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EXPERT ADVISORY COMMITTEE ON MEDICAL DEVICES USED IN CARDIOVASCULAR SYSTEM

November 15, 2002
Record of Proceedings

Committee Members Present: Dr. Raymond Yee (Chair), Dr. Michel Carrier, Dr. John Ducas, Dr. David Hilton, Dr. Charles R. Kerr, Dr. Louise Laramée, Jim MacDonald,CCP, CPC., Dr. Joaqim Miró, Dr. Brent Mitchell, Dr. Richard N. Rankin, Timothy J. Zakutney, M.H.Sc.,P.Eng.

Committee Members Absent: Dr. Sean Connors

Health Canada Representatives Present: Dr. R. Peterson, Dr. Roland Rotter, Dr. Denis Cheung, Dr. William J. Freeland, Dr. James McGarrity, Dr. Satish Chander, Ms. Nancy Shadeed, Ms. H. Shahbazian, Ms. Shelley Wagner

Health Canada Observers: Mr. Eric Ormsby

Opening Remarks (Dr. R. Peterson)

The Director General (DG) opened the meeting by welcoming the committee members and thanking them for agreeing to participate in this Expert Advisory Committee (EAC). He outlined the importance of their participation in providing advice to Health Canada (HC). He indicated that this committee will continue its work as an expert advisory board, this is a new concept where the Directorate seeks advice for device applications for problematic areas when there is a limited internal expertise. He stressed the fact that HC is not delegating the responsibility to make decisions.

The EAC members were informed that the proceedings of these meetings will be posted to the HC website. The DG described the need for a clear record of decision from the Chair of the committee.

The DG spoke briefly on Conflict of Interest (COI). It is important that there is no perceived appearance of COI. If an issue arises during the day that may be perceived to be in conflict, it is incumbent on the member to identify this issue and it will be dealt with accordingly.

The DG mentioned that the members must remember to exercise caution with regard to any confidential documents or issues that might be discussed by the EAC. They should ensure that any comments made to the press should be made clearly as their own personal views and not the opinion of the committee. Any inquiries from stakeholders, including the press, to the committee members on issues discussed by the committee should be referred to the Chair of the EAC.

Roundtable - Introductions/Chair's vision of EAC-MDUCS

After the members introduced themselves, the Chair gave a brief outline of the Mandate of the EAC and of his personal goals for the operation and results expected. He stated that the EAC should function based on a forum of open dialogue, and he encouraged views from varying perspectives in an effort to form a consensus with authoritative recommendations as an outcome.

He indicated that the timing of this Committee is opportune. HC reviewers need input - in order to expedite the regulatory process - this requires the input from external experts in the field.

He reminded the members of their role as an advisory body only, whose mandate is to try to reach consensus on the questions asked by HC and to provide information and recommendations to HC. In addition to this function it was noted that TPD would like to be advised if there are any emerging issues before receiving device applications. This is a two way communication.

Housekeeping items were discussed, details about the facility as well as the expense statements - how they are to be filled out and submitted.

The tone was set for future EAC-MDUCS meeting - namely free and open discussion and business casual dress code. All input collected during this meeting will be recorded in the final recommendations.

The frequency at which the EAC-MDUCS will meet will be discussed at the end of the meeting. Other forms of communication were discussed in general terms:
Video-conferencing
Tele-conferencing
E-mail

DG addressed the different modes of communication. He indicated that video-conferencing has limitations and is not a good option. He recommended that 2 day meetings should be scheduled if possible to allow sufficient time for discussion and advice. One or two members that are not able to travel may participate by teleconference. Suggestions from the committee members will be sent to Dr. Yee and Hripsime Shahbazian via email with respect to dates, times and locations of future meetings.

Dr. Yee suggested to identify an alternate in case the chair is unable to serve at a meeting. He will discuss this with the members and provide an alternate for a chair.

DG described nature of requests that will be brought to the committee for advice and recommendations including:

- Guidance documents (periodic)
- Specific issues dealing with specific applications.

He indicated that specific issues may be assigned to members who have the expertise and time to look at them and report to the committee. In case a member is not available to take this task TPD will look at other resources and appoint a panel.

In concluding his opening remarks, the chair stated that based on committee deliberations, draft guidance documents will be produced and distributed to all members for their review and input. The Chair agreed to take a lead role by preparing a template, and sending it to appropriate expert members to provide input. The recommendations from this committee belong to the group, and the draft guidance documents will be formed from a compilation of committee deliberations. All members must approve the documents before they are finalized. Details will be arranged between members.

Additional comments should be brought to the chair's attention.

Review Agenda (Dr. Raymond Yee)

The chair addressed the agenda, and suggested some flexibility, with the hope of reaching consensus on most issues by the end of the day. If this is not possible, he mentioned the possibility of further consultations, either by teleconference or e-mail to finalize some issues if necessary. The agenda was altered to switch items 9 and 11 - namely to address Ablation Therapy Issues first and Drug Coated Stent Issues second to accommodate the travel itinerary and premature departure of one of the members. The members agreed to have 30 minutes for lunch break. Also items 14 and 15 on the agenda were moved after lunch break to allow more time for discussion of presented questions. The agenda was accepted with these changes.

Terms of Reference (Dr. Raymond Yee)

Some members indicated that they would prefer to receive the background information electronically. It was proposed that the information packages be sent electronically in both WordPerfect and MS Word formats. It was also proposed that the electronic information packages be sent a minimum two weeks prior to the date of the meeting.

Committee Mandate was reviewed. It was suggested that the second paragraph in section 1 a) of the Mandate of the Terms of Reference be moved to the body of the text.

It was also suggested to include cardiac perfusion in section 3 c), paragraph 2 and paragraph 3 to specifically include intraoperative cardiac perfusion equipment

No other comments were put forth, and the TOR were accepted with these minor changes.

Conflict of Interest and Indemnification with respect to Expert Advisory Committees (J. Northey)

A brief presentation was made by J. Northey, Counsel from Department of Justice Canada to ensure that the members have a common understanding of legal issues associated with Health Canada Expert Advisory Committees. The presentation touched on Indemnification, Conflict of Interest and Access to Information Policy.

Overview of Legislation and Regulation (N. Shadeed)

N. Shadeed delivered a presentation intended to give EAC members a basic understanding of the authority and responsibility to regulate medical devices under the Food and Drug Act and Medical Devices Regulations. Members found the presentation informative.

Questions were asked regarding Special Access. Members asked if there is a review process before authorizing Special Access. It was explained that there is a summary review only. The intent of the Special Access is to ensure that existing regulatory process does not prevent the best treatment available for a patient. It was asked if a patient follow-up was conducted. DG explained that this is not a regulatory requirement at this time.

Premarket Review (Dr. Denis Cheung)

A general overview of premarket requirements for Class IV devices was given by Dr. Cheung. Questions were asked regarding peer review, supporting evidence. There was a concern regarding timely access to publications. Dr. Cheung explained that Medical Devices Bureau looks at all information provided at the time of the application.

It was asked if the company could withhold information regarding a product at the time of application. Liability of the manufacturer was discussed. It was indicated that HC could ask for additional information by Section 39 letter requesting more information, if not satisfied by the supporting data or becomes aware of issues surrounding the device in question.

Members raised the need for Canadian data to address patient diversity. There is no specific requirement for Canadian data at this time.

There was a concern that the clinical trials were conducted on men only. Shouldn't HC look at effectiveness and safety both in men and women? It was suggested that perhaps the labelling could indicate that "Efficacy and safety have been proven in men - remains to be proven in women". It was explained that there are no specific regulatory requirements for this. There needs to be a biological reason to go after that additional information. It would depend on nature of the device. This is referring to the applicability for scientific data, a debate better suited for another group.

After lunch break the members were asked to provide Hripsime Shahbazian with their availability for the next meeting that is tentatively planned for May-early June of 2003.

Ablation Therapy (Dr. S. Chander)

Dr. Chander presented the "Ablation Therapy Issues/Questions". General comments/questions arose from the members of the committee regarding the presented questions.

Question 1 - What are the safety and effectiveness criteria for evaluating "Mapping Technology" for determination of the targeted arrhythmia mechanism?

Question 2 - Recurrence of arrhythmia is noticed after ablation treatment. What are the Study End-Points? Desired and Undesired Effects. (How long should we monitor the patients after treatment?)

An informed debate ensued around the following issues:

- Does the product perform according to its claims?
- Does it provide the patient with any improvement?
- Are we looking at the results of the treatment?
- Are we considering efficacy?
- Is there a benefit to this therapy?
- Are we looking at how to evaluate a new product, what kind of questions should we ask to the manufacturer?
-How do we measure efficacy?
-How well did it help the patient?

The Committee felt that the issues of ablation therapy equipment and Mapping Technology are related but are distinctly different and should not be mixed. Mapping Technology assists in locating the desired areas of the heart to be ablated but is not, in and of itself, a treatment. Therefore, the efficacy of any Mapping Technology cannot be measured by ablation endpoints. It was agreed that the committee will address Question 2 first.

The members stated that, in the case of ablation therapy, we are not dealing with just a single disease but a group of diverse diseases with differing etiologies and mechanisms. Therefore, study design and endpoints to be measured in a clinical trial of new ablation technology will differ depending upon the specific arrhythmia and device application. As a general rule, a randomized clinical trial would be appropriate for many of these devices. The control comparator would usually be radiofrequency energy catheter ablation using already approved ablation catheters. Radiofrequency energy ablation therapy for most cardiac arrhythmias is safe and efficacy is well established for most arrhythmias. One of the members referred TPD staff to a recently published CCOHTA report on "Radiofrequency Catheter Ablation for Cardiac

Arrhythmias: A Clinical and Economic Review" [1]. We should encourage companies to conduct and submit results from randomized clinical trials where possible. Placebo control trial design is not applicable in most cases.

All members agreed that we need to set reasonable standards for clinical trial design and endpoints for evaluating safety and efficacy of ablation therapy. We need to look at what information is required to determine that the new device is as good as established treatments. Simply quantifying the extent to which cardiac tissue is ablated is not sufficient.

What type of endpoints should we be asking for? The chair suggested that there are well established endpoints. Endpoints are indication specific. It was agreed that the Chair will put together a draft document on acute and chronic endpoints and circulate it to members by e-mail for input.

The committee recommended that randomized clinical trials should be the basis for safety and effectiveness data whenever possible. The specific acute end-point for effectiveness will usually be elimination or isolation of the arrhythmia substrate and immediate procedural safety data. Long term effectiveness data will depend on the indications for use, e.g., 1 year follow-up for AF.

Question 1 was discussed next. It was agreed that we need to address convenience of methodology being used as well as how long the procedure takes, regardless of whether ablation is successful or not. It was restated that the mapping technology quality does not equate with ablation catheter's safety and effectiveness but may indirectly impact ablation success and complication rates in more complex arrhythmias.

The newer mapping technologies essentially perform the function that the physicians brain currently performs although much better and faster than the human mind can achieve. Usually the users decide what mapping technology they are going to use taking into account the type of arrhythmia and anatomic location of the substrate. New mapping technology, however, is evaluated primarily on safety and biomedical criteria. In other words, companies applying for approval of Mapping Technology need to provide data proving that the technology provides the accuracy and resolution claimed in addition to safety information. It was agreed that a biomedical point of view with respect to mapping is more applicable than clinical outcome.

It was concluded that committee recommendations would be in a form of a guidance document. The Chair will create a template for members to provide input based on deliberations of this meeting.

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[1] Noorani HZ, Yee R, Marshall D, Connolly S, Nichol G, O'Brien B. Radiofrequency catheter ablation for cardiac arrhythmias: a clinical and economic review. Ottawa: Canadian Coordinating Office for Health Technology Assessment. 2002. Technology report no 25.

DG indicated that the challenge is existing resources. It is the same backlogged staff that does the work on guidance documents. We need to make our expectations clear to sponsors. Based on the Committee's discussions, there is sufficient information to generate a guidance document. TPD will use committee recommendations to prepare a guidance document. The document will be published as a draft. TPD will post it for stakeholder consultation/comments. Once comments are received and collated they will be sent back to the committee for review.

Dr. Mitchell left the meeting.

Drug Coated Stents (Dr. J. McGarrity)

Dr. McGarrity presented issues with drug coated stents.

1. Considering patient safety and ethical issues and the possible emergence of confounding variables, i.e. co-morbidities unrelated to the use of the device, which can obscure the outcomes of long clinical trials; what clinical tests and follow-up periods can be recommended to support the safety and effectiveness of drug coated stents.

2. For licensing purposes, if it is judged that some flexibility can be afforded, what guiding principles can be recommended with regard to:

a. Indications for Use and
b. Stent diameters and lengths

3. What further clinical evidence is required for market authorization of

a. Restenosed coronary lesions,
b. Stenosed saphenous vein grafts,
c. Long lesions, e.g. tubular (10 - 20 mm in length) and diffuse lesions (>20 mm) and
d. Peripheral arteries.

The chair asked the members to look at the presented issues and deliberate.

The committee started by addressing the first issue: What clinical tests and follow-up periods can be recommended to support the safety and effectiveness of drug coated stents?

A lively and informed debate ensued with a quick review of recent clinical studies such as the RAVEL, SIRIUS, and the TAXUS study using various drug coatings (i.e. Sirolimus, Paclitaxel)[2].

[2]Garces K, Carere RG, Collins-Nakai RL. **Drug eluting stents: Managing Coronary Artery Stenosis Following PTCA**. Ottawa: Canadian Coordinating Office for Health Technology Assessment. 2002. Issues in Emerging Health Technologies Issue no 40.

Sirolimus eluting stents:
- RAVEL trial involved 238 patients with single primary target lesions in a native coronary artery
- SIRIUS trial was double blind, multicentre trial involving 1,001 patients with focal *de novo* native coronary arterial lesions.

Paclitaxel eluting stents:
- TAXUS program included several trials investigating paclitaxel.

It was stated that at present there are 30 different drug coated stent trials underway with different drugs, different eluting speeds associated with different polymers. In some cases polymers dissolve, in others they remain in a system.

Industry standard for follow-up is 6 months; however, new studies suggest that restenosis may occur after 6 months, up to 12 months. The members felt that it would be reasonable to ask for some information beyond 12 months. Some members suggested that we ask for anatomical pictures and data at 12 months, (angiographic or IVUS data), before approving a product. Others were not sure if the manufacturer would be able to provide this type of follow-up after 6-months. The difficulty and limitations in study follow-up were discussed.

Committee members agreed that when assessing these products we need to have international perspective. Usually studies are designed and conducted to meet the regulatory requirements of various jurisdictions aside from Canada as the basis for product approval and it may not be possible to obtain all the data that we would ideally like to have. Members indicated that one of the products, Cypher sirolimus eluting stent, that was recently approved for use in Europe for the treatment of *de novo* coronary artery lesions $\leq$ 30 mm in length in native coronary arteries with reference diameters ranging from 2.25 to 5 mm, has 12 month follow-up data.[3] It was felt that we might not have randomized data at 12 months but we need longer term surveillance, 12 months at least.

A consensus was finally reached that a well designed randomized study for 6-months and significant follow-up data at 12 month are required. It was agreed that anatomical information at 12 months (IVUS, angiography) was unlikely to be acceptable to the sponsors or the participants in these trials therefore some form of clinical assessment at 12 months should be acceptable.

The stent diameters and lengths were discussed next. It was stated that in device application submissions companies usually extrapolate data from one size stent to another. The members did not feel that there are substantive differences for different sizes of stents. It was felt that 8 mm is too short and 18 mm is too long. The shorter lengths (8 mm and 13 mm) don't seem to present any special concerns. The longer lengths were discussed and their performance was comparable

[3] **J&J coated stent launch expected in all international markets by may 20**. The Gray Sheet 2002;28(16):23

to shorter stents. The members questioned if a longer stent behaves the same way as a shorter stent. It was mentioned that there are some technical difficulties using longer lengths, i.e., the coating may strip-off during stenting process. This could result in high drug dosage delivered to a segment of the coronary artery thus potentially accelerating restenosis. It was felt that for longer stents restenosis rate increases. The issue of pre-dilatation and long-length stents was discussed. Members indicated that pre-dilatation is required prior to stenting, however it is not done in practice.

With regard to stent diameter, it was felt that there is ample evidence of safety and effectiveness for stents with diameters in the range of 2.5 to 3.5 mm.

The members agreed that information on outcomes using different lengths and diameters of stents is important. The committee recommended that we ask for additional data for the extremes of stent dimension.

Another question that arose related to whether it is reasonable to encourage the clinician to insert coated drug eluting stents into restenotic coronary lesions? No conclusion was reached on this issue.

The chair concluded the discussion stating that the committee advice will be in a form of a draft guidance document. Due to time constraints it was agreed that the committee will discuss remaining issues electronically and organize a teleconference if required.

As indicated in the TOR, the record of proceedings of the meeting will be kept to the minimum detail required to summarize effectively the proceedings and to reflect decisions taken. This document will be prepared within five working days after the meeting by the Secretariat and then will be certified for accuracy by the members through the Chair. The Record of Proceedings will be posted on the TPD website after the removal of confidential and personal information consistent with the provisions of the Access to Information Act.

Meeting adjourned.
Next proposed meeting: May or June, 2003.

Date Revised: December 12, 2002