Medical device production and software development at point-of-care: Achieving regulatory conformity (in a shifting landscape)

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ENGINEERING + PHYSICAL SCIENCES IN MEDICINE
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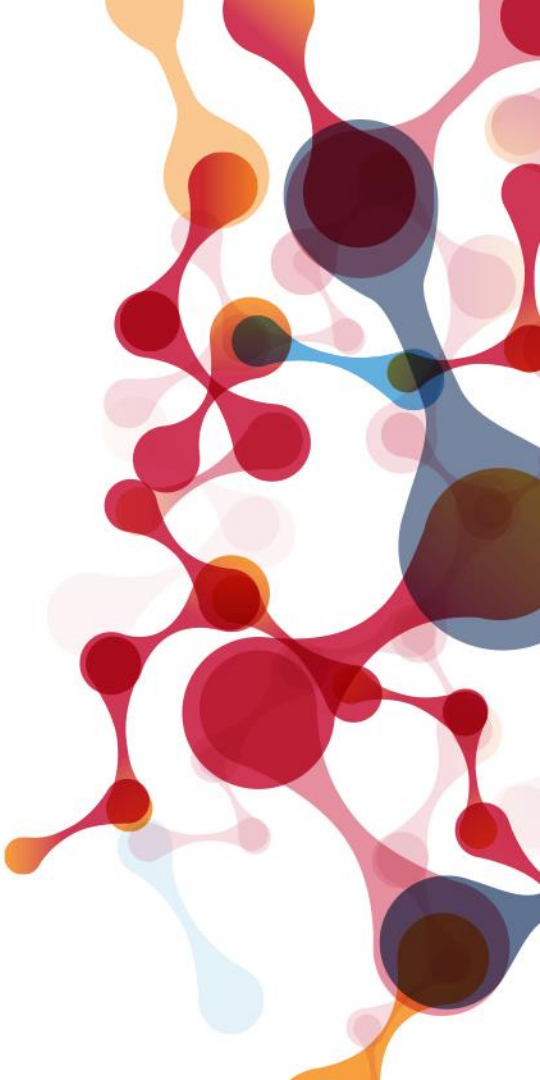
Disclosure

The presenter has advised that the following presentation is subject to **no** conflicts of interest and has **nothing** to disclose.

Some aspects of this work have been presented previously at ACPSEM Queensland Branch events.



Metro North Hospital and Health Service

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Disclaimer

The following advice has been developed via review of legislation, regulations, standards, and TGA advice; and discussions with the TGA, ANDHealth and many colleagues with varied experiences in device regulation, across the organisations where I work, and across the ACPSEM membership.

Disclaimer

This presentation is not intended to be a substitute for formal advice or a device assessment.

It should not be relied upon as such.

Regulations may change. You need to establish **yourself** whether your device or software is subject to regulations, and you need to monitor the regulations.

Image courtesy of DALL·E

Regulations

Why this topic?

Medical physicists manufacture devices and develop software. Frequently they do this with appropriate consideration of risk, and mitigate these risks through quality control and acceptance testing.

However they aren't necessarily well versed with formal quality management or clinical governance (except radiation management plans). This space is an opportunity for mid-career learning.

Regulations

In the lead up to the 2021 changes in regulation surround patient-matched devices, my department (and broader organisation) wanted to ensure that it was compliant with regulations,. This resulted in collaboration between medical physicists, radiation therapists, biomedical engineers, and safety and quality staff.

Since then, I've frequently been asked to discuss our 3D printing program and management of TGA requirements.

Hence this presentation!

Regulations

The term "medical device" can include any

- instrument, apparatus, software, material, …
- intended to be used on a human for diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease.
- *and* any accessory to a medical device.

Medical devices are regulated by the Australian Therapeutic Goods Association (TGA) and MEDSAFE in New Zealand.

In Australia, failure to comply with the *Therapeutic Goods (Medical Devices) Regulations 2002* is an offense under the *Therapeutic Goods Act 1989*.

Therapeutic Goods Act 1989

41BD What is a *medical device*

(1) A ***medical device*** is:

(a) any instrument, apparatus, appliance, software, implant, reagent, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

(i) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;

(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;

(iii) investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;

(iv) control or support of conception;

(v) in vitro examination of a specimen derived from the human body for a specific medical purpose;

and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or

(aa) any instrument, apparatus, appliance, software, implant, reagent, material or other article specified under subsection (2A); or

(ab) any instrument, apparatus, appliance, software, implant, reagent, material or other article that is included in a class of instruments, apparatus, appliances, software, implants, reagents, materials or other articles specified under subsection (2B); or

(b) an accessory to an instrument, apparatus, appliance, software, implant, reagent, material or other article covered by paragraph (a), (aa) or (ab); or

(c) a system or procedure pack.

Regulations

Supply of a medical device without meeting regulatory requirements is an offense.

The clinical use of a device manufactured or developed in-house, or at point-of-care, constitutes supply.

The barriers to point-of-care manufacturing and development are lower than ever, thanks well developed and often open-source software libraries, 3D printers and easy-to-use design tools, and online guidance.

Some of you are manufacturing and supplying medical devices. If you are, you have regulatory responsibilities.

