



Regulation of Combination Products – the Australian Approach

Shelley Tang
Head, Medical Devices Assessment Section
Office of Devices, Blood and Tissues
TGA



Overview

- TGA Structure/Responsibility for combination products
- The assessment process for combination products
- Experience to date



Product Regulators

- Office of Devices, Blood and Tissues (medical devices, blood and human tissues)
- Prescription medicines
- Non-prescription (OTC medicines)
- Complementary medicines
- **Biologicals**



TGA has Expert Advisory Committees

- Medical Devices Advisory Committee (MDEC)
- Australian Drug Evaluation Committee (ADEC)
- Medicines Evaluation Committee (MEC)
- Complementary Medicines Evaluation Committee (CMEC)
- Biologicals (cellular therapies – proposed)



Whole of Life Cycle approach

- Special Access Schemes for experimental products
- Clinical trial assessment
- Pre-market conformity assessment
- Post-market surveillance/monitoring
- Enforcement



Combination products

- Regulated in accordance with principal intended purpose and mode of action by appropriate product regulator
- Classification as device or medicine (or biological) determined in accordance with definitions in legislation
- Regulated as a device or medicine (or biological) in accordance with determined classification
- Internal (ad hoc) committee decides on appropriate path for borderline products



Eg IUD releasing hormone

- Primary purpose to deliver the medicine
- Regulated as a medicine
- Device aspects may be referred to device program
- Expect that the manufacturer of the device component will hold evidence to show compliance with Essential Principles, but device certification not normally required



- Non-prescription medicine – gingival retraction cords containing an antiseptic
- Complementary medicine – salt pipe (contains salt solution from a Transylvanian cave for inhalation)
- Biological – collagen matrix to be used a base for the growth of autologous cartilage cells for re-implantation



The Assessment Process (Device focussed)



- Devices incorporating a substance, that if used separately, would be a medicine and is intended to act on a patient in a way that is ancillary to the device, is Class III (highest risk)
- Such devices are subject to conformity assessment by the TGA



- If a medical device incorporates a medicine intended to act on a patient in an ancillary manner
 - the safety and quality of the medicine must be verified in accordance with the requirements for medicines, and
 - the ancillary action must be verified having regard to the intended purpose of the device.



Examples:

- Drug eluting stents
- Drapes incorporating an iodoform
- Catheters coated with albumin or antibiotics
- Dressings impregnated with silver
- Orthopaedic implants incorporating antibiotics



- Applications for such devices come in to the devices program by electronic lodgement
- The manufacturer must have a conformity assessment certificate from the TGA
- Extent of assessment depends upon the TGA's knowledge of the medicine and it's manufacturer



- The conformity assessment process is conducted within the device program
- The evaluation of the medicinal component is referred to the relevant medicines regulator, if required
- The medicinal evaluation is done in parallel with the device assessment.
- Final decision rests with the device program, which issues conformity assessment certification



Algorithm for referral to medicines evaluator based on:

- Is it already included in the ARTG for that manufacturer?
- Is it a generic - known substance, new manufacturer?
- Is the use in the device consistent with approved use as a medicine?

The Algorithm

Algorithm Start

Is the medicinal substance registered in Australia?

Yes

No

Pharmaceutical chemistry review

Toxicology & preclinical pharmacology review

Clinical data review (ODBT)

Is the manufacturer known to the TGA with respect to the drug substance ?

Yes

No

Pharmaceutical manufacturing review

Limited review of toxicology of impurities or degradation products if these differ from innovator product

Clinical data review (ODBT)

Is proposed incorporation of the medicinal substance consistent with its approved use?

Yes

No

Drug release kinetics review

Review of local tolerance and any other toxicology studies

Clinical data review (ODBT)

Review solely within ODBT



- The more the medicinal substance, its use and its manufacturer are known to the TGA, the less the requirement for evaluation or consideration by an expert committee outside the device program
- In the algorithm, the coloured boxes signify points at which the device program would seek assessment by the medicines evaluator.



For substances that would normally be a prescription medicine:

- a new chemical entity will go through the full drug evaluation process, including consideration by the ADEC prior to consideration by MDEC.
- a medicine already on the ARTG, but from a new manufacturer, will be treated as a new generic and an evaluation of the Drug Master File is required (covering toxicology and pharmaceutical chemistry aspects).
- an approved medicine for which the device application involves a new indication, will undergo clinical assessment within the device program and the application will be referred to the drug evaluation area for pharmaceutical chemistry aspects.



Process summary

- Application for conformity assessment to the device regulator
- Assessment by devices program (with referral to medicines regulator for advice – may go to ADEC, MEC or CMEC)
- Consideration by MDEC
- Device Regulator issues Conformity Assessment certificates to manufacturer, if approval recommended



5 Years Experience

Common problems



Compliance of medicinal components

- Must meet all regulatory requirements applicable to the medicine
- Requires agreement of medicine manufacturer
 - Access to DMFs
 - Evidence of GMP compliance
- Device manufacturer's QMS must take into account medicine supplier



Pharmaceutical chemistry issues

- Control and release specifications
- Uniformity
- Elution characteristics



Clinical evidence

- MDEC concerned about lack of clinical evidence specific to the device/combination product
 - Number of patients
 - Endpoints for trials



- Post-market review of DES
 - Expert Working Group on cardiac devices
 - Need for tracking/extended follow-up
- Regulation of device/biological combinations
 - To be addressed in time by new framework
 - Device component not a medical device in its own right



Priorities:

- Guidelines on process
- Work to develop links in the global context
- Guidelines for device manufacturers on content of dossiers



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

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