Advisory Committee on the Safety of Medical Devices

Meeting statement

Meeting 11 – 5 November 2015

Role of the Advisory Committee on the Safety of Medical Devices (ACSMD) in the TGA’s regulatory decision making process

The ACSMD is a statutory advisory committee established by the Therapeutic Goods Regulations 1990.

The TGA currently has ten statutory advisory committees from which it can obtain independent expert advice on specific scientific and technical matters to aid the TGA’s regulatory decision making and other regulatory processes.

The ACSMD provides advice to the TGA on, amongst other things, matters relating to the safety, risk assessment, risk management and performance of medical devices supplied in Australia.

How this statement should be read

The advice provided by the ACSMD is an important element in the undertaking of the regulatory functions of the TGA. However, it forms only one part of the total body of information that is available to, for instance, a TGA delegate making a regulatory decision under the Therapeutic Goods Act 1989 (“the Act”). Therefore, while appropriate consideration will be given to such advice, it is important to note that neither the TGA nor a TGA delegate is obliged to follow it.

It should also be noted that details of the committee’s advice may not become publicly available for some time after the committee has provided that advice. The purpose of this Meeting Statement is to describe in general terms the matters considered by the committee at each meeting and for it to be available as soon as reasonably practical after the relevant meeting.

Additionally, following publication of this statement, it is most likely that further work will be undertaken by the TGA to investigate, monitor and / or evaluate the medical devices considered by the ACSMD; and this will continue for some time into the future. It is therefore possible that further information about the medical devices will become publicly available at a later time and this will be pursuant to a regulatory decision under the Act being made and following further consultation with the device’s sponsor and / or manufacturer.
Overview of the medical devices referred for advice

The TGA continually monitors medical devices supplied in Australia to ensure their ongoing safety, quality and performance (as the manufacturer intended). As part of this process, the TGA routinely undertakes safety reviews of medical devices, seeks advice on proposed safety reviews and Risk Management Plans and also undertakes post-market monitoring of medical devices.

Safety / Post-market Surveillance Reviews

At this meeting, the committee’s advice was sought on a safety review which gave consideration to a number of adverse event reports received by the TGA in relation to the CardioCel Adapted Collagen Scaffold (“CardioCel”).

CardioCel Adapted Collagen Scaffold

The committee noted that the device is not currently included in the Australian Register of Therapeutic Goods (ARTG). It has been accessed in Australia via the Special Access Scheme (SAS)\(^1\) and Authorised Prescriber (AP)\(^2\) scheme. To date, only a small number of surgeons have sought access to the device under either of these schemes.

CardioCel is a bioscaffold material prepared from bovine pericardium procured from cattle originating in Australia. The device is a sterile, pre-cut flat sheet of acellular collagen, available in various sizes. The Instructions for Use (IFU) for CardioCel supplied in Australia state that the device ‘is indicated for use to close and repair cardiac septal defects or injured myocardial tissue’. The device’s use in Australia has been for complex congenital heart repair procedures such as aortic arch reconstruction in newborns.

The CardioCel devices have been sold worldwide and the manufacturer has been notified of 11 potential adverse events (including seven in Australia). Ten were reported for restenosis (at varying times, post-operatively) and one report was for thrombus formation. According to these data, it appears that the current overall adverse event rate is 0.5%. The current rate of restenosis is 0.45%.

Following its review of the adverse events and published literature regarding the use of autologous pericardial patches used in aortic arch reconstruction in newborns, the committee noted the TGA’s conclusion that the current rates of adverse events, including restenosis and thrombosis, are low compared to that seen in the literature.

The committee also noted the TGA’s conclusion that a number of outstanding issues remain i.e. the rate of adverse events in Australia is higher than that seen world-wide, it is difficult to conclude if the current rates are acceptable given the cohort of patients in whom the device is used and it is not clear if the seven adverse events in Australia highlight important factors that should be included in the IFU documentation.

The committee was asked to provide advice on whether the seven adverse events reported in Australia are known adverse events related to this device and surgery. The committee advised that they can be considered as known events and expected for the type

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\(^1\) Information on the Special Access Scheme (SAS) is available on the TGA website: [https://www.tga.gov.au/access-unapproved-therapeutic-goods-special-access-scheme](https://www.tga.gov.au/access-unapproved-therapeutic-goods-special-access-scheme)

of surgery, irrespective of the type of prosthetic material used. While the method of manufacture of CardioCel is novel, the procedures in which it or a similar device is used, are established. Stenosis and obstruction/thrombosis are recognised complications of congenital cardiac repair irrespective of the device used in surgery.

Based on the clinical pictures described in the Australian adverse event reports, the use of CardioCel in the seven Australian patients who experienced adverse events was consistent with its approval in the United States of America (rather than the narrower Australian IFU).

The committee was asked to provide advice regarding the rates of adverse events associated with this device. According to information provided by the sponsor, the rate of adverse events in Australia is approximately 5%; however, this is based on very low numbers used.

The committee advised that this apparent difference in rates of adverse events raises various issues. In particular, it is unclear if the reported adverse events are specific to the device, surgeon or are surgery-related outcomes.

The committee advised that the IFU supplied in Australia lists multiple adverse events which cover the range of adverse events observed to date. The committee also noted that the indications in the Australian IFU are narrower than that found overseas and that out of the seven reported adverse events, only one appeared to be outside the indications.

The committee advised that, given the limited information available at this time, monitoring of the use of CardioCel and adverse events should continue. The committee also advised that the device could be revisited at a future ACSMD meeting if necessary.

**Proposed Safety Reviews**

No proposed safety reviews were considered at this meeting.

**Risk Management Plans and Post-market monitoring**

A Risk Management Plan (RMP) is a set of pharmacovigilance activities and interventions designed to identify, characterise and/or manage risks relating to a therapeutic good. No RMPs were considered at this meeting.

At this meeting, the committee’s advice was also sought on performance testing of automatic external defibrillators (AED) supplied in Australia, specifically which waveforms are shockable or non-shockable and proposed ‘out of the box’ (useability) testing.

**Automatic external defibrillator (AED) waveforms**

AEDs are portable devices designed to automatically detect cardiac arrhythmias and automatically deliver an electric shock to the chest. The device consists of an external monitor with cardiac rhythm detection software and skin adhesive electrodes that assist in monitoring and delivering the shock.

At ACSMD Meeting 4 (8 August 2013), the committee’s advice was sought on a proposed safety and performance review of AEDs, as a large number of adverse event reports had been received by the TGA.

At that time the committee’s advice had highlighted the need for Instructions for Use (IFU) to cover issues of periodic inspection and battery life, that many AEDs in circulation may
no longer meet current standards, that a study which found that half of all reported incidents occurred during attempts to shock and also the importance of human factors.

Since receiving this earlier advice from the committee, the TGA has reviewed the IFU documents for these devices. The TGA has also commenced performance testing of selected devices, using simulated waveforms.

The committee was advised that limited, ‘out of the box’ useability testing is now planned with the aim to assess the ability of the intended users (lay-persons) to use the device, with limited training, in an emergency situation. AEDs can deliver life threatening shocks to patients and users/bystanders if the shock is inappropriately delivered or incorrectly delivered. Inability to operate the AED may prevent delivery of life-saving therapy.

The committee was asked to provide guidance on the ‘shockability’ of waveforms generated by a simulator. The committee provided advice on which waveforms are always shockable, which waveforms are considered to be indeterminate/contingent from a clinical perspective, waveforms which are always non-shockable and waveforms considered as being unrealistic rhythms and which would very rarely occur in patients.

The committee advised that the waveforms generally looked realistic and covered a comprehensive range of possible rhythms. No further waveforms that should be included in the test battery were identified. Waveforms that are unlikely to occur in real-life should be excluded from the tests.

The committee also advised that low voltage signals can lead to withholding of shocks and low voltages can be expected for certain patient characteristics (e.g. obesity). It is also not possible to cover every rare cardiac pattern (e.g. for patients with various sinus rhythms with intraventricular defects).

The committee was informed that the test series had been derived from the American Heart Association guidelines. The waveforms selected reflected the operational range of a standard cardiac simulator that service technicians would use in testing the AEDs, including testing at the extremes of performance. Technicians testing AEDs should be aware of both shocking classifications as well as waveform patterns. The committee concluded that a suitable range of settings and battery of tests have been selected by TGA.

The committee was also asked to offer suggestions for the conduct of, or issues to consider during the planned usability testing of AEDs by lay-persons. The committee reviewed a draft protocol for usability testing of AEDs against the framework of ‘formative testing’. Such testing is not designed to be comprehensive or provide statistical evidence, but to prioritise the testing of tasks based on risk analysis and task relevance; and thereby obtain insights into the user experience.

The aim of usability testing is to identify devices that need further investigation. The main tasks that could be tested are time from start to first shock (TTS), adequate pad placement, and safety throughout the process for the tester.

The committee suggested a number of amendments to the draft usability testing protocol, including consideration of conducting the testing as ‘user in the loop’ rather than ‘cognitive walkthrough’, reduce the number of devices tested, collect basic demographic information about test participants and acknowledge any selection bias, exclude or document test participants with prior knowledge of AEDs, increase the number of test subjects per device from 8 to 10 to allow statistical analysis, expand the testing scenario to the point of placement of the pads on a manikin, include videotaping of the test performance, amend the test questions to include some prompts, determine a benchmark of what is a desirable/adequate TTS prior to testing and create a sense of time pressure, within the bounds of ethical conduct of the test.
Regarding analysis of the results, with a suitable number of test participants, statistical review may be undertaken of the TTS. For other observations, thematic analysis should suffice. The committee advised that 'what constitutes a critical problem' should be defined prior to testing.

The TGA advised that while considerable variation in how devices switch to paediatric mode had been observed in the pilot performance testing of AEDs, paediatric testing would not be part of usability testing. The committee concurred with this approach.

The committee noted that given the increasingly wider distribution of AEDs in public places, adherence by the purchasers to the maintenance schedule for the devices is of increasing importance. Further, given the place of AEDs in the delivery of first aid in various settings (workplaces with trained first aiders, or in public places), the committee suggested that the instructions should also include 'call for a first aider' as well as the advice to 'seek emergency medical assistance'.

**Stakeholder engagement**

From time to time representatives from other statutory committees and international regulators are invited to attend a TGA statutory advisory committee meeting.

In this context, it is a standing arrangement for representatives from New Zealand's Medicines and Medical Devices Safety Authority (MEDSAFE), to participate in ACSMD meetings as observers.

**Subcommittee update – Orthopaedic Subcommittee (OSC)**

There has been no OSC meeting held since ACSMD 10 on 26 August 2015. As advised in the Meeting Statement for ACSMD 10, the next meeting of the OSC is scheduled for 7 December 2015.

**Further information**

Meeting statements are made publicly available after each meeting.

For further information on the ACSMD, please visit the ACSMD webpage or contact the ACSMD Secretary, Mr Craig Davies on 02 6232 8641 (telephone) or via email: acsmd.secretariat@tga.gov.au