CAPRA Education Day
May 31st 2007
DoubleTree International Plaza Hotel, Toronto

Meeting minutes from Breakout Session:
Clinical Trial Applications – Understanding and Improving the Current Process
Presenter: Yadvinder Bhuller (Manager, Office of Clinical Trials – Group II – Health Canada)

1. What is TPD's position regarding Batch Analysis?

Some sponsors have clarified that in situations where the protocol is for international studies results from the clinical batch for the sites in Canada may not be available. In this situation, the Office of Clinical Trial's Quality Division will accept a fully representative batch as long as:

- The representative batch has the same manufacturing process, formulation for the drug product and equipment, batch size, specifications, container closure system, and storage conditions as the Canadian clinical batch; and
- The sponsor commits to provide the Canadian batch analysis information preferably prior to dosing.

1(b) The challenge is that in some instances the analysis information from the Canadian batch may not be available.

Mr. Bhuller requested for sponsors to do the following and preferably for the Rx&D meeting with TPD in June:

- Clearly identify what the issue is (as you have told me today);
- Provide a rationale/justification as to why the requirements can not be met; and
- Provide proposals/options for the OCT to review.

This is the approach that Mr. Bhuller uses when dealing with clinical issues and it has been well accepted and productive. Having said that, the clinical decisions have not always been favourable, but at least the sponsor has been provided with the scientific and/or regulatory justification.

1(c) Why is Health Canada asking for more information then other regulators such as the US FDA?

Regarding the comparison with other agencies, Mr. Bhuller commented on the fact that the requirements are similar between US FDA and Health Canada, based on a presentation which was already presented to Rx&D by Mr. Michel Bourdon of the OCT.

2. Has the OCT received CTAs for microdosing studies? If so, what are the requirements for these studies and how will they be classified?

Mr. Bhuller indicated that best to his knowledge and assuming that the inquirer was referring to studies referred in the US FDA GD for Phase 0 trials, the OCT has yet to receive such a study for review. With respect to the requirements, the sponsor may refer to the US FDA GD, but the OCT will be reviewing these type of CTAs on a case-by-case basis. It is also recommended that the sponsor have a pre-CTA meeting with the OCT prior to submitting such a study for review. With respect to the classification, depending on the proposed study, these may be classified as Phase

Other, where the sponsor can then specify the type of trial (this is currently used in the HC3011 form for studies such as Phase IIa, IIb and IIIb) or Phase I.

3. Is the sponsor required to complete the QOS Phase I template instead of the template for biostudies for a repeat dose study that is using a product that is already on the market?

The OCT recognizes that there is some confusion with respect to the QOS templates and that is why they are in the process of creating separate templates for Phase I, II and III trials. With respect to this particular question, it is requested for the inquirer to send this question, with specific and additional details directly to Mr. Bhuller, who can then have the relevant, internal discussion with Dr. Rajkumar Kumarathasan prior to providing a response.

4. Is it acceptable for the manufacturer-sponsor to use a Product Monograph (PM) in lieu of the Investigator's Brochure (IB) for a clinical trial that is using a product that is on the Canadian market? If it is acceptable, how will the manufacturer-sponsor submit the annual update?

As indicated in the Guidance Document for Clinical Trial Sponsors, for products marketed in Canada, a copy of the PM may be submitted in lieu of the IB. As you are away, the OCT does require a sponsor to submit an updated IB that includes all safety information and global status, annually or more frequently if the IB is updated more frequently. In this situation, the sponsor would need to submit any additional, relevant safety***** information and changes in global status, if applicable, annually, as an "addendum" to the PM.

Having said that, the sponsor is also requested to clearly identify in the cover letter for the annual updates the control #, protocol # and CR file # for all ongoing trials that will be impacted with this update. More importantly, the sponsor will need to clearly identify what the key changes were in the update and if these changes have or have not had any impact on the ongoing trials. If it has had no impact, the sponsor will need to provide their rationale. Providing this information will greatly facilitate the review process of the annual IB updates.

*******There are instances where the product monograph does change. Thus as a sponsor, you will need to confirm that there has been no change to the product monograph that was submitted with the original/parent CTA. This may involve contacting the manufacturer of the product. If there have been changes, please provide the revised/up-to-date product monograph and your cover letter should provide the information requested above. If no, your cover letter should clearly state that you have confirmed that there have been no changes and once again, the cover letter should provide the information requested above. Having said that, there are instances where the product monograph has not changed but a sponsor has provided information from the public domain (e.g. scientific articles from PubMed) as an addendum to the monograph since these articles are not only applicable to their trial, but have also had an impact on their study (e.g. resulted in a particular change).*

5. What is Health Canada's position on adaptive designs?

While Mr. Bhuller could not comment on Health Canada's position, from OCT's perspective he did mention that adaptive designs are not a new concept. That is, several oncology trials have utilized a similar approach in the protocol in order to deal with dose limiting toxicities (DLT). What is 'new' is incorporating this design in other therapeutic areas and expanding its use to also assess efficacy. Having said that, one of the challenging aspects related to these types of designs is the assessment of the data for statistical and clinical significance. This was also discussed at

the last Canadian DIA conference. Furthermore, at this point in time it is important for the sponsor to recognize that the use of this type of design may or may not be appropriate depending on several factors, including the phase of the trial (e.g. having an adaptive design for a pivotal phase III confirmatory study may not be appropriate). Thus, what he did suggest (especially if you are planning to do a pivotal Phase III trial) was to meet with TPD (e.g. via a preCTA meeting) prior to submitting your CTA.

