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Building a GHTF Regulatory Framework for Australia

Mike Flood
Office of Devices, Blood and Tissues
Therapeutic Goods Administration
AUSTRALIA

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What does the TGA do?

- Regulates the safety, quality and efficacy of therapeutic goods available in Australia.
  - Oversees a >$9 billion therapeutic goods sector with exports of $2 billion
- Maintains national regulatory system for Genetically Modified Organism's
- Chemicals - oversees $20 billion industry
- Provides advice on the use of chemicals to other agencies
- Operates under cost recovery arrangements

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How does the TGA regulate therapeutic goods?

- Operates under the Therapeutic Goods Act 1989 and associated legislation
- Sets Standards
- Evaluates safety, quality and efficacy before entry to market
- Licensing of manufacturers and ongoing audits
- Maintains Australian Register of Therapeutic Goods (ARTG)
- Monitors products on the market (Postmarket)
- Controls access to unregistered products

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Post market activities

- Controls on advertising therapeutic goods
- GMP audits of manufacturers
- Adverse reaction/incident monitoring
- Recalling unsafe products
- Enforcing the law - surveillance
- Risk based product testing

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Consumer Concerns

- Timely access
- Information
- Independence
- Community service obligation
- Consumer participation in decision making

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(Historical)

Authority & Instruments of Regulation (historical)

- Department of Health & Aged Care
  - Therapeutic Goods Administration
    - Office of Devices Blood & Tissues
      - Therapeutic Goods Act 1989
      - Therapeutic Goods Regulations 1991
      - Various Regulatory Instruments
        - » DR 4 - Device Requirements under the Therapeutic Goods Act 1989
        - » Therapeutic Goods Orders

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(Historical)

Classification (Historical)

- Defines the requirements for supply
- Defines which part of the ARTG
- Based on 'lists' found in the legislation
- Lists define inclusion & exclusion
- Requires a change in Legislation to re-classify a device

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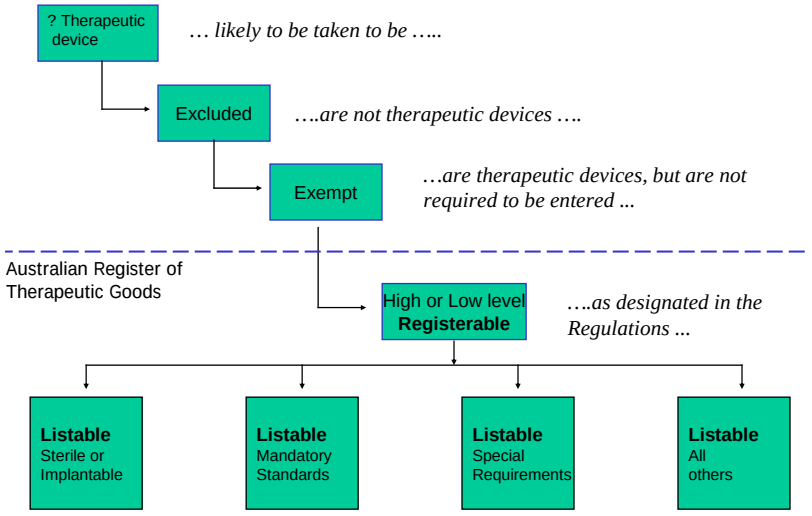
(Historical)



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(Historical)

Registered Devices

- Heart Valves
- Active Implants
- Drug Infusion Systems
- Human/animal origin
- Intra-ocular lenses
- Intra-uterine devices
- Breast prostheses
- Barrier contraceptives
- Instrument Grade Disinfectants
- HIV, Hep C Diagnostic Kits

- Satisfactorily establish -
  - **Quality**
  - **Safety**
  - **Efficacy**
- Evaluation of -
  - **Design**
  - **materials**
  - **design validation**
  - **Manufacturing**
  - **GMP**
  - **Sterility**
  - **Biocompatibility**
  - **Pre-clinical studies**
  - **Human clinical trial data**

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(Historical)

Listed Devices

- Examples
  - Syringes/needles
  - Wound drains
  - Bedside monitoring
  - Non-active implants
  - Hearing aids
  - Stents
  - Endoscopes
  - Catheters
  - Bedside monitoring
  - CT & MRI scanner
  - Linear Accelerator