Therapeutic Goods Act 1989

supply includes:

(a) supply by way of sale, exchange, gift, lease, loan, hire or hire-purchase; and

(b) supply, whether free of charge or otherwise, by way of sample or advertisement; and

(c) supply, whether free of charge or otherwise, in the course of testing the safety or efficacy of therapeutic goods in persons; and

(d) supply by way of administration to, or application in the treatment of, a person.

Importing & supplying medical devices: Information for health professionals

What are the penalties associated with importing and supplying medical devices that do not meet regulatory requirements?

Sponsors and health professionals who do not comply with the import and supply regulations for medical devices could face civil or criminal penalties of up to five years imprisonment and/or 5000 penalty units (one penalty unit is currently valued at $170 under the *Crimes Act 1914*).

Offences include:

- supplying therapeutic goods not included on the ARTG
- importing and/or supplying medical devices that do not meet the essential principles
- failing to apply conformity assessment procedures (for more information see the Australian regulatory guidelines for medical devices)
- misrepresenting medical devices
- failing to report adverse events.

Regulations

Some definitions:

Sponsor: Person who imports or manufactures the device for supply in Australia. Responsible for ensuring regulatory requirements are met, ongoing obligations.

Manufacturer: Person responsible for design, production, packaging, etc.

Excluded: Not regulated, because it is not a medical device, or is specifically excluded under an excluded goods order (e.g. spectacle frames, wellness apps).

Exempted: Regulated, but exempted from some regulatory requirement (e.g. ARTG inclusion).

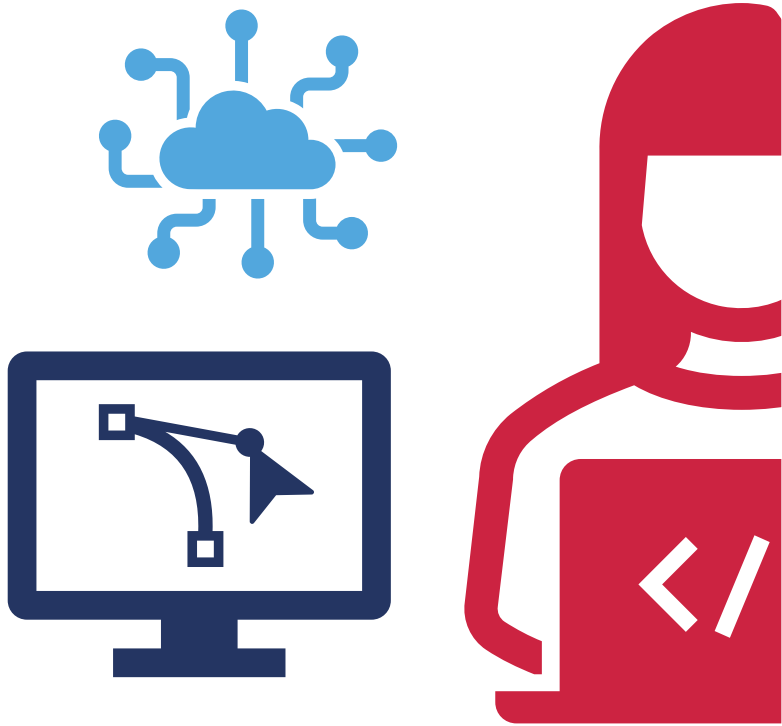
Regulations

The definition of medical device is broad. If it

1. has an intended medical purpose, and
2. does not meet any exclusion criteria defined in an excluded goods order,

it is regulated as a medical device.

This definition includes **many** devices and software that are manufactured or developed within the clinic.



Regulations

There are many excluded goods, ranging from spectacle frames and wellness apps.

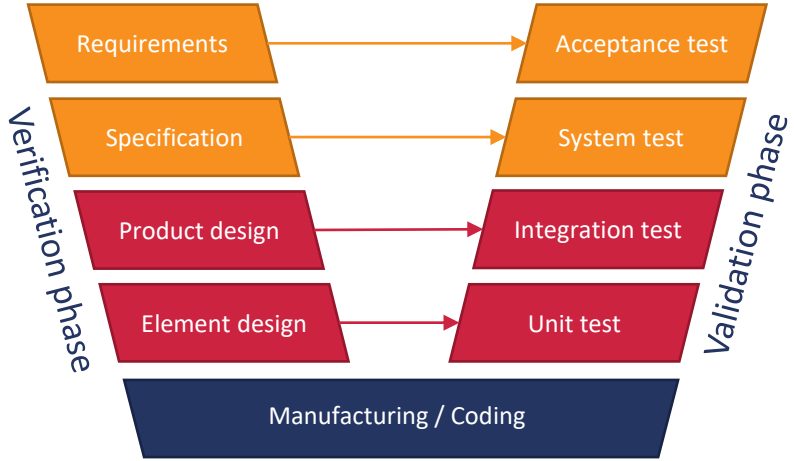
Of relevance to medical physicists, excluded devices may include software that

- facilitates storage and transmission of patient information or images
- that displays simple calculations performed using published data that can be validated,
- facilitates population-based data analytics.

Regulations

A component or element of a medical device, not available independently (e.g. as an accessory) is regulated as part of the parent device. That includes software that controls another device (**software in a medical device**), materials, and libraries.

