International Standards – its role in the regulation of medical devices and IVDs

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Outline

- Standards – relevance, usage and benefits
- Australian Regulatory Requirements
- Examples of Standards
  - Case studies
- IMDRF standards working group
- Issues with Standards
  - Case studies
- Standards review – TGA involvement
- Call to action!
- Support and further resource

What is a Standard?

Standards are voluntary documents that set out specifications, procedures and guidelines that aim to ensure products, services, and systems are safe, consistent, and reliable.

https://www.standards.org.au/standards-development/what-is-standard

The use of Standards

- Standards are key to public health and safety – developed by people from all areas of expertise and around the world, who work to collaboratively develop the best approach to the subject at hand – promotes regulatory science at national and international levels
- Appropriate use of standards encourages innovation and competition among product developers by providing a level playing field, while at the same time reducing burden by harmonizing expectations across multiple regulatory jurisdictions.
- Participation by all stakeholders in standards development including - *especially* - regulators
  - Opportunity to influence standards during development
- Streamline assessment / more efficient review process
- Speeds patient access to safe, effective devices

Types of Medical Device Standards

- Specifications
- Performance standards
- Guidelines/Technical Reports
- Systems standards
- Product Standards

Horizontal versus Vertical Standards

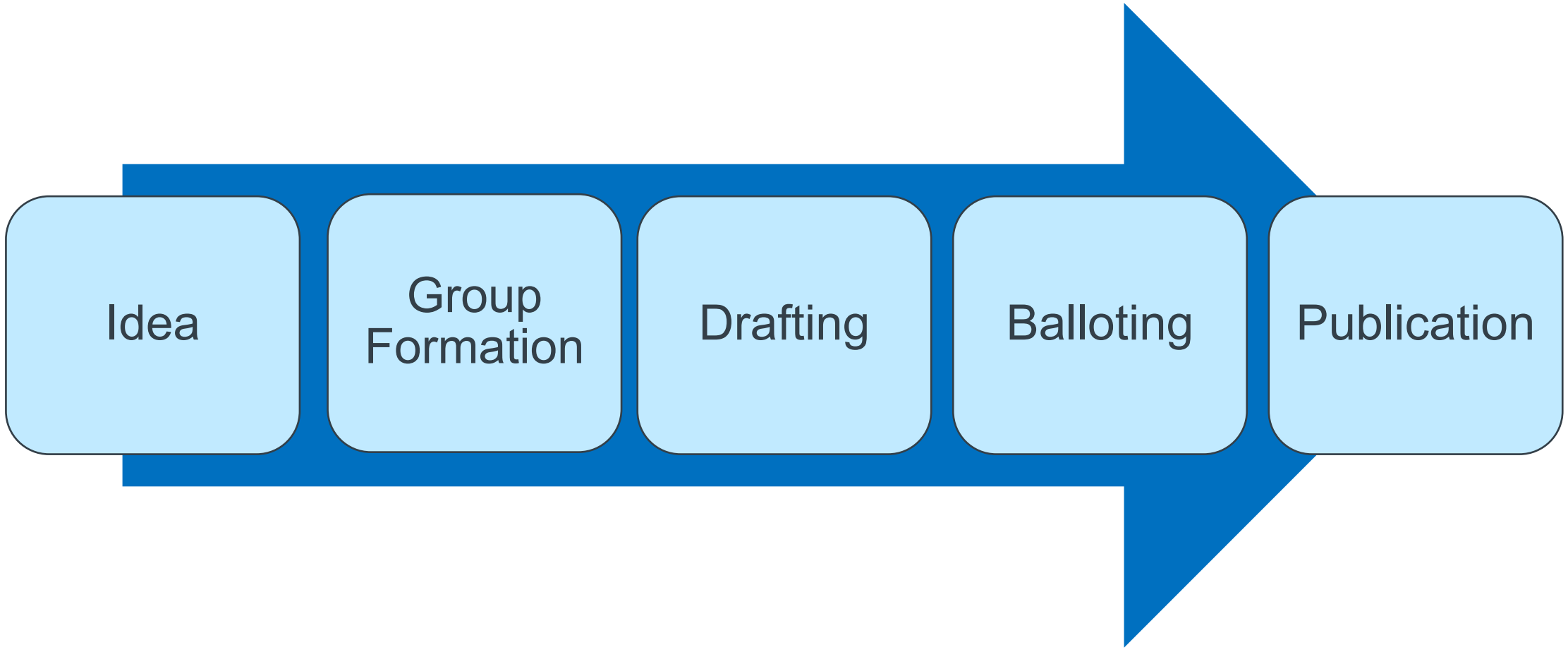
Horizontal (cross-cutting)