- Minimal evaluation -
  - **Safety**
  - **Quality** (for some devices)
  - **Labelling**
  - **Mandatory standards** (for some devices)
  - **Special conditions** (for some devices)

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Disadvantages of Old Framework

- Device classification system is unique to Australia
- Use of schedules for classification reduces the flexibility to appropriately evaluate high risk devices using new technology
- Does not establish a-priori
  - a set of minimum requirements of safety and performance for all medical devices
  - a method of demonstrating compliance with these minimum requirements

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Why Change

- Minimum set of safety & performance requirements for **ALL** devices
- Public Health will be enhanced by a system of device classification which manages technology changes more quickly
- Devices appropriately assessed according to the level of risk
- removes duplication - globally aligned system eliminates unique Australian requirements

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Considerations in Establishing a Regulatory Framework

- Public health protection
  - Proportional to
    - Risks presented
    - Benefits gained
    - Resources expended
- Political accountability
  - Within a legislative framework
- Resources
  - Efficient use of
    - Funding
    - Expertise
    - Support infrastructure

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Considerations in Establishing a Regulatory Framework

- Least burdensome approach
- Regional/global harmonisation
- Transparency & predictability – no surprises !!!

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Considerations in Establishing a Regulatory Framework

- Appropriate Quality Management Systems
  - Based on risk
- Demonstration of compliance
  - Essential Principles of Safety & Performance
  - Risk based classification
  - Conformity assessment

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Considerations in Establishing a Regulatory Framework

- Postmarket programs
  - Incident reporting
    - Manufacturers & Sponsors
    - Users
  - Pro-active Vigilance
    - Audits of Sponsors & Manufacturers
    - Compliance Testing
  - Formal recall processes
  - Enforcement
- Control of promotion/advertising
- Access to unapproved devices
  - With conditions
  - In the event of demonstrated clinical need

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Considerations in Establishing a Regulatory Framework

- Opportunities
  - Alignment of regulatory frameworks
    - Mutual Recognition Agreements
    - Memorandums of Understanding
    - Regional/Global alignment or harmonisation
    - 'Recognition' of external assessment processes
    - 'Recognition' of external Conformity Assessment Bodies
  - Value add rather than re-assess

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Regulatory Framework Elements - Australia

- Conformity Assessment
  - Essential principles
  - Classification
  - Technical File review
  - Quality Management Systems
- Registration of entity responsible for placing the product on the market
  - Manufacturer
  - Importer
- Inclusion of medical device(s) on the Australian Register of Therapeutic Goods
- Clear Roles & Responsibilities
  - Manufacturer
  - Importer
  - Regulator

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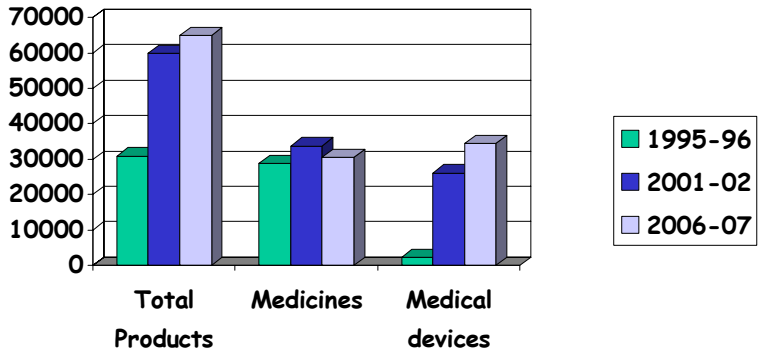
Product trends - Australia



Source : TGA ARTG

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The Device Market

- ~ 1500 sponsors
- > 30,000 different devices
  - between 400 - 600,000 catalogue items
- >85% of devices are imported
- <10% of devices could be classified as high risk
- Australia < 2% of world market