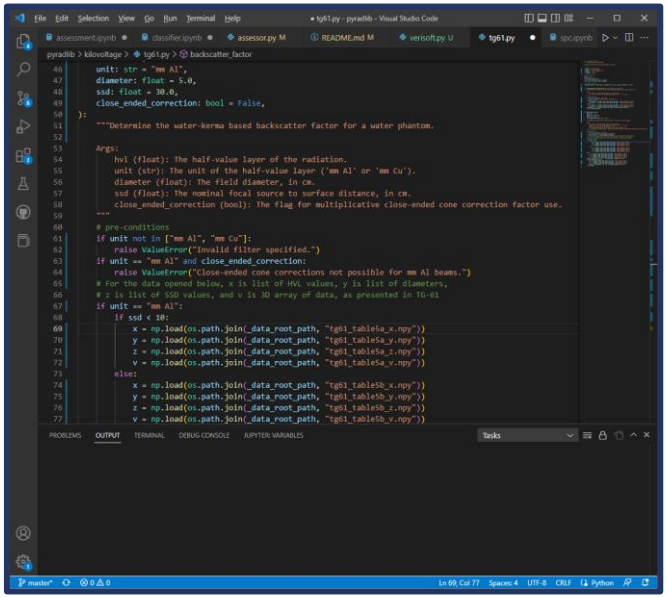
If you use open source software, or software of unknown provenance, within a device you supply, you are responsible for ensuring that the completed device you supply is safe and meets applicable requirements, which will require testing of those elements and validation of integration in your completed device.



Regulations

The development and use of scripts, macros, templates, database queries (all of which might satisfy the definition of software) within an existing medical device might be considered as an intended use of the parent device so long as:

1. These do not extend functionality of the device beyond the manufacturers **intended** purpose (e.g. what is described in user manuals or marketing copy, or otherwise detailed by the vendor themselves).
2. These do not increase the risks associated with the use of the device (e.g. by removing health professional judgment).



Requirements

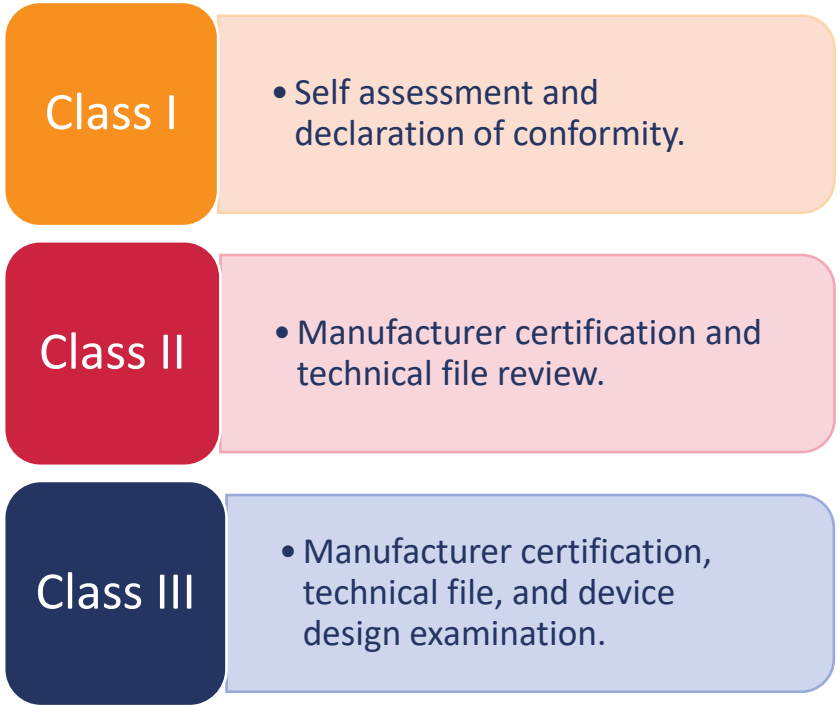
If the device has an intended medical purpose and is not excluded, it is subject to regulations, including but not limited to:

1. Compliance with essential principles for a medical device, including safety, performance and application of relevant standards.
2. Quality management processes to ensure ongoing compliance with essential principles.
3. Inclusion on the Australian Register of Therapeutic Goods, unless exempted.
4. Reporting of adverse events, annual reports, potential issue of recalls and hazard alerts as required.

Requirements

These requirements vary slightly with risk classification, which depends on:

- Risk to individuals (death, serious disease or condition, harm, etc.) or public health.
- The intended purpose of the device.
- The risk classification of any other device that the device is designed to interface with, drive or otherwise influence.



Requirements

Inclusion on the ARTG requires the supply of evidence that the safety and quality of your device is ensured, i.e. that a system for quality management ensures conformity with essential principles; in addition to a small fee.

The requirement for inclusion on the ARTG is waived for exempted devices, including some clinical decision support software and custom-made devices.

Exemption does not mean the device is not regulated. You still need to provide notification.

Requirements

Custom-made devices?

- for sole use of a specific patient or health professional,
- manufactured accordance to written request of health professional, which must specify the design of the device,
- supplied in low quantities, such that evidence of performance cannot be feasibly collected,
- do not meet the definition of patient-specific or adaptable medical device.

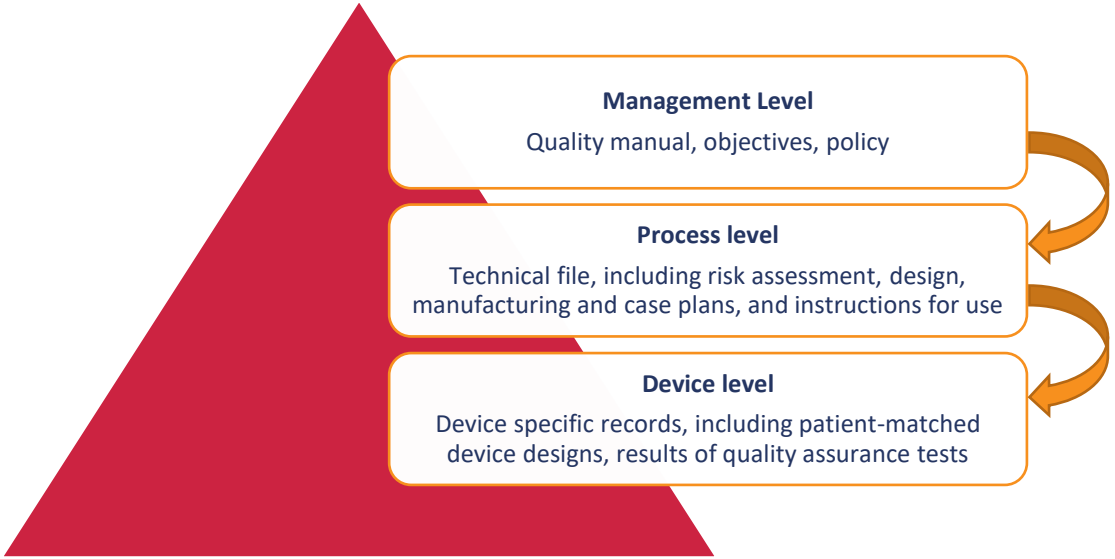
Clinical decision support software?

- intended to provide or support a recommendation to a health professional about preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury
- not intended to directly process or analyse a medical image or signal from another medical device; and
- not intended to replace the clinical judgement of a health professional in relation to making a clinical diagnosis or decision about the treatment of patients

Management

Ensuring conformity with essential principles is a matter of quality management.

Can categorise requirements for quality management at three levels:



Management and process levels describe how subsequent levels are managed.

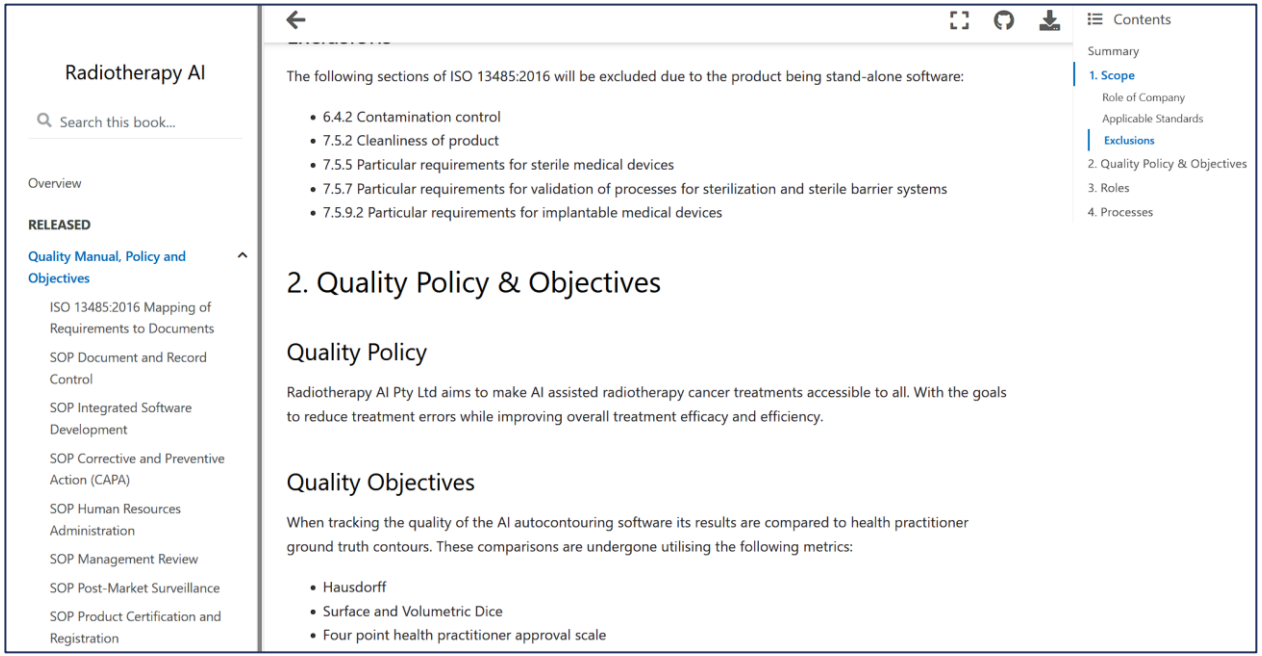
Management

Quality manuals describe high level management.