ISO 13485: Quality systems
ISO 10993: Biocompatibility
IEC 60601-1 : General and Electrical Safety

Vertical (device-specific)

ISO 81060-2: Non-invasive sphygmomanometers
ISO 11318: Cardiac defibrillators
IEC 60601-2-33: MRI

Standards – Development Process



Standards – Lifecycle

- Standards are periodically reviewed (usually every 5-10 years) to determine if they need to be revised, reaffirmed or withdrawn.
- The process is consensus-based among the countries/stakeholders having a vote in the area of concern
- If a standard is being used, but does not need any technical changes, it is usually reaffirmed or reconfirmed.

Standards development – why participate?

- Opportunity to influence standards early on
- Advance notice of what is coming
- Best understanding of language and intent
- Network with other subject matter experts
- Ensure sufficient diversity in technical knowledge/experience within committees
- Take part in creating something that benefits patients, users and our industry

Standards – Benefits

Medical Device regulators

- Provides assessment of state-of-the-art
- Provides criteria for product evaluation
- Reduces review/approval times
- Facilitates of agile regulation
- Advances regulatory science

Patients, consumers, the public

- Assures device safety, effectiveness, quality
- Increases affordability
- Improves access to technology-enabled diagnosis and treatment

Medical Device Manufacturers

- Provides assessment of state-of-the-art
- Details product requirements
- Clarifies pathway for regulatory approval
- Provides presumption of compliance
- Limits unfair liability
- Promotes international trade

Clinicians, healthcare providers

- Assures device safety, effectiveness, quality
- Eases evaluation of devices (acquisition)
- Facilitates delivery of state-of-the-art healthcare

Select list of Standards Developers involved in Medical Device Standardization

International (National Voting)	International (Stakeholder Voting)	Regional (National Voting)	National
IEC ISO ITU	AAMI ASTM International CLSI CTA HL7 IEEE DICOM (NEMA) PDA RENSA GS1	Country specific	Country specific

Australian Regulatory Requirements

Conformity Assessment

QMS (Manufacturer)

Could include:

- Overview of manufacturing stages
- Quality manual
- Purchasing requirements/supplier control
- Process validations and Change Controls
- Procedures for post-market monitoring system

Product Assessment

Could include:

- Device Description and History
- Essential Principles Checklist
- Risk Analysis and Control Summary (e.g. ISO 14971)
- Design and Manufacturing Information
- Clinical Evidence Report
- Performance Evaluation
- Product Validation and Verification
- Stability
- Information to be Supplied with the Medical Device

Essential Principles

1. Use of medical devices not to compromise health and safety
2. Design and construction of medical devices to conform to 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 side effects
7. Chemical, physical and biological properties
8. Infection and microbial contamination
9. Construction and environmental properties
10. Medical devices with a measuring function
11. Protection against radiation
12. Medical devices connected to or equipped with an energy source
13. Information to be provided with medical devices
14. Clinical evidence

Standards – relevance and usage in Australia

- The Australian medical device regulatory framework is “principles based” rather than prescriptive and does not prescribe compliance with specific standards or industry codes.
- However, manufacturers must be able to demonstrate compliance with the Essential Principles throughout the life cycle of the medical device.
- This flexibility allows for technological advances and changes in the development of new medical devices.
- Common avenues for manufacturers to demonstrate compliance with the Essential Principles is to demonstrate compliance with relevant generally acknowledged state-of-the-art and best-practice, via technical standards, guidelines, or other validated methods.
- Standards are often used by Sponsors and Manufacturers of therapeutic goods to demonstrate compliance with certain regulatory requirements.
- The TGA uses international standards as the basis for verifying quality and performance of therapeutic goods when conducting post-market reviews, investigations and testing.

Examples of Standards

- ISO Standards
  - *ISO 13485:2016 Medical devices, Quality management systems, Requirements for regulatory purposes*
- ASTM Standards
  - *F1223-20 Standard Test Method for Determination of Total Knee Replacement Constraint*
- TGA's Medical device standards orders
  - *Medical Device Standards Order (Endotoxin Requirements for Medical Devices) 2018*
- TGA's Conformity assessment standards orders
  - *Therapeutic Goods (Conformity Assessment Standard for Quality Management Systems) Order 2019.*

Standards – QMS example

Manufacturer demonstrating compliance with some of the accepted international standards can claim compliance with Australian regulatory requirements (i.e., conformity assessment and Essential principles) for medical devices.