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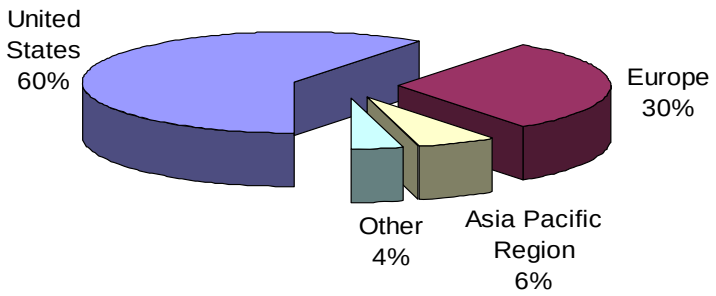
Sources of Australian Imports



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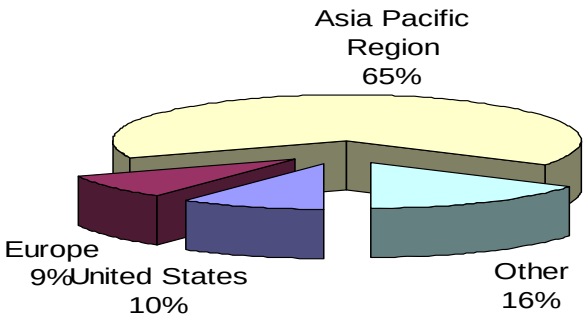
Destination of Australian Exports



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Therapeutic Goods (Medical Devices) Amendment Act, 2002

- Regulations modelled on the recommendations of the **Global Harmonisation Task Force**
- Mutual Recognition Agreement with the European Union – since 1998

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Therapeutic Goods Amendment (Medical Devices) Act 2002

- Passed through the Parliament 4 March 2002
- Regulations in place 4 October 2002
- First transition period ended 4 October 2004
- **all devices** subject to the new legislation from 4 October 2007

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Elements of New Regulation

- 14 Essential Principles of safety and performance
- 22 Rules of Classification based on Risk to user and/or patient
- Quality Systems - ISO 13485
- Independent Assessment and on-going surveillance of Quality Systems
- Entry on the **Australian Register of Therapeutic Goods**
- **Postmarket monitoring of device performance**

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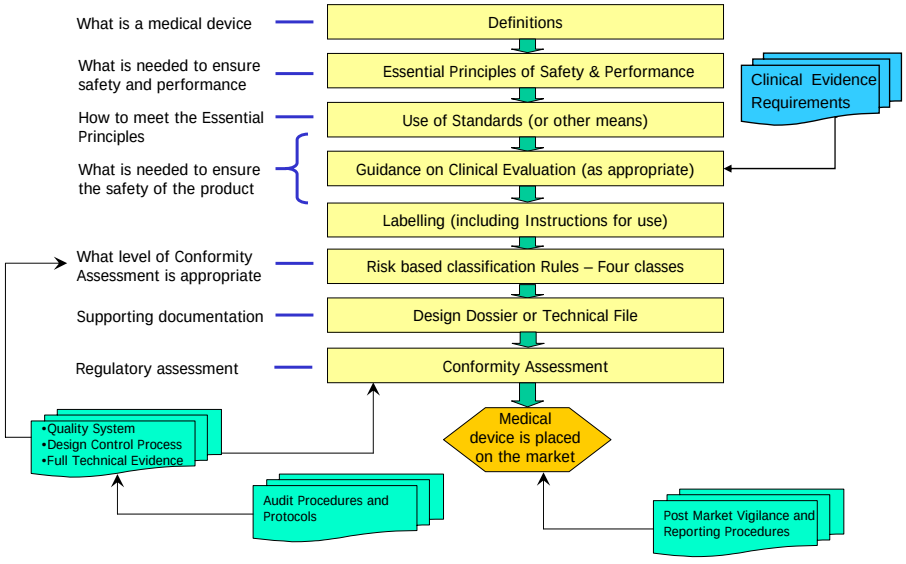
And where do these harmonised principles come from …..

GHTF

GHTF Model

Pre-market Technical Requirements



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Considerations in Establishing a Regulatory Framework

- Opportunities
  - Alignment of regulatory frameworks
    - Mutual Recognition Agreements
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    - 'Recognition' of external assessment processes
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  - **Value add rather than re-assess**

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Assessment Mechanisms

- The assessment mechanisms of
  - conformity assessment certification
  - the consideration of overseas assessment reports; and
  - application audits

  … would not be possible without harmonised definitions of

  - the classification rules;
  - the conformity assessment procedures; and
  - the essential principles.

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Pre-market Assessment

- All medical devices must comply with the Essential Principles regardless of Class
- All manufacturers must apply a conformity assessment procedure
- Many of the procedures require an independent assessment of a product or a Quality Management System

But, how are the assessments performed? ……..

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Assessment – three possibilities

- Entry and approval without review
  - Using evidence (certification) of assessment of the manufacturer and products in a jurisdiction with an equivalent regulatory framework
- Application Audit
  - Review of documentary evidence generated as part of an assessment undertaken in a jurisdiction with an equivalent regulatory framework
- Conformity Assessment
  - by the TGA

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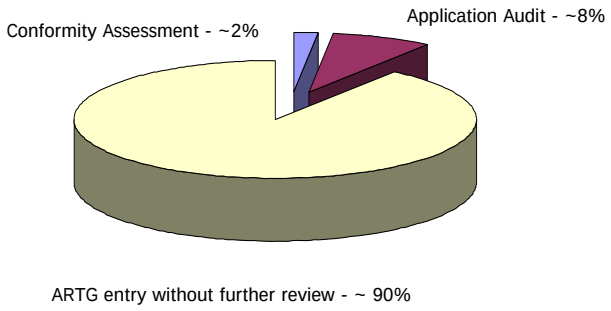
Assessment Mechanisms – three possibilities



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Assessment Mechanisms – Entry onto the ARTG

- Sponsor submits copies of evidence of appropriate Conformity Assessment evidence - EC certificate(s)
  - Register evidence database is scoped using GMDN
- Sponsor applies for entry of device(s) on to the ARTG
  - Binding declarations made at time of application
    - Correct classification
    - Correct conformity assessment procedure has been applied
    - Complies with essential principles
    - Mechanism in place to obtain info from manufacturer on request by the Agency
    - Postmarket processes in place
      - Etc, etc
- Inclusion Certificate is issued and device is entered on to the ARTG without further review

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Assessment Mechanisms – Application Audit

- may be performed when the TGA has not performed the full conformity assessment certification
- mandatory and randomly selected documentation audits
- performed at the time that a Sponsor applies for an entry on the ARTG

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Assessment Mechanisms – Application Audit

- Shorter process
- Desk audit of documentation -
  - Essential Principles checklist
  - Risk Analysis
  - EC Certification(s)
  - Design Exam Report (Class III & AIMD only)
  - Audit Report (Full QMS audit & most recent surveillance audit)
  - Summary of Clinical Evidence (expert report)
  - Labelling
  - DOC to Therapeutic Goods (medical devices) Regulations 2002

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Selection for Application Audit

Mandatory

- barrier contraceptive
- implantable contraceptive device
- implantable breast prosthesis
- instrument grade disinfectant
- active implantable medical device
- prosthetic heart valve
- implantable intra-ocular lens
- intra-ocular visco-elastic fluid
- class III device not assessed under an MRA

Non-mandatory

- applications suspected of containing false information
- where the device incorporates a new, different or emerging technology
- devices that were previously unregulated
- questionable regulatory history
- Random selection

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Application Audits - level 1

- Original or notarised Declaration of Conformity
  - (to the Therapeutic Goods (medical devices) Regulations 2002
- Original or notarised evidence of third party certification of the quality system - eg EC or and/or design exam certificates
- Labelling
  - General labelling
  - Instructions for use
  - Advertising material

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Application Audits - level 2

- Level 1 audit data **plus** –
- Risk analysis performed by manufacturer
- Summary of Clinical evidence
  - expert report
  - trial report
  - literature report
- Essential principles checklist (Australian, not EU)
- Most recent QMS Audit or re-audit report
  - including close out of non-conformities
- Design Exam or Type Exam report (if applicable)
- Special Process validations

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Assessment Mechanisms - Conformity Assessment Procedures

- Conformity Assessment Certification
  - The TGA must perform the assessment as selected by the Medical Devices Rule for
    - Selected types of devices
    - Selected types of manufacturers
  - For all other assessment the TGA will take into account the assessments performed by other regulators performing similar assessments overseas.
  - The TGA will decide if the products are suitable for supply in Australia

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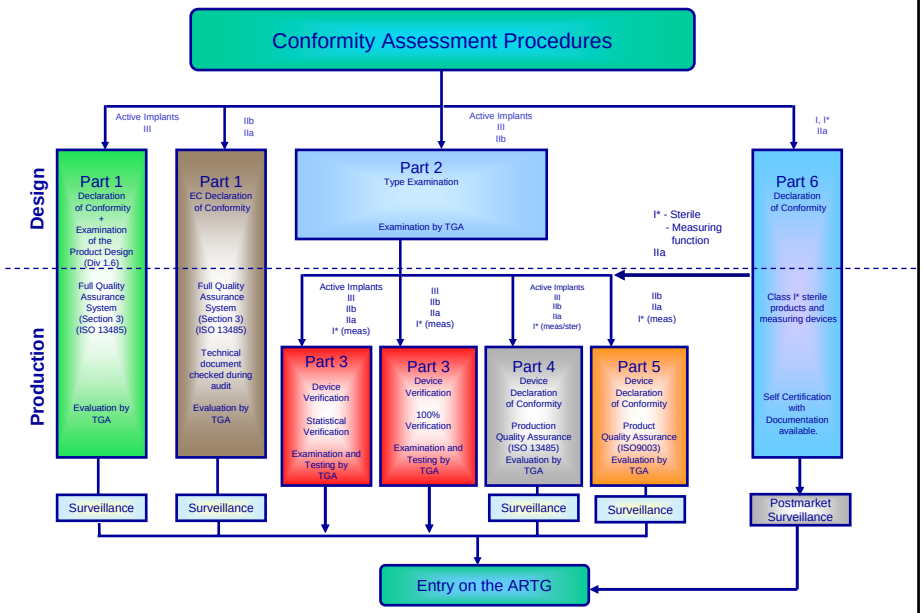
Assessment Mechanisms - Conformity Assessment Procedures

- A set of activities that the manufacturer must do
  - procedure is selected by the manufacturer
    - based on the risk class of the product
    - using classification rules
  - procedures are available for devices used for a special purpose
    - custom made
    - procedure packs
  - Combination device - medicine products
    - Must confer with TGA medicines regulator
    - Must meet regulatory requirements for medicines



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Assessment Mechanisms - Conformity Assessment Procedures

- Types of Manufacturers
  - products from Australian manufacturers
- Types of Products
  - contains tissues of animal origin
  - contain tissues, cells or substances of microbial origin or recombinant technology
  - incorporating stable derivatives of human blood or human plasma
  - incorporates a medicine with an ancillary action

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Assessment Mechanisms - Conformity Assessment Procedures

- Procedures require
  - application of a quality management system (QMS)
  - design or type examination assessments, by the TGA
  - manufacturer's post-market review:
    - Corrective & Preventative Action (CAPA) and adverse event reporting
  - initial and surveillance audit of the QMS, by the TGA
  - the keeping of records
  - a declaration of conformity referencing Therapeutic Goods (medical devices) Regulations 2002

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Assessment Mechanisms - Conformity Assessment Procedures

- The TGA issues a "Conformity Assessment Certificate" at the successful conclusion of an assessment
- Scope of certificate is specified in terms of GMDN Code for relevant devices

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Australian Register of Therapeutic Goods

- Record of
  - Manufacturer
  - Sponsor
  - Conformity Assessment Body
  - Conformity Assessment Procedure
  - Kind of medical device
    - Manufacturer
    - Sponsor
    - Class
    - GMDN Code
    - Other device specific information (Class III & AIMD only)
- Entry on the ARTG is the basis for legal supply

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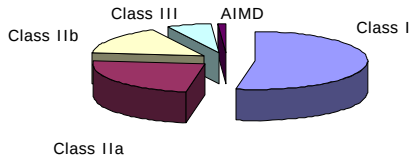
The ARTG today……

- 1830 Sponsors
- 6100 manufacturers
- 25000 'kinds of medical device'



- Distribution
  - 12100 Class I
  - 250 Class I measuring
  - 950 Class I sterile

    52.5%
  - 6000 Class IIa devices

    24%
  - 4000 Class IIb devices

    16%
  - 1600 Class III devices

    6.5%
  - 250 Class AIMD devices

    1.0%

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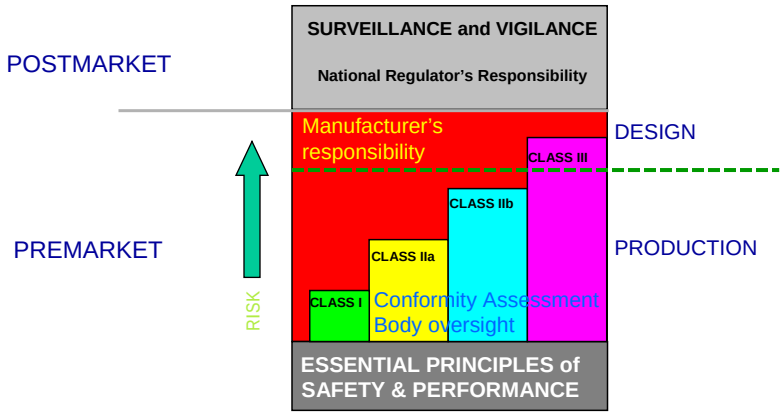
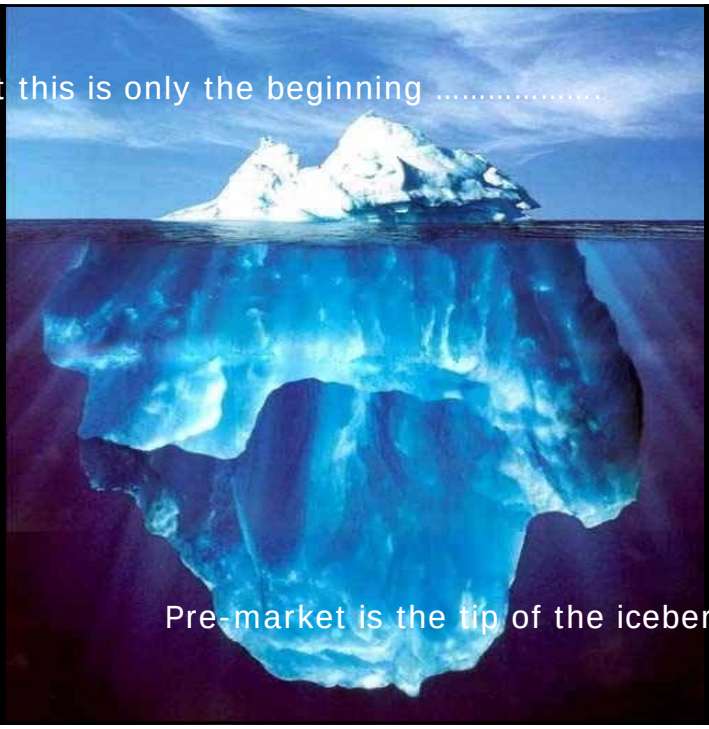


But this is only the beginning ……



Pre-market is the tip of the iceberg !!!

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Abridged pre-market assessments **must** be supported by a strong post-market program

- Incident reporting
  - Manufacturers
  - Clinical users
  - General public
- Pro-active vigilance systems
  - Epidemiological studies
  - Audits
    - Product
    - Sponsor/distributor
    - Manufacturer
  - Formal recall processes
  - Enforcement

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From Design to Obsolescence

- The product life cycle
  - Design
  - Bench testing & validation
  - Clinical testing
  - Risk based pre-market review & approval
  - Market entry
  - Post-market review and evaluation
  - Replacement

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Post-market

- Questions of interest -
  - Long term safety
  - After clinical trial - use in the broader population
  - Change of user setting
    - eg hospital to home use
  - Adverse events
  - Unusual pattern of adverse events which may not lead to product recall

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Where does the data come from

- Case control studies
- Non-clinical testing
- Product registries
- 'Sentinel' users
- Epidemiological studies
- Manufacturer reporting to NCA (eg TGA)
- Sponsor reporting (mandatory in Australia)
- User reporting (clinical, patient, etc)

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Post-Market Activities

- Manufacturer's Post-Market Surveillance.
  - pro-active and reactive - carried out by the manufacturer and/or sponsor
- Post Market Vigilance
  - Reporting of serious medical device adverse events and 'near miss' events to regulatory agencies
  - Subsequent regulatory agency investigations and dissemination of information about those events.