- What are the objectives? What is needed to achieve those? How are those efforts supported? How is all of this communicated? Whose signature is on this?
- For any given process, who is responsible, accountable, consulted, and kept informed? How are those roles allocated? Is there training or credentialing?
- For any type of device what documentation shall exist? Where will that be kept? How is access controlled? How are revisions managed?
- How do you identify risks, and how do you develop controls or testing to reduce or mitigate those risks? How are tolerances defined?
- How do you manage unintended or non-conforming devices? How do you monitor the quality management system, and improve it?

Management

Physicist Simon Biggs has shared a quality manual at https://docs.radiotherapy.ai/



Management

This might seem like a lot, but the template exists: ISO 13485. And these are themes you might already be familiar with:

Theme	ISO 9001:2015 Quality management systems	NSQHS clinical governance standard	ARPANSA C-5 radiation management plan	ISO 13485:2016 Medical device – QMS
Context and background	Sections 1-4	-	Section A.1.a	Sections 1-4
Leadership and roles	Section 5	Actions 1.01-1.06, 1.25-1.26	Section A.1.i, A.2.a	Sections 5.1-5.3, 5.5
Planning and risks	Section 6	Actions 1.10, 1.15	Section A.2.b	Sections 5.4
Support and resources	Section 7	Actions 1.16-1.24, 1.29-1.33	Sections A.1.i-k, A.1.n-o, A.2.b	Section 6
Operations and controls	Section 8	Actions 1.07, 1.27-1.28	Sections A.1.b-h, A.1.l	Section 7
Performance evaluation	Section 9	Actions 1.08-1.09, 1.13-1.14	Sections A.1.l, A.1.n-o	Sections 5.6, 8.1-8.2, 8.4
Quality improvement	Section 10	Actions 1.09, 1.11-1.12	Section A.1.m	Sections 8.3, 8.5

Management

The other levels are very well established medical physics practices: risk assessments, work instructions, operating procedures, etc.

The technical file for a type of device will include:

- Descriptions of the type of device, its requirements, how it is designed, manufactured (including materials or tools used), and tested (including tolerances).
- Instructions for use (including cleaning, disposal, storage, etc.)
- The process for reporting and recording issues with the device.
- What is recorded for each device (including request, design, QA results, etc.)

Most important is the **risk assessment**. It allows completion of the essential principles checklist. It informs what goes in the above documents.

E.g. The instructions for use should be written to reduce risk of incorrect use. QA/QC is designed to ensure device meets requirements for safety and quality.

[i] not relating to software as a medical device

Management

The essential principles assessed during risk management include:

General requirements

1. Use of medical devices not to compromise health and safety
2. Design and construction of medical devices to conform with safety principles
3. Medical devices to be suitable for intended purpose
4. Long-term safety
5. Medical devices not to be adversely affected by transport or storage
6. Benefits of medical devices to outweigh any undesirable effects

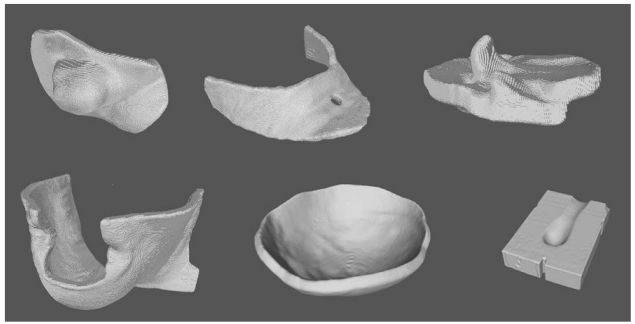
Design and construction principles

7. Chemical, physical, biological properties[i]
8. Infection and microbial contamination[i]
9. Construction and environmental properties
10. Medical devices with a measuring function
11. Protection against radiation[i]
12. Medical devices connected to or equipped with an energy source[i]
13. Information supplied by manufacturer (including patient information, and software version and build numbers)
14. Clinical evidence
15. Principles relating to in vitro diagnostics[i]

Bolus example

To illustrate what these things look like, lets look at process documents for a simple Class 1 device: radiotherapy bolus.

We had this included as a patient-matched device in the ARTG in Feb 2021. Previously we had provided TGA notification of printed bolus as a custom-made device.



Australian Government
Department of Health
Therapeutic Goods Administration

Public Summary

Summary for ARTG Entry:	355606	Queensland Health - Metro North Hospital and Health Service - Radiation therapy bolus, reusable
ARTG entry for	Medical Device Included Class 1	
Sponsor	Queensland Health - Metro North Hospital and Health Service	
Postal Address	Post Office Royal Brisbane and Women's Hospital, Herston, QLD, 4029 Australia	
ARTG Start Date	25/02/2021	
Product Category	Medical Device Class 1	
Status	Active	
Approval Area	Medical Devices	

Conditions

- The inclusion of the kind of device in the ARTG is subject to compliance with all conditions placed or imposed on the ARTG entry. Refer Part 4-5, Division 2 (Conditions) of the Therapeutic Goods Act 1989 and Part 5, Division 5.2 (Conditions) of the Therapeutic Goods (Medical Devices) Regulations 2002 for relevant information.
- Breaching conditions of the inclusion related to the device of the kind may lead to suspension or cancellation of the ARTG entry; may be a criminal offence; and civil penalties may apply.

Manufacturers

Name	Address
Metro North Hospital and Health Service T/A Royal Brisbane & Womens Hospital	Levels 1 2 & 3 Ned Hanlon Building Butterfield Street Herston, QLD, 4029 Australia

Products

1 . Radiation therapy bolus, reusable

Product Type	Single Device Product	**Effective Date**	25/02/2021
GMDN	58022 Radiation therapy bolus, reusable		
Intended Purpose	The Patient Matched Radiotherapy Bolus is a radiation attenuating material used during a radiotherapy treatment to perturb the radiation beam, such that the distribution of dose within the patient is improved. Specifically, this can mean providing an increased dose at the patient skin, e.g. for a superficial tumour, or decreasing the range of dose deposition, to spare normal tissue located "downstream" from the target volume. Historically a bolus has been produced with near-water-equivalent material prepared by treatment centre staff (e.g. wet gauze, wax, gels, thermoplastics), or using non-patient-matched sheet bolus. The Patient Matched Radiotherapy Bolus will be manufactured via 3D printing using 3D images of the patient, to improve conformity with patient topography and achieve the precise shift of dose distribution desired by the patient.		

Specific Conditions

No Specific Conditions included on Record

Public Summary

Bolus example

Supporting this submission for inclusion were 10 documents (though it wasn't strictly necessary to provide them all with the submission, they would need to be provided if the TGA requested them).

1. Declaration of conformity 1 page
2. Essential principles checklist
3. Hazard and risk assessment 4 pages
4. Design plan 11 pages
5. Manufacturing plan 7 pages
6. Quality and packaging plan 3 pages
7. Case plan 2 pages
8. Case summary 2 page
9. Instructions for use 1 page
10. Post-market surveillance plan 2 pages

This wasn't optimised for length – the templates developed as part of the broader quality management work were designed to support models of supply other than the design, fabrication and clinical use of bolus within one department.

Bolus example

1. Declaration of conformity

Just a letter declaring conformity under TGA (Medical Devices) Regulations 2002. The letter included manufacturer's name and address, device name, classification, GMDN code and scope of application.

2. Essential principles checklist

Template provided by the TGA was used. This document was effectively a reformatted version of our own risk assessment. There were many requirements that were not applicable (e.g. bolus does not produce heat). Where requirements were applicable, the standards applied (frequently local standards) and the evidence of compliance were directly referenced. E.g.

> "The design is checked by a medical professional (refer to Case Plan)."
>
> "Geometry confirmed via measurement".

Bolus example

3. Hazard and risk assessment

Spreadsheet containing the potential hazards identified in the essential principles checklist. Contained failure modes, effects of failure, severity and likelihood ratings, risk controls, and residual ratings. Initial assessment was led by one physicist, and subsequently revised by physicists and RTs, before sign-off by Director.

Potential Hazard	Applicable?	Potential failure mode	Potential effects	Risk evaluation			Risk control	Residual risk			Verification of control	Acceptable?
				Severity	Likeli-hood	Risk rating		Severity	Likeli-hood	Risk rating		
1.1 Inadequacy of performance characteristics for the intended use	Yes	Modelling or manufacturing/post-processing error.	Poor conformity to patient topography or incorrect radiological attenuation, resulting in uncertainty in radiotherapy dose delivery.	3	3	9	Perform QC: medical professional review (T1), visual and mechanical inspection (T2), dimensional checks (T3), density checks (T4), ongoing verification (T5).	3	1	3	Design Summary, IFU.	Yes
1.8 Energy – Heat	No	Device has no heat I/O function	N/A	N/A	0	0	N/A	N/A	0	0	N/A	Yes

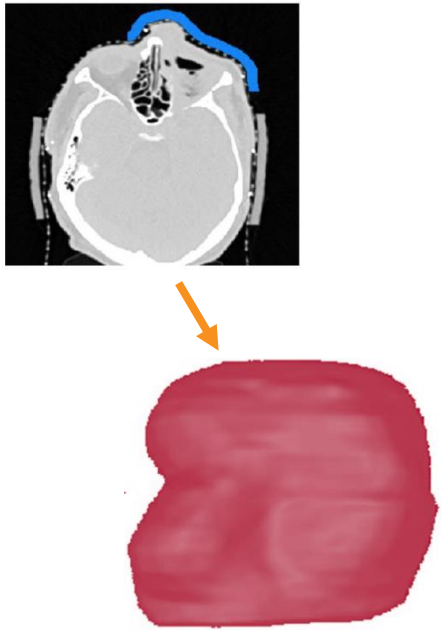
Bolus example

4. Design plan

This was the largest document. It summarised the responsibilities of staff associated with manufacture and supply of bolus, and identified stakeholders and their interests.

The design case outlined the following, with reference to environment (tools and software) and handling (movement of components, devices and files):

- Modelling – segmentation and approval, STL export, pre-processing.
- Manufacturing – slicing, printing, removal and post-processing, labelling, packaging and transport.



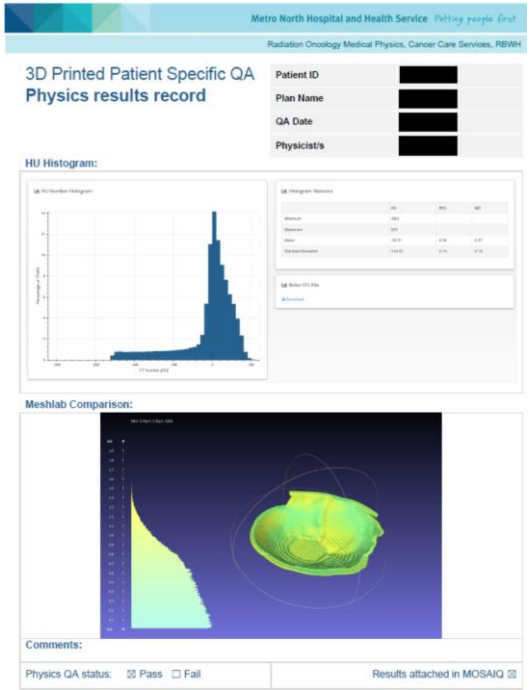
Bolus example

4. Design plan (cont.)

- Testing – list of verifications and validations, including review, visual inspection, dimensional test by scanning, radiological test by CT, ongoing assessment during use.
- Use – placement on patient.
- Disposal.

The design requirements, design envelope and limitations on design (e.g. maximum size) were also described.

All of this was supported with illustrative figures.



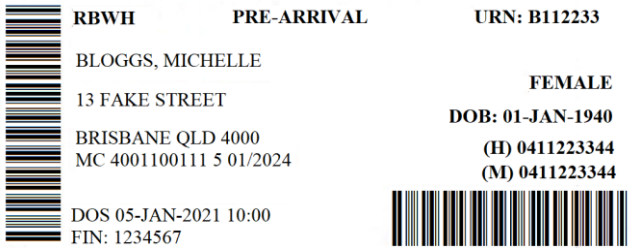
Bolus example

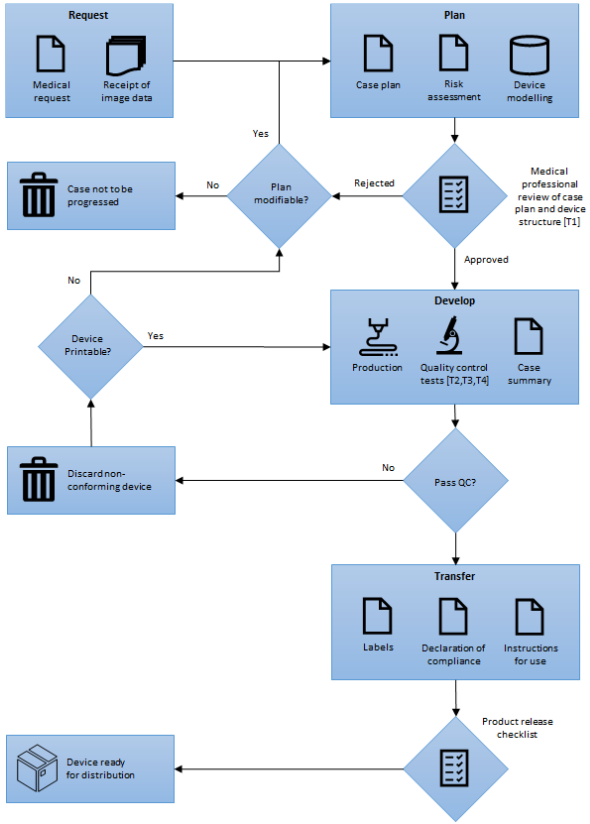
5. Manufacturing plan

This file described the design and manufacturing in more detail, e.g. selection of material, completion of records kept in MOSAIQ QCL, instructions for slicing and printing, troubleshooting processes, etc.

6. Quality and packaging plan

Provides instructions for packaging, labelling and storage.





Bolus example

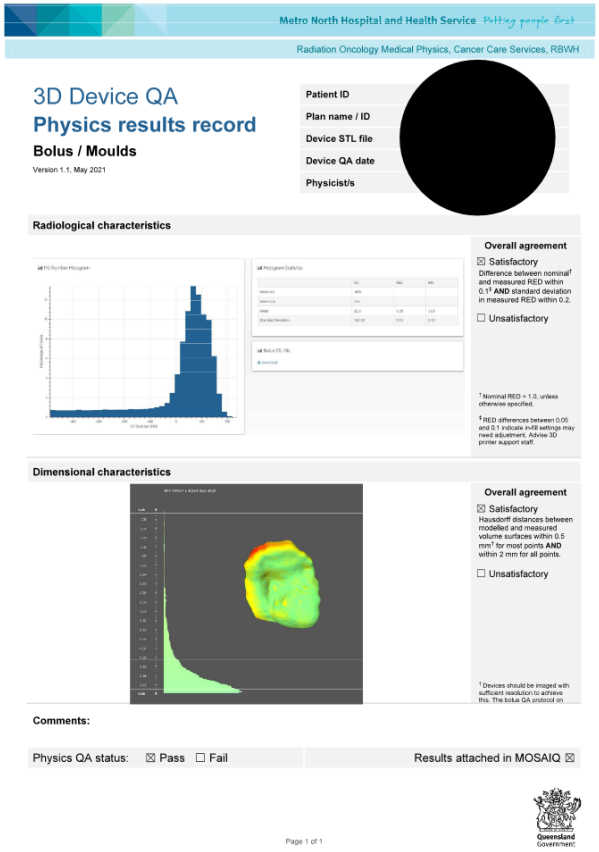
7. Case Plan

Template capturing the details provided in the initial device request. Type of device, desired density, desired material, desired QA requirements, markings, quantity for production, requesting health professional, etc.