6. What is the Office of Clinical Trial's goal with respect to issuing Clarifax requests?

Prior to responding to this question, Mr. Bhuller indicated that he was also requested to address an issue regarding CTA-Notifications (CTA-N) and the time it takes to review one. Briefly, Mr. Bhuller mentioned that reviews within the OCT follow a priority (i.e. CTA and CTA-A and then CTA-N). That is why, CTA-N are not subject to a 30-day default review. Having said that, Mr. Bhuller indicated that there are instances where a CTA-N is actually a CTA-A. As an example, his office recently received 5 notifications that were actually amendments. Thus, he suggested that when in doubt, sponsors should contact the office before filing. In addition, in terms of the notification procedure, an acknowledgement letter simply indicates that the submission has gone for review. This is some what challenging since unlike CTAs and CTA-As, a CTA-N is not subject to an NOL since it is not subject to the 30 day default review. Thus, while most notifications do not require a lot of time to review, especially if they are 'true' notifications that have minor administrative changes, the sponsor should not normally receive any clarifax questions. Having said that, if the CTA-N is actually an amendment the sponsor may be notified at the screening stage (most cases) or sometimes during the review stage (which also includes request for clarification if there is a potential safety concern). In addition, Mr. Bhuller has also noted that reviewing the annual IB update also takes a significant amount of review time (which could be spent on reviewing CTAs and CTA-As). This is why he requested for specific changes (see question 4).

With respect to the clarifax requests, Mr. Bhuller mentioned during his discussion, the OCT has no control over the number and types of CTA it will receive on a daily basis. Having said that, the OCT generally attempts to get their clarifax comments to sponsor by or prior to day 20 of the review. This internal target will ensure that the Assessment Officer will have sufficient time to review the comments provided by the sponsor prior to formulating their recommendation. In addition, this should also give the manager sufficient time to review and discuss this recommendation with the Assessment Officer (and sponsor, if necessary).

6(b) Can you comment on the consistency of clarifax requests from the OCT.

Ensuring consistency is an integral component for any organization, including the OCT. In general, the OCT attempts to send same drug to the same Assessment Officer and the restructure has greatly improved this process, especially in the clinical divisions. In addition, the Quality Division of the OCT also has panel discussions in order to ensure consistency. Having said that, there are situations (e.g. increased number of CTAs or vacation) where the CTA may go to another Assessment Officer and as you are aware, all the Assessment Officers bring their own experience and value to a review. Thus, in this situation, one Assessment Officer may request for a clarification, which may have not been asked by the other officer. Having said that, the OCT generally sends the same drug to the same Assessment Officer and the restructure has also greatly improved this process, especially in the clinical divisions. In addition, the OCT also utilizes other approaches (e.g. informal, internal meetings/sessions (e.g. Reviewers' Rounds), panel discussions, posting notices on our website) in order to ensure a more consistent approach.

7. 30-day default - stop-the-clock mechanism [Open Discussion]

In general, sponsors indicated that while they recognize the need to have a 'stop-the-clock' mechanism in cases where an extension is required (e.g. Global is closed (or on holiday)), the withdrawal without prejudice mechanism appears to be working well. Having said that, Mr. Bhuller did request for the sponsor to have the relevant, internal discussions since problems continue to persist in situations where sponsors have withdrawn CTA's based on the fact that they need input from global, but can not get that input in the allocated, default time-frame. Mr. Bhuller also indicated that this 'stop-the-clock mechanism' would only be acceptable under pre-defined situations.

7(b) Can you give us an example of how this mechanism would work?

One suggestion could be that when a sponsor requests for an extension under pre-defined and accepted conditions, the suggestion for refilling the requested, additional information could include the option of assigning a 'new' control, without sending the CTA through screening. This way, the 30-day default would start again and once the sponsor sent the requested information, it would go directly back to the same reviewer.

8. What are the procedures for scheduling a preCTA meeting?

Mr. Bhuller indicated that for the most efficient way to initiate this process, please refer to the e-manual. He also indicated that for late phase submissions (i.e. phase III), it is suggested that sponsor's should request to see if members of the NDS review bureau can be present during the pre-CTA meeting. In addition, in the request for a pre-CTA meeting the sponsor should propose 3 days, but Wednesday afternoons appear to be the best time, based on experience to date. This request should also have a brief summary of the drug and also provide the potential questions that the sponsor would like TPD to address. The brief summary and questions allow Mr. Bhuller to determine if the product is (a) a drug and (b) if it is a clinical I or II drug and the questions allow Mr. Bhuller to see if he should consult with his colleagues in the review bureau and/or other directorates. The package should be sent at least 3-4 weeks in advance of the meeting. Finally, request for meetings have been turned down when not justified, but this is done in consultation with the sponsor and currently, holding a pre-CTA meeting one month in advance can be accommodated.

9. Other – PSEAT

Mr. Bhuller mentioned that the PSEAT will eventually replace the PCERT, especially since the PSEAT is more in line with the ICH CTD format. However, in the interim he requested for sponsors to start using the PSEAT since the OCT staff spend a considerable amount of time converting the PCERT to a PSEAT. Mr. Bhuller also indicated that when completing the PSEAT, the goal should not be to repeat information that is already in the IB. Rather, the sponsor should summarize the information when possible and/or cross refer to relevant sections of the IB.