- Example: If a manufacturer's Quality Management System (QMS) complies with the ISO 13485 standard, the TGA will treat the QMS to comply with the relevant parts of the conformity assessment procedures. This is specified or enforced through the TGA’s Conformity assessment standard order.

Standards – IVD Example

International standards help to establish the state of the art by clearly communicating known hazards relevant to the types of devices they describe and how their potential for impact can be determined. For example: TGA accepts the following as representing state-of-the-art standard for IVD medical devices:

- ISO 14971 addresses principles and processes for risk management of medical devices
- ISO 23640 addresses stability requirements for IVD medical devices

Guidelines from other regulators with comparable evaluation frameworks are adopted by the TGA and considered state of the art. For example:

- WHO guidelines and European Common technical specifications outlining the requirements for Rapid Antigen Tests
- CLSI EP19-ED2:2015 A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures, outlining clinical evidence requirements for IVD medical devices.

IMDRF

Affiliate Members

Official Observers

World Health Organization

Regional Harmonization Initiatives

APEC
Asia-Pacific Economic Cooperation

African Medical Devices Forum

Pan American Health Organization

Global Harmonization Working Party
GHWP Towards Medical Device Harmonization

Management Committee (MC) Members

IMDRF
International Medical Device Regulators Forum

www.imdrf.org

IMDRF International Medical Device Regulators Forum

IMDRF Standards Working Group

Findings

- **Poor participation by regulators around the globe** – can lead to the development of standards that do not include substance and language useful for regulatory purposes
- **Unbalanced representation** – can result in some groups' disproportionate voice in and impact on standards development
- **Content of standards can be too flexible** – can render standards less useful as they may not adequately identify appropriate requirements for quality, safety and/or effectiveness/performance

Recommendations

- Improve standards for regulatory use
- Enhance participation in standards development – through Standards Liaison Program, Official Observer Status

IMDRF International Medical Device Regulators Forum

Standards should feature -

- Strong rationale that explains the general requirements and identifies test methods and/or other means of demonstrating compliance
- Identification of risk and direction on how to address it
- A clear scope
- Terms and definitions established and accepted in other standards
- Means to assess performance as part of the normative requirements
- Clear and quantitative acceptance criteria
- Explanation of how conformance can be met if no acceptance criteria are included
- If acceptance criteria are not mandatory, justification for why, and how to demonstrate conformance to the standard
- Well-accepted and verified test methods (including for new or unfamiliar methods)
- An annex or table that cross references the standard's clauses to the IMDRF Essential Principles

Issues with Standards

- Unclear scope and/or contradictory purpose
  - Example – standards intended to assess performance of materials used in medical devices but are (apparently) not intended or suitable for assessing performance of finished products.
  - Example – standards intended for “initial classification” of products, but not intended to be used for ongoing monitoring of quality.
- Standards not being updated as novel designs are developed and brought to market.
- Differences in interpretation and application of standards between parties
  - Example – Manufacturer vs Regulator
  - Commonly due to ambiguous or subjective wording of requirements, or the lack of normative requirements for critical parameters.

Issues with Standards (cont'd)

- Divergence between originating standards and ISO standards as one or the other are updated
  - Example – ISO 22609 & ASTM F1862 were equivalent in 2004. Since that time ASTM F1862 has been updated 4 times while ISO 22609 remains unchanged. The two standards now have several significant differences, yet several other product standards still reference both as being equivalent.
- Lack of uniform approach across standards for products of common classes
  - Example – inconsistent approach to issues such as sampling in standards for different medical PPE including gloves, gowns, masks etc.
- Errors in standards regarding sampling plans
  - Example – stating AQLs and sampling plans without regard to other relevant factors such as batch sizes or inspection levels.

Case study - Standard Deficiencies

Ventilators, CPAP and BiPAP devices

- Concerns raised regarding the long-term safety of these devices
  - risks associated with breakdown of polyester-based polyurethane (PE-PUR) sound abatement foam component.
- Safety standards such as ISO 10993:2018, ISO 18562:2017 and EPA TO:15 may not be sufficient to evaluate the intended use of the devices.
  - To comply with ISO 18562:2017, **30 days** of testing is required. However, these devices are intended to be used for 5+ years.
- Adaptation of the standard would be required to reflect the worst-case scenario that the device may be used in, which may involve elevated temperature or pressure testing to represent different operational lifetimes.