8. Case Summary

Template describing what is recorded during each step of the manufacturing process, i.e. MOSAIQ QCL and physics QA check form (attached to patient record).

Task
3D Device Structure Approved
3D STL Exported for Production
3D Print Preparation
3D Print and Post Processing Complete
3D Device Wax/Pb Production
3D Device Visual and Manual Inspection
3D Device Physics QA
3D Device labelled and Packaged
3D Device Delivered
3D Pre-Treatment Fitting Required
3D Device Code Capture



Bolus example

9. Instructions for use

Instructions provided with each device – how to use, store, clean, dispose, ensure ongoing suitability for use, and contraindications for use (e.g. acceptable air gap).

Prior to each fraction of the procedure/intervention ensure:

- ⚠ The device matches the specific patient – check the device label.
- ⚠ The device is still applicable for the specific patient by:
  - Physically evaluating the fit of the device on the patient anatomy.
  - Ensuring no gaps exceeding 5 mm exist between the patient and the device where any medical images are obtained during the procedure/intervention (e.g. cone-beam CT).
- ⚠ Ensure appropriate environment (cool, dry, hygienic) and hygiene of all personnel who are to handle the model

10. Post-market surveillance plan

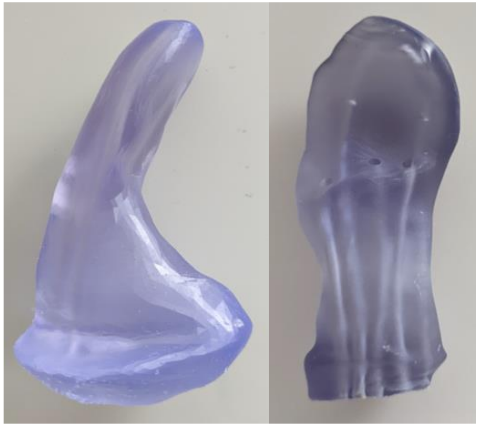
Details who is responsible for maintaining documents, tracking issues with devices, where those details are recorded, how they are distribution, and both routine and adverse event reporting to the TGA.

Other devices

The documents I described support your processes that ensure your device satisfies the Essential principles. You prepare these systems and documents, and submit an application or notification to the TGA.

We have used the same template for positioning equipment and intracavitary patient-matched applicators.

You don’t need to use the same approach – you could reduce the length seen here (30ish pages) by merging some of the documents discussed.



Other devices

This was for a Class I patient-matched device, for which you self-declare conformity. For higher risk devices, that assessment needs to be done by an external party.

For other devices, there will be differences.

- For software, you'll discuss unit and integration testing, version control and numbering, etc.
- For higher risk devices with non-transient use or in contact with mucosa/blood/etc, you may need to discuss sterilisation processes and how you ensure materials and the final product are biocompatible.

The quality manual could be 10-50 pages, depending on scope and risk of devices.

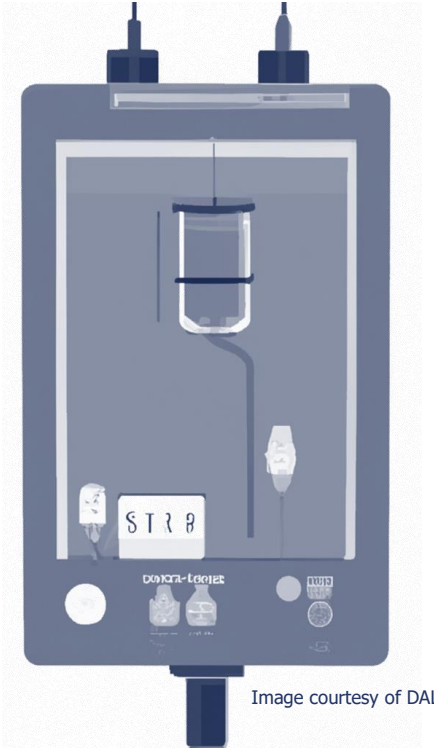


Image courtesy of DALL·E

Conclusion

At time of writing, few oncology departments have included in-house produced devices on the ARTG.

- Perhaps others have provided notification of custom-made devices?
- Perhaps others have accessed the transition arrangements provided by the TGA during the 2022 regulatory changes?
- Perhaps others are hoping the regulations change to be less burdensome where a medical professional is involved, or where an independent conformity assessment is currently required.

Conclusion

Next steps?

Medical device production systems and devices designed and manufactured by health professionals are the most likely targets of changes to regulations.

But you shouldn't wait for *potential* changes which would likely only result in other exemptions, not exclusions. You will need to have quality management systems in place for in-house devices.

My suggestion is that if you haven't already started developing a system of quality management that would pass an independent assessment, you should.

Physicists should play an active role in this space, and in broader high-level quality management and clinical governance.

Conclusion

Acknowledgements

Tania Poroa, Emily Simpson-Page, Alex Livingstone, Rachael Wilks & the RBWH team.

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