Cook Medical’s comments to the Consultation Paper:

*Draft clinical evidence guidelines – Medical devices*

June 2016
Cook Medical and William A. Cook Australia Pty. Ltd.

Cook Medical, based in Bloomington, Indiana, USA, is one of the world’s largest privately owned medical device companies. Throughout its 51 year history, Cook Medical has pioneered many of the medical devices currently used to perform minimally invasive medical procedures. The company has grown to now serve 13 specialties with over 16,000 products.

Cook Medical’s Australian business, William A. Cook Australia Pty. Ltd., is based in Brisbane and employs more than 450 people in manufacturing, R&D, operational and sales capacities. The Brisbane facility is also Cook Medical’s Asia Pacific (APAC) headquarters and provides support for the more than 1,000 staff across the APAC region. Cook is one of only a few medical device companies that continue to utilise Australia as a manufacturing base. From this facility, Cook exports Australian made products to over 135 countries around the world. Through our R&D activities, William A. Cook Australia Pty. Ltd. has grown to become a centre of excellence for the design, development and manufacture of endovascular aortic devices and products designed for use in reproductive health.
Introduction

This response is a collation of feedback received from multiple contributors throughout a number of Cook Medical companies, globally. The contributors include regulatory and quality system specialists, clinical evaluators and clinicians that have many years of experience with medical devices of all risk classifications.

Cook is supportive of the creation of the “draft clinical evidence guidelines - medical devices”. These guidelines have the opportunity to provide valuable information to manufacturers and sponsors about the TGA’s expectations for clinical evidence. Although the draft guidelines, in general, adopt a reasonable approach, Cook is of the opinion that certain key areas should be reviewed before publication of the final document.

1. Definitions - definition of “predicate”

Cook is concerned that the TGA’s definition of a “predicate” (page 15) could cause confusion as it is not consistent with the definition used by other international regulatory bodies. For example, the definition of the very commonly used term ‘predicate’ by the US Food and Drug Administration (FDA) is very different to that described by the TGA. A predicate under the 510(k) framework does not necessarily need to be from the same legal manufacturer as the subject device.¹ Cook would suggest that a single term consistent with international regulations be considered; such as “equivalent device” i.e. “a device that meets biological, technical and clinical equivalency”. It is irrelevant whether the device is what the TGA describes as a “Predicate” or a “Similar Marketed Device”.

2. Reference to “sponsor” instead of “sponsor/manufacturer” throughout the guidance

The beginning of the guidance describes the intended audience for the document as being “sponsors and manufacturers” (page 3). This wording continues until page 15 and then in many places thereafter only “sponsor” is referred to. It would be considered rare that the sponsor would make decisions on the type of clinical evidence to collect and evaluate. It is the responsibility of the “sponsor” to provide the clinical evaluation report (and the supporting documents) to the TGA, but it is the manufacturer’s responsibility to meet the Essential Principles and have documentation to demonstrate compliance, not the sponsor.

3. Description of the submissions for which the guidance is relevant to

The guidance should explain whether the clinical evaluation described would be expected for ALL types of submissions, i.e. those prepared for review by a clinical reviewer as part of a full conformity assessment (with or without design examination) AND submissions (for all device classes) based on previous CE marking (and therefore, abridged applications) if this is the intention of the TGA. This should be clarified, particularly for the benefit of less experienced manufacturers or sponsors.

4. Preference for randomized controlled clinical trial (RCT) data

In the requirements for specific high risk devices, the guidelines state there is a preference for RCTs. While understanding the hierarchy of evidence, we suggest that this is qualified e.g. with “where possible or appropriate.” For example, for a device that is intended to treat a small patient population, the ability to conduct an adequately powered RCT may be extremely difficult. Likewise, many of the devices in the high risk category e.g. on page 51 do not lend themselves to a RCT due to ethical considerations. Although

¹http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/
these are guidelines, we are concerned that this “preference” sounds absolute and has the potential to be directly enforced without consideration of its applicability to the device and the pathology at hand.

5. Supporting documents

The draft guidance states that the following supporting documents should be provided with the Clinical Evidence Report (CER):

- Full technical and physical specifications of the device (page 27)
- Risk analysis and [?risk] management documents (page 27)
- Quality Management System (pages 53, 61, 71, 80 and 92)

6. This suggests that almost the entire Technical File or Design Dossier plus additional QMS documentation should be supplied as ancillary documents to the CER. This would certainly be unsuitable for devices being submitted based on previous CE marking. For all high risk and devices undergoing full conformity assessment (with or without design examination) the Risk Analysis and Risk Management Reports are already requested by the TGA separately to the CER. Likewise, Quality Management System documents are requested by TGA separately to the CER for all devices undergoing full conformity assessment. These devices will then have TGA QMS audits. For devices which are being submitted for abridged review based on CE marking, the manufacturer’s QMS has been reviewed and is continually audited by their EU notified body. Requesting that these documents be attached to the CER will therefore be repetitious and will create an unnecessary burden for manufacturers. **Structural issues in the Guidance**

Certain sections of the document could be edited to improve readability. The statements below indicate these areas:

- The appendices for the high risk devices could focus purely on the TGA Rapid Review (RR) methods and references to standards etc. The safety and performance outcomes (e.g. Table 11 on page 141) should all be incorporated in the relevant section as it may be confusing to sponsors and manufacturers to have the information presented in two different ways. For example, Table 26 (page 174) in the appendix is a summary of safety data on supportive devices. However, it doesn’t include all of the complications described in the supportive devices section such as brain tissue scarring, new epileptic seizures or mortality as mentioned in the patches section on page 87.2
- Throughout the document the headings are not consistent and do not describe the subsequent wording well. In some cases the choice of font and the lack of sub-section numbering add confusion.
- If sponsors and manufacturers were to read only the section of interest, without reviewing all of the introductory sections, it is possible that TGA’s expectations will not be clear. As an example, on p170 of the draft, there is a heading discussing the search methodology used for high risk devices (Appendix 11). The opening paragraph relates to the search strategy employed and it is not initially obvious that this was the search strategy that the TGA employed, not what is expected by sponsors and manufacturers in their CERs (i.e. sponsors/manufacturers are required to perform systematic literature reviews, not rapid reviews).

---

2 Note: the table referencing also needs refreshing, e.g. *Appendix 11: supportive devices*, Table 24 is referred to on page 87 presumably should be Table 26.
The guidelines can be repetitive. Where the guidelines provide guidance for the high risk devices, they could focus on the product-specific issues and refer to chapters 3 - 5. For example, remove the following paragraphs, which have been described earlier in the guidance:
  o P49 – “It is recommended that the sponsor supply post-market data if the device is approved....”
  o P49 – “When submitting a comprehensive literature review, full details of the search method....”

7. Recommended structure of the Clinical Evaluation Report

A few alterations in the recommended structure of the CER shown on page 21 could increase the likelihood that TGA are provided with the information they require. For example, it appears that a section such as “State of the Art” is absent. It is therefore unclear which section would be used to explain the existing therapies. Also, item 9. “Risk Analysis and risk management” is located after 8. “Post Market Data”. Consider placing this section before item 4., “Summary of any pre-clinical data” as you would present the product risks which may need mitigating in subsequent sections such as the pre-clinical and clinical study sections.

8. Search strategy employed by the TGA for high risk devices

To increase transparency, the TGA should disclose what search terms were used in their rapid reviews (RR) of high risk devices instead of simply citing “appropriate search words and subject headings.” As the measures identified by these RR will potentially act as benchmarks e.g. x% for an adverse event, it should be clear to sponsors and manufacturers how the outcome measures were sourced.

9. Requirements for High Risk Devices

Guidance provided on specific devices should be accurate and reflective of current practice. For example, for guidance provided for AAA grafts:

i. Surrogate markers for predicting implant failure for AAA

On Page 49 – it is suggested that a Type II endoleak would be a suitable surrogate marker for predicting implant failure. Type II endoleak could be considered to be a marker of disease progression, but not a surrogate marker of the implant failing. A better choice of surrogate marker for implant failure (AAA Endovascular Grafts) would be “Persistent increasing aneurysm size”. This is supported by the reference used by the TGA – ref# 88 – Chaikof EL et al. where they state “changes in aneurysm dimensions have been used as surrogate markers for clinical efficacy for EVAR...”.

ii. Statement Regarding EVAR replacing Open Repair of AAA

On page 50, the statement “Open surgical excision of an aortic aneurysm with placement of a sutured implant is increasingly being replaced by endovascular surgery.” This sentence needs qualification. Open surgical repair remains the treatment of choice for many patients who can undergo open repair, such as those who are younger and have few co-morbidities. This situation is unlikely to change in the near future.

Note: The word “excision” should be replaced with “repair” as the aortic aneurysm is not excised.
10. Lack of definition and guidance on requirements for Post Market Surveillance

Post Market Surveillance (PMS) is an important part of the Quality System and should be described and detailed within this guidance document (in the absence of TGA guidance on PMS). Throughout the document there is some reference to “Post Market Surveillance”, for example on page 6. There is no definition of PMS presented within in the guidance, but PMS is mentioned under the definition of Clinical Investigation:

“Clinical investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

This term is synonymous with ‘clinical trial’ or ‘clinical study’ (these terms are used interchangeably in this document). Clinical investigations include feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing approval.

Routine post-market surveillance may not constitute a clinical investigation (e.g. investigation of complaints, individual vigilance reports, literature reviews).”

The term “post market surveillance” is not mentioned again until Section 6 - Requirement for High Risk Devices, page 44 where it is used in the context of a joint registry:

“...the post-market surveillance data from national registries for jurisdictions where the device is approved for clinical use.”

According to previous GHTF guidance documents, the TGA had a definition of Post Market Surveillance back in 2006, but this needs to be updated to meet the current TGA requirements:

"Medical device post market surveillance" means those activities carried out (by either the regulator or the manufacturer) to gain information about the quality, safety or performance of medical devices which have been placed in the market. In contrast to Vigilance, Post Market Surveillance measures are usually proactive.”

It is important that this guidance clearly defines what is expected by the TGA for Post Market Surveillance and whether it incorporates Vigilance plus other active surveillance activities such as post market clinical studies, literature searches, registries and regulator advisory notices etc.

11. Role of the Clinical Expert and others involved in CER preparation

The guidance is unclear as to the exact role of the ‘Clinical Expert’ and other individuals involved in the generation of the CER. Page 10 refers to Part 8 of the TGA Medical Device Regulations which states that the clinical data is “critically evaluated by a competent clinical expert…”, but then on page 19 it states that a “report must be provided, written by a competent clinical expert … It is recommended that reviews are prepared by researchers skilled in systematic review methods in conjunction with a clinical expert. This will increase the scientific rigour of the review.”

On page 27, it is suggested that the clinical expert for a coronary stent submission should be a practising interventional cardiologist. This seems unnecessary unless the device was based on a very novel treatment. It also states that “Any convergence of interests or potential for conflict with the sponsor or manufacturer must be acknowledged and addressed.” All clinical experts involved with
the preparation of a CER would have a conflict of interest as they are working for and probably being paid by the medical device company to do so.

On Page 30, it explains that the clinical expert who critically evaluates the clinical data and endorses/signs the CER is expected to have direct clinical experience in the relevant field using similar devices or performing similar procedures. Many clinicians would have the skills to assess clinical risk without direct clinical experience in the relevant field. This is especially true for lower risk devices.

In reality, a good CER is likely to be produced and reviewed by a team of suitably trained individuals with a range of expertise.

12. Guideline updates

Given the broad product offerings in the medical device field, it is important that the guidelines have the flexibility to consider new and innovative products. Therefore, to keep the guidelines current, the TGA will need to incorporate new benchmarks and outcome measures as a consequence of innovation and the introduction of new high risk devices. It is also important that any limitations/issues with the guidelines that may become known be acknowledged and addressed within a reasonable time frame. Finally, it would be useful for stakeholders to know about the frequency of planned updates and be part of the consultative process of review.

13. Other

- Page 19 – When referring to “recalls”, should add “recall for product correction” (as per the URPTG) as this covers other safety related actions which may not incorporate product removal. Also consider adding “other corrective action occurring in the market” as using the word “recall” means “product removal” in other regulatory jurisdictions.
- Page 50 – “Non-invasive transcatheter closure of PDAs...” – the procedure is invasive to some extent, “Minimally invasive” may be more appropriate.
- Page 50 – “The filters are metal alloy devices, generally in an umbrella shape, that mechanically traps fragmented clots in the deep leg veins” – this is incorrect, filters are placed in the inferior vena cava and trap clots that come from the deep leg veins.
- Page 52 – “for every year since launch, the number of adverse events and complaints...” – This would not be necessary/appropriate for all devices e.g. high volume devices and/or low risk devices which have been on the market for a long period of time.
- On page 57 – “Implants for AAA repair” – Table 2 is referred to but it does not seem relevant to these devices.
- Page 59 – “… use appropriate study designs with sufficient power to detect rare events.” – this could result in study designs requiring unachievable sample sizes. Even within large drug trials rare events may not be seen until the drug enters the market and is used in thousands of patients. Rare events would then be picked up as part of PMS.
- Page 94 – “Other information that should be provided for all IMDs includes:” – This list includes items that would not necessarily need to be provided for all IMDs, needs some clarification.
- Page 111 – “Substantial Equivalence confirms that the new device is as good as, as safe as...” – consider removing “is as good as”.
- Page 115 – Post-Market Surveillance is given the abbreviation “PS” – it is usually abbreviated to “PMS” – for example, throughout the GHTF PMS guidance.
Conclusion

Cook appreciates the opportunity to provide comments on the proposed Draft Clinical Evidence Guidelines – Medical Devices. Clear and informative guidelines will assist companies to understand the clinical requirements of both new and existing products and ensure that appropriate information is provided to both the regulator and the medical community.