Case study - Redrafting of ISO Standard

Breast Implants

- Several issues with breast implants over the years
  - PIP in 2012, Silimed glass fibres in 2015, and BIA-ALCL in 2019
- The relevant standard ISO 14607 did not adequately cover safety requirements for these products
  - E.g. impurities in silicone gel, particulate quantification and characterisation, biological safety and surface texture classification
- International Working Group formed in 2019
  - TGA, FDA, MHRA, HPRA, ANSM, IGJ, RIVM, ICOBRA, National Breast Device registries
  - Requested ISO to redraft the standard
  - Work commenced in late 2019. TGA nominated as Convenor of the ISO Working Group. Draft International Standard just approved (Nov 23) by international ballot to move to the final review stage. Publication anticipated for 2024.
- Much of this work has been based on TGA expertise – biocompatibility, particulates, surface topography, chemistry, toxicology.

Standards – PPE Example

- The COVID-19 pandemic lead to unprecedented focus on medical PPE standards.
  - Identified many issues of inconsistency within and between standards, and how they are interpreted
- The TGA adopted a multi-pronged approach to address these issues:
  - engaged heavily in standards committees to advocate for updates to the standards
  - published guidance and hosted webinars for industry to clarify how medical PPE standards should be interpreted and applied by manufacturers and test labs.
  - participated in 'mask testing forums' with industry, and government and university laboratories to share information
  - provided expert technical advice and testing support to our National Medical Stockpile (NMS) to ensure procurement of fit for purpose PPE.
- Issues covered in TGA guidance, forums, standards advocacy, and expert advice include:
  - Which standards and tests apply to different products.
  - How ambiguous aspects of testing should be interpreted – e.g. testing all areas of difference separately for resistance to penetration to synthetic blood.
  - Regulatory expectations for on-going batch monitoring by manufacturers, and appropriate sampling plans to demonstrate compliance to applicable Acceptable Quality Limits (AQLs)

Standards – Face masks & Respirators

Design and complexity varies!

Standards – applicability to more complex designs

Face masks

Facemask standards:

- Australian (AS 4381), USA (ASTM F2100), Europe (EN 14683), China (YY/T-0969)
  - Developed primarily for simple rectangular flat pleated masks.
  - Different interpretations on how to apply test methods to more complex designs (tri-fold, duckbill etc).
  - US standard requires tests for Particulate Filtration, but Australian and European Standards donot.
  - US and Australian standards require fluid resistance for all classifications (Level 1, 2, 3). European Standard includes two classification that do to require fluid resistance (Type I, Type II).

Standards – differing technical details

Respirators

Respirator Standards:

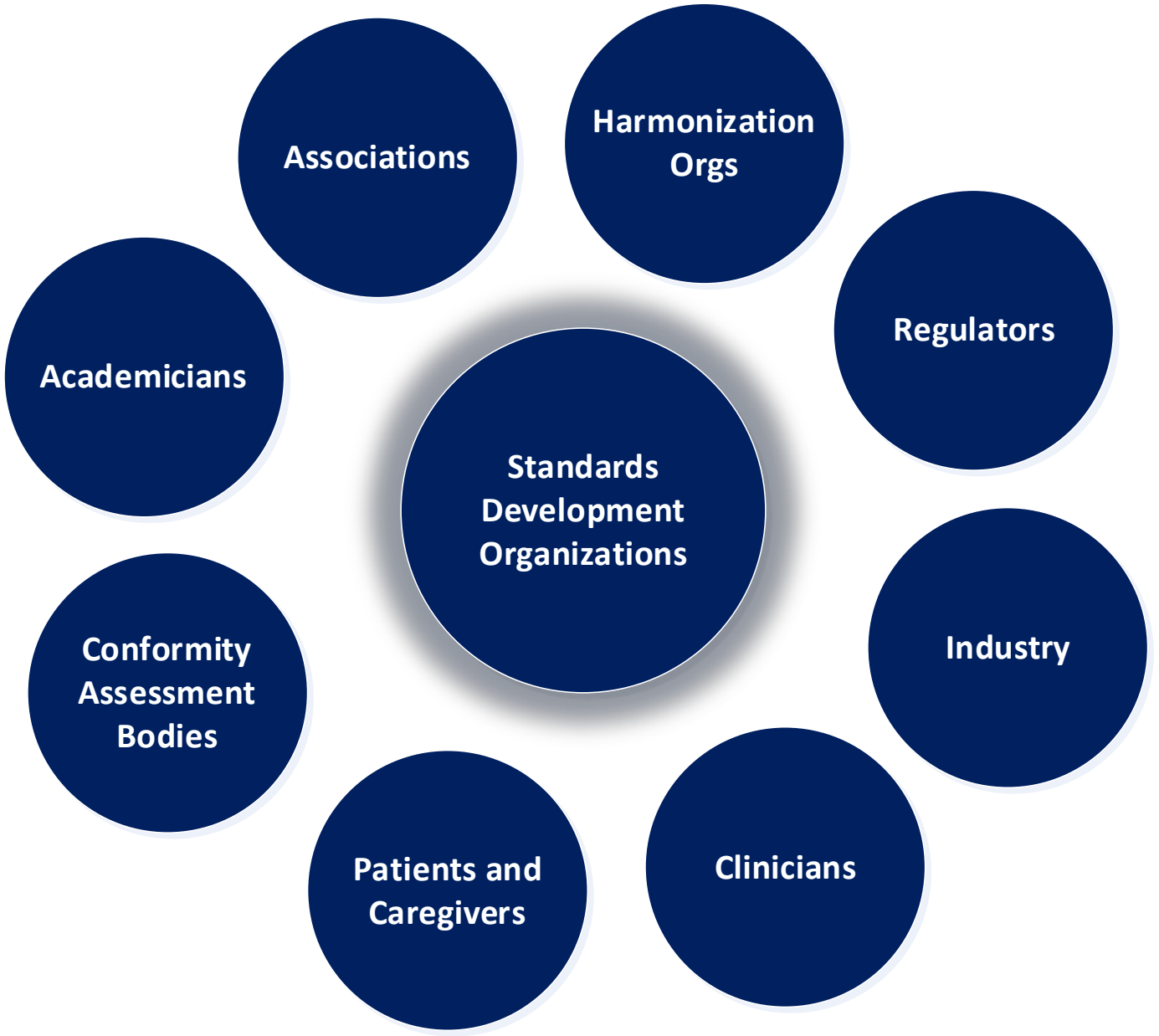
- Australian (AS 1716), USA (42 CFR 84), EU (EN 149), China (GB2626), Canada (CZA Z94), ISO (16900)
  - Developed primarily products used in industrial setting, not medical/surgical respirators.
  - Technical differences between each. E.g.
    - Parameters for Particulate Filtration Efficiency (PFE) testing vary slightly between standards.
    - Australian and European standards require Total Inward Leakage testing, USA and others do not.
    - Number of specimens to test varies, and some do not specify.
- TGA implemented a universal 'rapid-screening' test method for Particulate Filtration Efficiency (PFE). During the pandemic we used this universal test method as a minimum benchmark to test all products tested under same conditions, regardless of which standard they claimed to meet.

Standards Review – TGA involvement

- TGA has representation at Standards Australia and has ongoing engagement and collaboration with other regulators, for medical device and IVD related standards and guidelines and actively provides input into the review of these standards and guidelines.
- Many TGA staff are members of various standards committees. Examples include:
  - Standards Australia technical committee – *HE-30 Biological and Clinical Evaluation of Medical Devices*
  - ISO Technical Committee 121 - *Anaesthetic and respiratory equipment*
- Our involvement allows us up-to-date visibility of the development and amendment of the international standards, including the ability to influence where appropriate standards development

Call to Action!

- Promote the use of standards
- Join a committee
- Contribute early!
- Continue discussions



Support and further resources

- IMDRF Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices: 2018 WG/N47 https://www.imdrf.org/documents/essential-principles-safety-and-performance-medical-devices-and-ivd-medical-devices
- International Organization for Standardization (ISO) https://iso.ch/home.html
- International Electrotechnical Commission (IEC) http://www.iec.ch/about/activities/standards.htm?ref=home
- WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices https://www.who.int/publications/i/item/9789241512350
- TGA Standards, guidelines & publications (medical devices & IVDs)
  - https://www.tga.gov.au/resources/resource/guidance/standards-orders-and-medical-devices
  - https://www.tga.gov.au/about-tga/legislation/legislation-and-legislative-instruments/medical-devices-notices-and-standards-orders
  - https://www.tga.gov.au/standards-guidelines-publications-medical-devices-ivds

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration