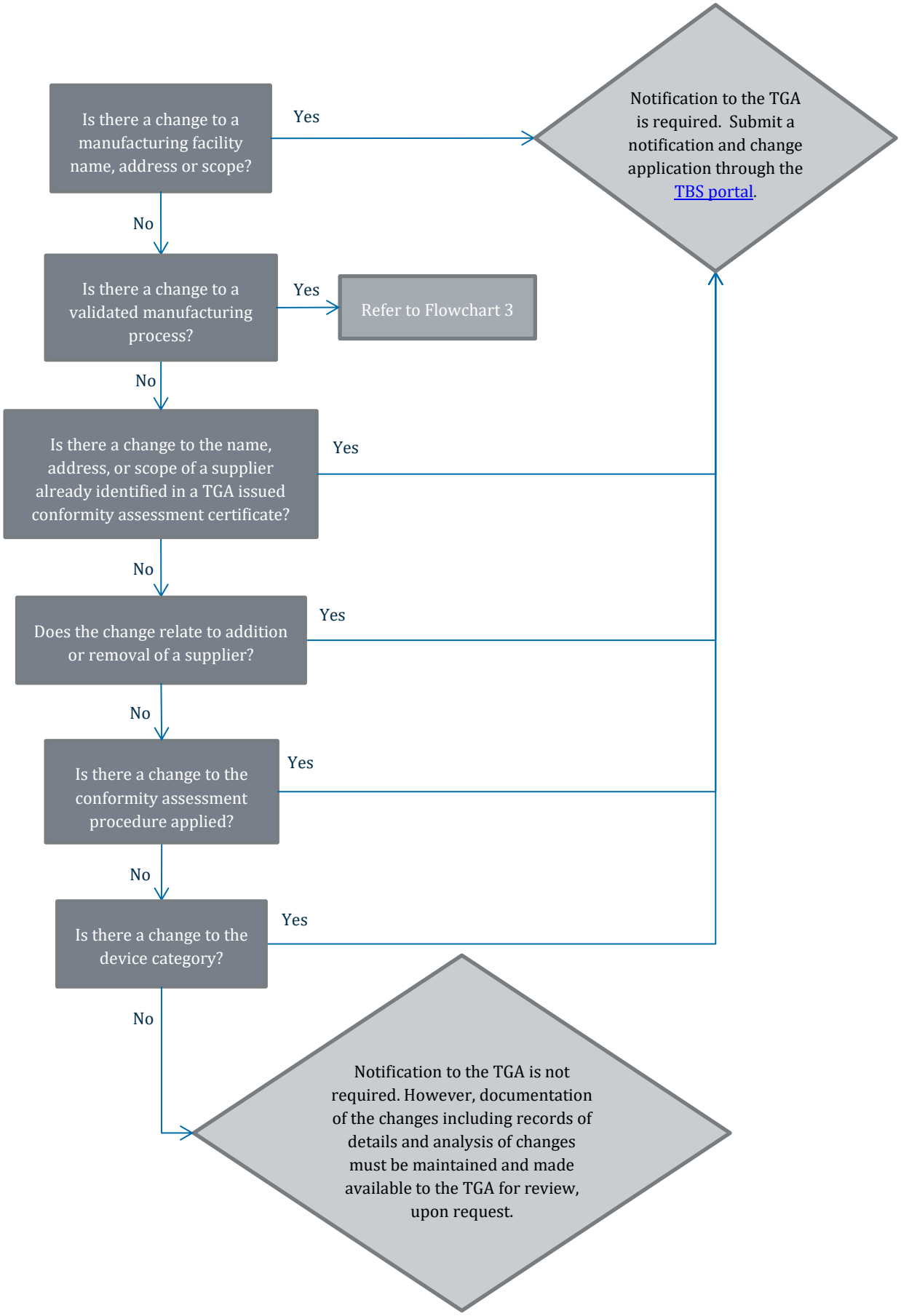
Changes to the kinds of medical devices (including IVD medical devices)

A change to the kinds of devices to which the QMS has been applied must be notified to the TGA. Subsection 41EJ (3) of the Act, and the conformity assessment procedures in Schedule 3, Part 1 of *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations), set out the requirements to notify such changes. The kinds of devices covered within the scope of a QMS certificate is specified on the certificate under *Device Categories*.