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Post-Market Activities

- Post Market Monitoring (TGA)
  - Activities carried out by TGA to ensure ongoing market compliance eg.
    - Post-market Testing
    - Product survey (technical file audits)
    - Surveillance
    - Post-market QMS and GMP audits

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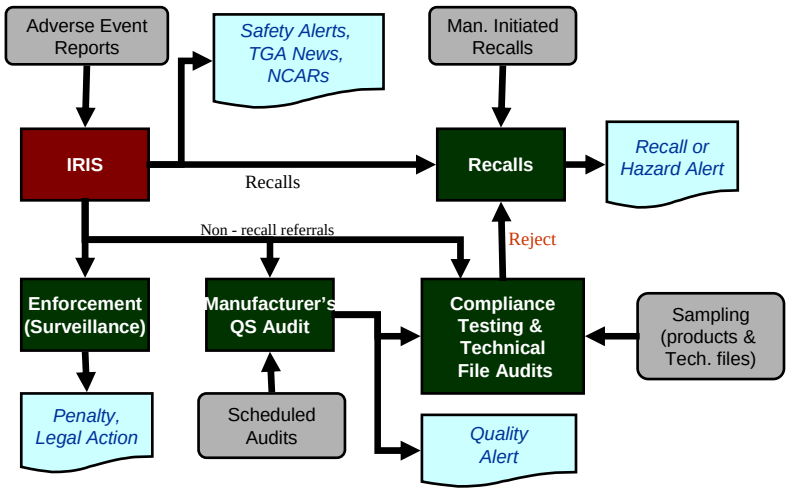
TGA's Vigilance and Market Monitoring Systems



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Post-Market Surveillance

- Manufacturer/Sponsor obligations:
  - Records to be kept and made available on request that demonstrate compliance with essential principles.
  - Establish and maintain a post-market surveillance, reporting and corrective action system for problems and complaints (no matter how minor)
  - Make information obtained using this system available upon request

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Post-market Monitoring

- The TGA conducts…
  - Post-market testing of certain types of products.
  - "product surveys" to check for compliance with information requirements and for meeting essential principles.
  - Post-market QMS audits.
- And …….
  - Encourages user reporting to both the sponsor and the TGA.

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Post-market Vigilance

- Sponsors must report the details of events associated with their device(s) that have resulted or could have resulted in serious injury or death
- This is now law... (always has been for that matter !!)
- Guidance will allow some exemptions
- Guidance will detail information required

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Post-market Vigilance

- AE Reporting timeframes...
  - Within **two days** of becoming aware of an issue of serious public health threat or concern that will require prompt action to reduce the hazard
  - Within **ten days** of becoming aware of a death or serious injury
  - Within **thirty days** of becoming aware of an event that might have led to serious injury or death

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Post-market Vigilance

- The TGA …
  - Collects and investigate adverse events reports from
    - sponsors and manufacturers
    - other regulatory agencies
    - medical device users
  - Disseminates information and/or oversee corrective actions taken as a result of adverse event report investigations
  - Exchanges vigilance information to other regulatory agencies in accordance with various MRA and GHTF agreements

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User Reports

- Evidence suggests that a substantial number of medical device adverse events and malfunctions are not reported to either the manufacturer or the TGA.
- The TGA regulates the supply, not the use …..
- The TGA can encourage, promote and entice user reporting, but not enforce it.

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Case Studies

- Heart Valve with Silzone Coating
- Most manufacturer's Zirconia Hip Prosthesis
- Pacemaker
- UHMW Acetabular Cup
- Tempo Pacemaker

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Common Themes

- All received significant media coverage at the time
- All devices had good previous market history
- All devices passed final QC checks
- All are implantable devices
- All require surgery to correct
- Significant mortality associated with some corrective surgery for these devices

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Common Themes

- All received regulatory approval, after evaluation, in significant markets
- All corrective actions will have (had) a large impact on the National health budget

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Conclusions ……..

- Pre-market assessment processes must be supported by rigorous post market programmes
- Regulatory approval is not a once off exercise, but requires continuous post-market monitoring is required to ensure continued safety of medical devices

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Thank you

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