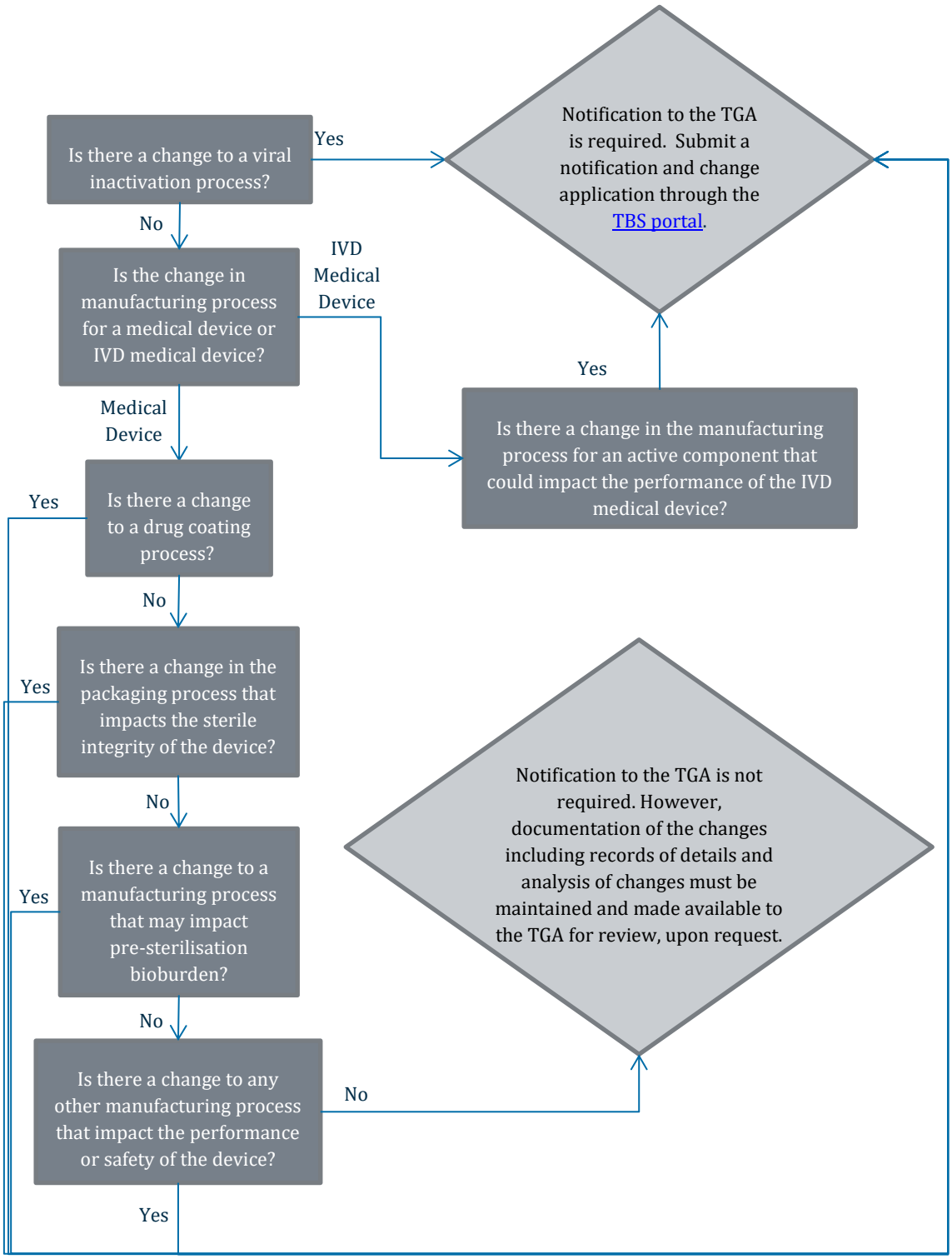
For IVD medical devices, the requirement to notify the TGA of changes to the individual products under each 'kind of device' (i.e. the device category as listed on the Schedule 3, Part 1 conformity assessment certificate) is based on classification of the device and possible risks associated with the change (with regard to safety and performance). In general, for Class 2 and 3 IVD medical devices included within the scope of a TGA issued conformity assessment certificate, provided the affected IVDs remain "the same kind of device", and there is no major change to methodology or processes used during manufacture, the environment the device is intended to be used in, or to the intended user group, then a systems-based approach that relies on the manufacturer's QMS to identify and control the changes can be used. Documentation of the changes including records of the details and analysis of changes made to Class 2 and 3 IVD medical devices should be made available to the TGA for review, upon request.

Note: The Regulations specify that references to kinds of medical devices, in the context of conformity assessment procedures including changes, also include a reference to an individual medical device.

Flowchart 2: Changes to the manufacturer's QMS



Flowchart 3: Changes to manufacturing processes



4.2 Changes to product design

This section applies to all medical devices with TGA issued conformity assessment certification, including IVD medical devices, and not just those kinds of devices that are subject to design or type examination procedures. A modification to a device may involve changes to its design,

functionality, variants, materials, packaging, specifications and storage conditions, that are likely to introduce new hazards, alter the likelihood, severity, or detectability of harm, or consequences that were not previously documented by the manufacturer in their risk analysis and therefore may impact compliance with the essential principles.

Flowchart 4 and Flowchart 5 detail specific questions and answers to assist applicants and manufacturers in determining if a change to product is considered to be substantial and requires notification to the TGA and submission of a "change to an existing certificate" application.

Changes to final product design specifications

For example, changes to:

- Magnetic resonance (MR) status of a device (i.e. change from MR unsafe to MR conditional)
- Addition of new variants outside the range previously approved by the TGA
- Mechanical, electrical, physical or biological properties of the finished device
- The indications for use of the device, including patient populations, anatomical locations, intended user or environment of use; and in addition for IVD medical devices – extension of recommended specimen types, or changes to stability of specimen types (e.g. environmental conditions, duration of storage, or living donor versus cadaveric specimens)
- The analytical and clinical performance characteristics for an IVD medical device as a result of a change in reagent formulation
- An IVD medical device for self-testing that may increase the risk of error in the use of the device, handling of the sample, or interpretation of results, or that may increase the complexity of use of the device for the user

Note: For the purpose of this document, the TGA considers "intended purpose" as being interchangeable with "intended use" and "indications for use".

Changes in materials for medical devices (excluding IVD medical devices)

For example, changes to:

- The materials or formulations used in the medical device, particularly when they may impact the biological safety or the mechanical performance of the finished product
- The species, origin, or source of animal or microbial origin materials in medical devices, or the viral inactivation process on material that is used as a component of a medical device
- The manufacturing process, quantity or type of medicinal substance incorporated in a medical device
- Materials during manufacturing that may result in new processing residues/degradants that impact the quality, safety and performance of the finished product
- Packaging that may impact the sterile integrity of the medical device

Changes to the manufacturer/supplier or manufacturing methods of the raw materials are considered changes to the manufacturer's QMS (see Section 4.1). These changes may impact the safety and performance of final products. Notification to the TGA is required.

Changes in materials for IVD medical devices

Changes in materials for IVD medical devices require an application for a change to an existing conformity assessment certificate to be submitted to the TGA. The extent of assessment or review by the TGA will depend on the materials changed and the possible impact on the performance characteristics of the IVD medical device. For example, a change to a generic reagent (e.g. buffer) requires notification, but is unlikely to require further assessment. However, for changes to active components such as capture antibodies, it is expected that extensive validation would be conducted by the manufacturer. Review by the TGA of the manufacturer's validation data would be required to ensure that the device remains compliant with the essential principles. Changes to reagent formulation, such as component concentration, are considered as changes to design specifications (see Section 2.2, sub-section Changes to design specifications).

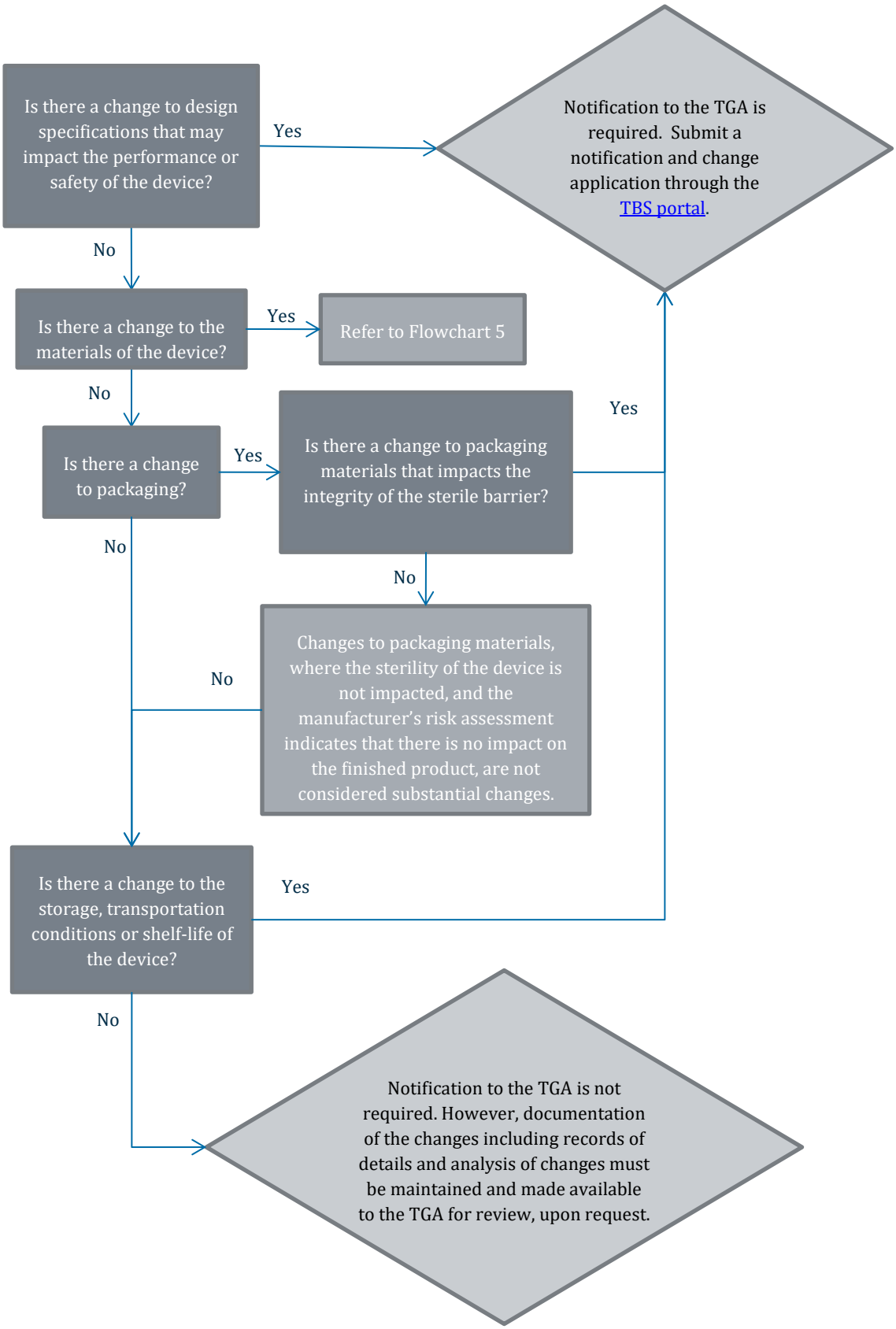
Changes in the supplier of reagent components identified in the conformity assessment certificate are considered changes to the manufacturer's QMS (see Section 4.1).

Changes in storage, shelf-life, and packaging for medical devices, including IVD medical devices

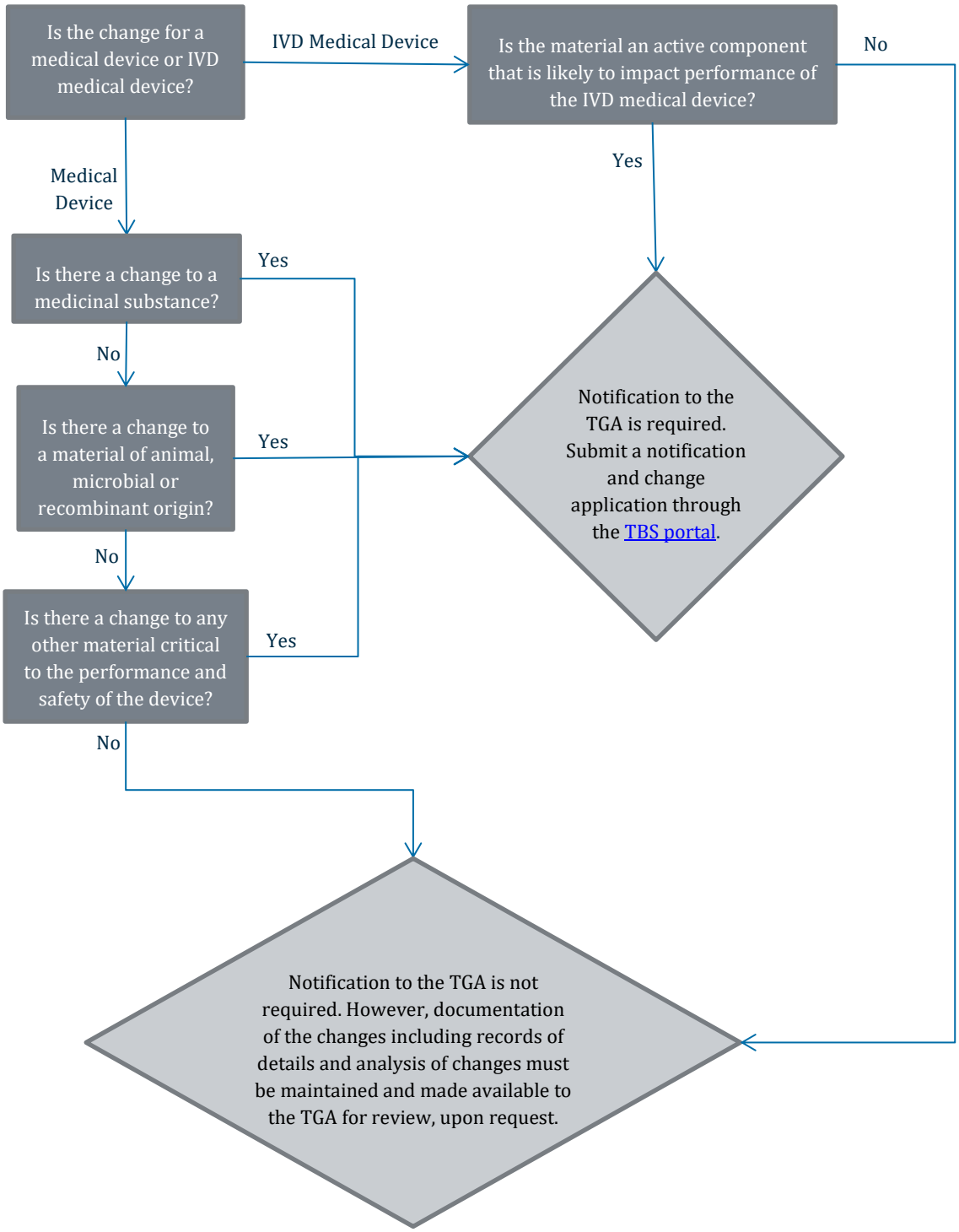
Changes that may impact the sterile barrier integrity of a device, or its performance after storage require are considered substantial and require notification to the TGA. For example, changes in:

- Primary packaging materials or configuration (e.g. from tray in tray, to pouch in pouch)
- Storage or transport conditions
- Shelf-life/stability claims

Flowchart 4: Changes to product design



Flowchart 5: Changes to product materials



4.3 Changes to the information to be provided with medical devices, including IVD medical devices

According to the Regulations, the intended purpose of a kind of medical device is ascertained from one or more of the following:

- Information provided with the device (labelling)

- Instructions for Use (IFU)
- Patient Information Cards and Patient Information Leaflets (PIC/PILs)
- Any advertising materials relating to the device
- Technical documentation describing the mechanism of action of the device

In addition, essential principle 13 requires some specific content to be included in the information provided with a device. This includes, among other things, the:

- Intended purpose and intended patient group for the device
- Conditions under which the device should be stored
- Warnings in relation to the use of the device

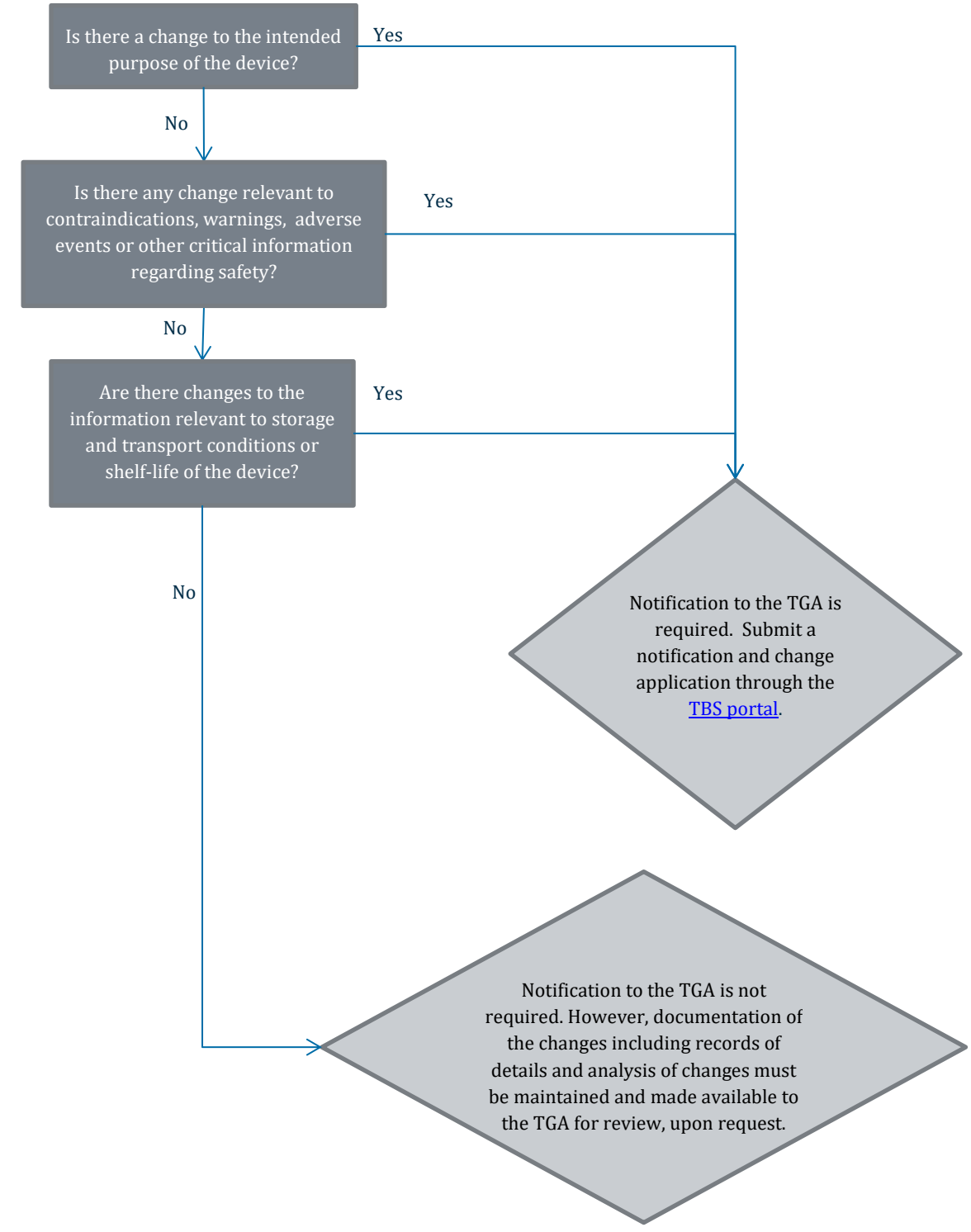
Therefore, some changes to labelling and the IFU may be considered substantial changes requiring notification to the TGA. Examples include (but are not limited to):

- Changing information regarding the safe use of the device
- A labelling change from single use to re-usable
- Adding a 'non-pyrogenic' claim on the labelling of a device
- Adding a new procedure for a use or purpose not originally assessed
- Changing the MR compatibility status of a device
- Changing the storage conditions that are considered critical for the performance of the device
- Changing the name of the device
- Changes to the IFU for extension or amendment of indications including use in a different patient population, or via a different surgical procedure,
- Amendment of instructions for use of the device

Note that for changes to the IFU that reduce indications or restrict patient populations, the requirement to notify the TGA is dependent on the potential risks associated with the change, the reasons for change and consideration to the impact of the change on the overall risk-benefit profile of the device.

Flowchart 6 details specific questions and answers to assist applicants and manufacturers in determining if a change to information to be provided with a medical device, including an IVD medical device is considered to be substantial and therefore requires submission of notification to the TGA prior to implementation.

Flowchart 6: Changes to information to be provided with a medical device, including an IVD medical device



Note: The IFU and labelling of a device can be an important part of mitigating the residual risk associated with the use of the device. If this information is changed on the existing labelling and IFU, for example to add or remove a contraindication, warning, or other important information about safe use of the device, then actions in accordance with the URPTG may be required for devices already in the field.

5. What is not considered a substantial change

The following categories of changes illustrate some types of changes that would **not be considered by the TGA as substantial**, and therefore do not require notification:

- Changes to non-critical parts or materials or suppliers that do not affect the final product's acceptance criteria established by the manufacturer
- Changes to manufacturing equipment or processes which have negligible impacts on the final product's safety and performance or are unlikely to increase the level of risk imposed to the user or patient
- Changes to the artwork, colour, font, or layout of the packaging and labelling of a device that does not alter compliance with essential principle 13
- Changes to manufacturing processes by suppliers identified in the conformity assessment certificate, including the processes performed by suppliers to those identified suppliers, unless the changes:
  - require validation/re-validation;
  - result in a change to the specifications of materials/components or final product;
  - result in a change to the process parameters; or
  - result in a change to the specification or acceptance criteria of in-process or end of process testing.

Although notification to the TGA is not required for the above changes, the Regulations require the manufacturer to ensure they continue to meet the requirements of their QMS for the handling of the change.

The manufacturer must maintain documentation of any changes as part of the QMS for traceability and recordkeeping purposes. Documentation of the changes must be available for review by the TGA upon request.

Examples of changes that do not require an application for a change to an existing certificate to be submitted to the TGA are provided in Appendix B.

6. Transfers of conformity assessment certificates

Transfers of a TGA issued conformity assessment certificate to a new person or body corporate as a result of certain events are **required to be notified to the TGA within 3 months** following the transfer, with the relevant supporting evidence.

Note: In addition to a name change, you must notify the TGA of **any other proposed substantial changes** in relation to a certificate transfer.

Ensure you notify the TGA in accordance with this guideline and implement the proposed substantial change(s) after the TGA's approval.

6.1 Events that trigger a transfer

Division 4.3 of the Regulations applies to a manufacturer of a medical device in respect of whom a conformity assessment certificate is issued, and includes provisions about when a conformity assessment certificate is taken to be transferred to a new person or to a body corporate.

The Regulations state that such transfers occur where the manufacturer:

- dies, becomes bankrupt, or is wound up;
- disposes of the business or amalgamates with another manufacturer; or
- changes its name.

The manufacturer ceases to exist, becomes bankrupt, or is wound up

Regulation 4.6 of the Regulations provides that in this case:

- the personal legal representative, trustee in bankruptcy or liquidator, as the case may be, is taken to be the person in respect of whom the certificate is issued (i.e. the new holder); and
- the new holder must notify the TGA of that event **within 3 months** of it occurring; and
- provide the TGA with sufficient documentary evidence of the relevant event (Regulation 4.10).

Disposal of business or amalgamation with another manufacturer

Regulation 4.7 of the Regulations provides that where the name of the manufacturer changes because either:

- the manufacturer agrees to dispose of a business concerned with the manufacture of the medical device and it is agreed that the disposal is to include the transfer of the relevant conformity assessment certificate; or
- the manufacturer, being a body corporate, amalgamates with another body corporate under a different name;

then

- the person to whom the business is disposed of, or body corporate with whom the manufacturer amalgamates is taken to be the person in respect of whom the certificate is issued (i.e. the new holder); and
- the new holder must apply for the name of the manufacturer to be changed on the conformity assessment certificate **within 3 months** of it occurring; and
- provide the TGA with sufficient documentary evidence of the relevant event (Regulation 4.10).

Manufacturer changes its name

Regulation 4.8 of the Regulations states that if the name of the manufacturer is changed, the manufacturer (as renamed) is taken to be the person in respect to whom the certificate was issued, and requires the manufacturer of the medical device to:

- notify the TGA **within 3 months** of a change of its name, and

- provide the TGA with sufficient documentary evidence of the relevant event (Regulation 4.10).

Examples of events that result in transfers that require notification to the TGA are provided in Appendix C.

6.2 When does the transfer actually take place?

The TGA does not make a determination as to when the transfer actually takes place. This is determined by the timing of the relevant event (e.g. the bankruptcy) as set out in Division 4.3 of the Regulations.

Once an event occurs, the new person or business is taken to be responsible for meeting the requirements related to the conformity assessment certificate, regardless of whether the TGA has:

- been notified of the transfer or change, or
- issued a new version of the conformity assessment certificate.

If a conformity assessment certificate is transferred because of the operation of Regulation 4.6, 4.7, or 4.8:

- the legal and regulatory responsibilities transfer to the new holder of the certificate; and
- the new holder can continue to produce the medical device(s) covered by the certificate while the certificate remains valid.

Manufacturers (and prospective new manufacturers) should seek their own advice about:

- the impact of Regulations 4.6, 4.7 and 4.8 on their status; and
- their obligations under the Act and its associated regulations when a conformity assessment certificate is transferred.

Note: If the TGA becomes aware that an event that triggers a certificate transfer has not been notified within 3 months of it occurring, the TGA may suspend or revoke the conformity assessment certificate related to the event.

7. Notification of substantial changes and transfers

7.1 For notification of a substantial change

Substantial changes must be notified and assessed by the TGA prior to supplying any products (kinds of devices) affected by those changes.

Substantial change notification and application is submitted via the TGA Business Services (TBS) portal. For guidance on how to do this, please go to: Application for conformity assessment certificates.

Note:

- On the first page of the TBS application form, under 'Applicant Type Details', ensure you select the option for ***"substantial change notification and application"***
- In the ***Applicant's reference*** field, ensure you include: *Change to conformity assessment certificate*.

What happens after you submit a notification?

Following the receipt of an effective application in relation to the substantial change, the TGA will contact the applicant or the manufacturer (or their representative) for additional information required to assess the change. Where it is determined that no further assessment is required no assessment fees will be charged; and a new certificate with the change history included will be issued.

Manufacturers should allow adequate lead time for the TGA to complete the assessment of the proposed changes prior to implementation. The assessment may require an on-site audit which will be incorporated into the TGA's audit programme and may not always be conducted prior to the approval of the change.

7.2 For notification of a certificate transfer

Notification of a conformity assessment certificate transfer is done via the TBS portal. For guidance on how to do this, please go to Application for conformity assessment certificates.

Regulation 4.10 states that if a person is required to notify the TGA of an event that results in transfer of conformity assessment certificates, the person must also provide the TGA with sufficient documentary evidence of the relevant event (e.g. evidence of amalgamation of a business, evidence of the bankruptcy of a manufacturer, etc.).

Transfers must be notified to the TGA **not later than 3 months after** the change has taken place.

Note:

- On the first page of the TBS application form, under 'Application Type Details', ensure you select the option for "***Initial application"***
- In the **Applicant's reference** field, ensure you include: *Transfer of conformity assessment certificate*.
- Please complete and include the Transfer of conformity assessment certificates form as part of your supporting evidence.

Appendix A: Examples of substantial changes

Please note that the examples are not all-inclusive and may not be applicable in all cases[3].

Quality Management System – Medical Devices, including IVD Medical Devices

1. The manufacturer intends to change the source of raw material used in a medical device, from porcine origin to bovine origin. This may impact the quality, performance or specifications of the finished medical device. Data to support the appropriate verification and validation of processes for viral inactivation or minimisation needs to be assessed. This is considered a substantial change.

2. The manufacturer of a tissue heart valve decides to add an alternate abattoir for the supply of bovine pericardium to avoid any potential shortages of the current supplier with no changes to the existing viral inactivation processes that is undertaken by the manufacturer. This is considered a substantial change. Evidence of the manufacturer's supplier control for the addition of the new abattoir, verification of bioburden results for the tissue sourced from the new abattoir, along with risk management review is required for assessment by the TGA.

3. The manufacturer of a medical device changes the sterilisation process cycle parameters such as process temperature or load size, with no changes to any other aspects of the device. This is considered a substantial change, as the change may affect the quality and safety of the finished product.

4. The manufacturer decides to change the sterilisation method for a medical device from gamma irradiation to ethylene oxide (EO) without changing any other aspects of the device. Assessment of the manufacturer's sterilisation validation is required to ensure the minimum sterility assurance level (SAL) is achieved, and that EO residuals remaining on the medical device are below minimum accepted levels. Therefore, this is considered a substantial change.

5. The manufacturer of a drug-eluting stent changes the supplier that provides the medicinal substance incorporated in the medical device. This is considered a substantial change. The manufacturer is required to provide evidence (such as Letter of Access for an existing Drug Master File and/or Certificate of Suitability) to support the quality and safety of the medicinal substance incorporated in the device, as well as documentation to support the manufacturer's control over the new supplier.

6. The manufacturer intends to change the sodium hyaluronate raw material specification to accommodate changes proposed by the raw material supplier. Validation test results have shown there is an impact on the quality, performance, and specification of the finished medical device. This is considered a substantial change.

7. A manufacturer intends to add a production line for a new group of IVD medical devices that use nucleic acid technology (NAT) to detect infectious disease markers, whereas previously they have only been certified to produce immunoassay kits for detecting the same infectious markers. Even though the new NAT assays are the same 'kind of device' as the immunoassay kits that were previously assessed by the TGA, this is a substantial change to the manufacturing process.

[3] Some of the examples below have been modified from the U.S. Food and Drug Administration's guidance: *Deciding When to Submit a 510(k) for a Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff* (October 2017).

8. The manufacturer decides to transfer the manufacturing of drug-coated stents from an existing facility to a new manufacturing facility as an alternate measure to prevent loss of critical processes. This is considered a substantial change. Assessment of the manufacturer's equipment and process qualification as well as transfer validation evidence is required to determine that the process transfer results in no impact to the quality, safety and performance of the finished medical device.

Product design – Medical Devices (excluding IVD medical devices)

9. The IFU for a pacemaker lead states that the medical device is safe for conditional use within MR-environments of up to 1.5T. The manufacturer performed additional testing on the device and test results have shown that the device can be conditionally used within MR-environments of up to 3T. The manufacturer would like to change the IFU to reflect this new information. Given that exposure of an implanted medical device to higher magnetic field strengths is likely to introduce new risks for the patient, this is considered a substantial change.

10. The allowable upper storage temperature for a medical device has been increased due to new stability data becoming available. No other changes have been made to the device. This may affect device performance and is therefore considered a substantial change.

11. Due to real-time aging data becoming available (or further accelerated-aging testing), the manufacturer of a drug-coated stent intends to extend the claimed product shelf-life from 12 months to 24 months. This is a substantial change to the packaging and shelf life of the medical device.

12. The manufacturer of a coronary stent includes a new stent that has a larger diameter than the existing family of coronary stents. The stent diameter is outside the range of the previously approved variants for the stents. As the larger diameter could significantly affect device related safety and performance, this is considered a substantial change.

13. The manufacturer of a coronary stent increases the thickness of the wire in the stent to reduce the potential for stent fracture. The thickness is important to the performance of the stent and could affect the safety or efficacy of the device. Therefore, this is considered a substantial change.

14. The manufacturer of a hemi-arthroplasty femoral stem/head changes the taper/bore angle of the device. This change is likely to affect the biomechanics of the joint replacement device and hence the performance of the device. Therefore, this is considered a substantial change.

15. The manufacturer of a biological surgical repair mesh intends to add an additional manufacturing stage to provide surgeons with pre-cut meshes. This cutting work is currently being performed by surgeons in theatre during operations. This design change involves adding a manufacturing process that has not been previously assessed. Therefore, this is considered a substantial change.

16. The manufacturer of a medical device intends to implement design changes that are driven by recent changes in the standards that were originally used to demonstrate compliance, or due to recent post-market data becoming available. Such changes are likely to affect the device quality, safety and performance. Therefore, this is considered a substantial change.

17. During research and development processes, the manufacturer of an approved active implantable medical device has found new software algorithms (except for that only affecting the graphical user-interface of the device) that improve the devices' function and usability. This change requires new design validation and verification and is therefore considered a substantial change.

18. Using previously approved manufacturing processes, the manufacturer of an intraocular lens (IOL) has made changes in the haptic geometry of the IOL and a change to the endotoxin specification limits (i.e. <0.2 Endotoxin Units per device) as recommended in the Medical Device Standards Order (Endotoxin Requirements for Medical Devices) 2018. However, the optical performance specifications of the device have not changed. The changes related to haptic geometry are likely to affect the device performance and interaction with internal tissues whilst changes to endotoxin limits impact the final product specification. This is considered a substantial change.

19. The manufacturer of a balloon catheter changes the material of the polymer tubing used to manufacture the catheter from polymer A to polymer B and the manufacturer has not previously used polymer B (even if there were other similar devices on the market that use polymer B). The manufacturer would have no knowledge of the formulation or manufacturing processes of polymer B tubing in the competitors' devices and would be required to assess the biocompatibility and performance of polymer B tubing in its own catheter. This is considered a substantial change. However, if the manufacturer has used polymer B tubing, with the same formulation and processing, in another previously approved catheter with the same type and duration of body contact and the same performance specifications then it may be acceptable to document the change to the QMS and update the technical file only. The updated technical files may be assessed/verified by the TGA during a subsequent on-site audit.

20. The manufacturer of a catheter system decides to change the materials of the guide wire that is supplied with the system. As the guide wire would be in direct contact with the circulatory system, the change in material is likely to affect the biocompatibility of the medical device; and, the quality and safety of the new materials requires assessment and any impact on performance should be considered. This is considered a substantial change.

Product design – IVD Medical Devices

21. A manufacturer changes the design of an IVD medical device for detecting human immunodeficiency virus types 1 & 2 (HIV 1 & 2) to meet less stringent performance specifications. The change affects both sensitivity and specificity. Although the change does not alter how the device is used, or require labelling changes, it does alter the performance characteristics of the assay when compared to those established under previous clinical performance studies. This is considered a substantial change.

22. A change in the IFU for a Class 4 IVD medical device, to include a new anticoagulant for plasma samples that are to be tested using the device, or any other new sample type not previously assessed is considered a substantial change.

23. An IVD medical device manufacturer makes a material change to a reagent (for example, changing a monoclonal antibody used in an ELISA kit, or the RNA primers included in a NAT assay) and the risk assessment shows that this could result in a change to the performance of the device outside the performance changes already approved by the TGA. This change has the potential to affect clinical decision making and is therefore considered a substantial change.

    Note that if the manufacturer conducts verification studies to determine the impact of the change on the performance of the IVD medical device, submission for a change is required so that the TGA can assess the verification conducted. This applies whether or not the verification studies demonstrate changes in performance for the IVD medical device.

24. A manufacturer has previously conducted stability validation studies for a new IVD medical device by periodically testing kits selected from three production lots that have been stored under recommended storage conditions for a period of 13 months. The manufacturer has generated sufficient data to demonstrate that performance remains consistent throughout

the specified storage period and approval was granted to the manufacturer to assign a 12-month shelf life to the kits.

The manufacturer continued to monitor the ongoing stability studies for a further period of 6 months as outlined in the existing stability protocol, and sufficient real time stability data generated over the cumulative storage period of 19 months under the recommended storage conditions is available. The results continue to meet the assigned acceptance criteria throughout the storage period, therefore the manufacturer may assign a longer shelf life of 18 months based on the extension of testing under the existing stability protocol. As part of the ongoing stability monitoring program, the manufacturer should periodically monitor the performance of the product at the end of the assigned shelf-life to ensure routine production batches continue to meet the required specifications. The extension of shelf-life is considered a substantial change.

However, if there were no changes to the protocol or the assigned acceptance criteria, the TGA may determine that no further assessment is required. In this case, no assessment fees will be charged, and a new certificate with the changes reflected in the certificate history will be issued.

Information to be provided with medical devices, including IVD medical devices

25. The IFU of a medicated balloon catheter are updated to provide instructions on how to access different vessel types that were not previously addressed in the labelling or IFU. This would change the intended use of the medical device and the techniques used during the procedure and is therefore considered a substantial change.

26. The manufacturer removes a contraindication for a medical device in the IFU, without making any changes to the device. This change effectively broadens the indications for the device and is considered a substantial change. This is also the case if a manufacturer adds a new (previously unapproved) indication to the IFU.

27. The manufacturer removes a precaution and/or warning previously stated for the medical device, or IVD medical device, in the IFU, without making any changes to the device. This change impacts the mitigation of risk and is considered a substantial change.

28. A change in labelling and/or IFU of the medical device to add a statement that the device is non-pyrogenic or endotoxin free is considered a substantial change.

29. The manufacturer decides to change the Unique Product Identifier (UPI) of the medical device, or IVD medical device, with no other changes to the device, which will result in changes to the device labelling and IFU. This is considered a substantial change.

30. After clinical investigations, the manufacturer of a dermal filler decides to add recommendations for use of a certain type of cannula in their IFU as part of the surgical procedure. The manufacturer clarifies that this cannula will not be packaged together with the product. However, this change is likely to be substantial since the new operation procedure or technique will involve specific training and verification.

31. The manufacturer decides to change the form of the IFU supplied with the device intended for professional use from paper format to electronic or online format. As this change impacts the mitigation of risk for the implementation of electronic IFUs, including consideration for any potential impact of the changes on sterilisation processes if the device is supplied sterile, this is considered a substantial change.

Appendix B: Examples of changes that do not require an application for a change to be submitted to the TGA

Please note that the examples are not all-inclusive and may not be applicable in all cases[4].

1. The manufacturer changes the supplier of the polyethylene packaging for their sterile medical devices; the packaging configuration and specifications remain the same. The manufacturer uses the same packaging integrity test protocols as that previously approved and an analysis shows the new packaging has no impurities that could affect the devices' biocompatibility. This is not likely to require notification to the TGA. However, it is still a requirement of the Regulations that after any change the manufacturer must ensure its devices continue to meet the requirements of their QMS and the essential principles. Documentation of the change would be required and may be followed up for review at a subsequent TGA QMS audit. The Technical file for the product should also be updated.

2. The manufacturer decides to add certified foreign language translations of the labelling and IFU for use in other regulatory jurisdictions, while no change is to be made to the content of the approved product labelling. Since this change is unlikely to introduce new risks associated with the use of the medical device, or IVD medical device, notification to the TGA would not be necessary, but the change should be recorded in the QMS documentation.

3. The manufacturer of a range of coronary stents intends to begin manufacturing a new stent with a different diameter to those already approved for that stent range. The new stent diameter falls within the previously approved variant range and there are no other changes (i.e. to length of stent). The manufacturer has determined that the additional stent diameter does not represent the worst-case for any physical parameters that require testing, and the risk assessment for the change indicates there are no new risks being introduced with the additional size variant and therefore it has no impact on the safety or performance of the device. This is not considered a substantial change, however, the product technical file is required to be updated, and made available upon request.

   Note, the manufacturer would be required to submit a Device Change Request application to the TGA, to update the Australian Register of Therapeutic Goods (ARTG) certificate so that it accurately reflects the number of variants supplied in Australia for that kind of medical device.

4. The manufacturer of a hip joint implant intends to reduce the manufacturing tolerances allowable during production, enabling them to manufacture the medical devices closer to their design specifications without introducing new design features. Since the tightening of acceptance criteria is not expected to introduce any new risks, the change is not likely to be considered a substantial change. However, it is still a requirement of the Regulations that for any change, the manufacturer must ensure the device continues to meet the essential principles. Documentation of the change would be required and may be followed up for review at a subsequent TGA QMS Inspection. The Technical file for the product should also be updated.

5. A manufacturer extends the shelf life of a Class IIa non-sterile medical device (covered by a TGA Schedule 3, Part 1 certificate). The extension of shelf-life is carried out under the manufacturer's QMS procedures for change control. This change does not require notification to the TGA. However, it is still a requirement of the Regulations that for any

[4] Some of the examples below have been modified from the U.S. Food and Drug Administration's guidance: *Deciding When to Submit a 510(k) for a Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff* (October 2017).

change, the manufacturer must ensure the device continues to meet the essential principles. Documentation of the change would be required and may be followed up for review at a subsequent TGA QMS Inspection. The Technical file for the product should also be updated.

6. A manufacturer intends to make a change to a generic reagent (e.g. buffer) included in the formulation of an IVD medical device as a result of a change in supplier. The raw material specifications for the replacement reagent are identical to the previous reagent. Results of the risk analysis and the validation and verification studies conducted by the manufacturer indicate that there is no impact on performance and therefore no new safety or performance concerns. The manufacturer should document the changes and relevant tests in the QMS and the technical file for the product should be updated.
7. The manufacturer of an IVD medical device has updated the information supplied with a device to include a new limitation relating to the performance of the device when used on patients who have been treated with a new medicine which could interfere with the result. The medicine does not affect the indications for use for the device, nor significantly affect the risk profile. The manufacturer should document the change in the QMS and the technical file for the product should be updated.
8. The manufacturer rebrands or renames a Class 2 or 3 IVD medical device covered under a device category listed on the manufacturer's TGA Schedule 3, Part 1 conformity assessment certificate. The change is required to be documented under the manufacturer's QMS. However, an application for a change to an existing certificate is not required to be submitted unless there are additional changes to the device that impact the intended use or intended user of the device.
9. The manufacturer rebrands a Class 4 IVD medical device, resulting in a change to the UPI. This change requires notification to the TGA. However, this application would not require further assessment, and a new certificate (with the updated UPI included) would be issued.

Appendix C: Examples of certificate transfers

Examples below illustrate some events that would be considered to trigger the transfer of a TGA issued conformity assessment certificate.

1. A manufacturer holds a TGA issued Conformity Assessment Certificate for the manufacture of several Class 4 IVD medical devices. The company also manufactures a range of lower class IVD medical devices. The manufacturer decides to separate the Class 4 IVD medical devices from the rest of the business through sale of the lower class IVD medical devices to another company. The Class 4 IVD medical device manufacturer retains the same QMS but changes its name. In such a case, Regulation 4.8 would require the manufacturer to notify the TGA about the change of name within 3 months.

2. A corporation has multiple divisions, some medical device (or IVD medical device) and some pharmaceutical. Each division maintains its own QMS. The corporation decides to separate the pharmaceutical and device businesses into two separate entities. The pharmaceutical business is to retain the current business name and registration. The device businesses are to change name and register as new business entities. The device businesses hold TGA Conformity Assessment Certificates for the manufacture of the devices. The certificates are transferred to the new entity. In such a case, Regulation 4.7 would require the new business to apply to the TGA for the name of the manufacturer to be changed on the conformity assessment certificate within 3 months.

3. A manufacturer holds a TGA issued Conformity Assessment Certificate and amalgamates with another corporation that manufactures medical devices (or IVD medical devices) that do not require a TGA issued Conformity Certificate for supply in Australia. The new entity (business) takes on a new name but retains all the current manufacturing sites of the two

prior corporations. The TGA issued Conformity Assessment Certificate is transferred to the new entity, but the scope of the certificate does not increase to cover the devices at the second site. In such a case, Regulation 4.7 would require the new business to apply to the TGA for the name of the manufacturer to be changed on the conformity assessment certificate within 3 months.

4. A manufacturer holds a TGA issued Conformity Assessment Certificate and declares bankruptcy. The Trustee in bankruptcy becomes the legal manufacturer of the medical devices (or IVD medical devices). In such a case, Regulation 4.6 would require the trustee to inform the TGA of the event within 3 months.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Branch	29/06/2017
V2.0	Updated to reflect current policies and procedures	Medical Devices Branch	

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Reference/Publication #