Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




CLINICAL TRIAL APPLICATIONS

Understanding and Improving the Current Process

Canada

Objectives

- Current Structure
- Current Process
- What are the issues?
- What is Health Canada doing?
- Contact Information (Current OCT Managers)
- References

CURRENT STRUCTURE

Senior Medical Advisor Bureau ➡ **Office of Clinical Trials**

A/Director
Dr. John Patrick Stewart

Special Access Programme
Mr. Ian MacKay

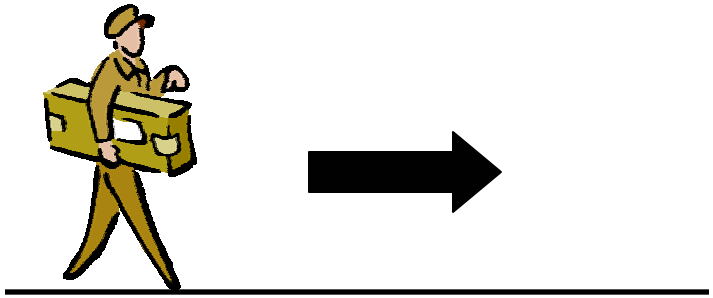
A/Associate Director
Mr. Adam Gibson

A/Manager – ADR Division
Dr. Hoda Eid

A/Manager – Quality Division
Dr. Rajkumar Kumarathasan

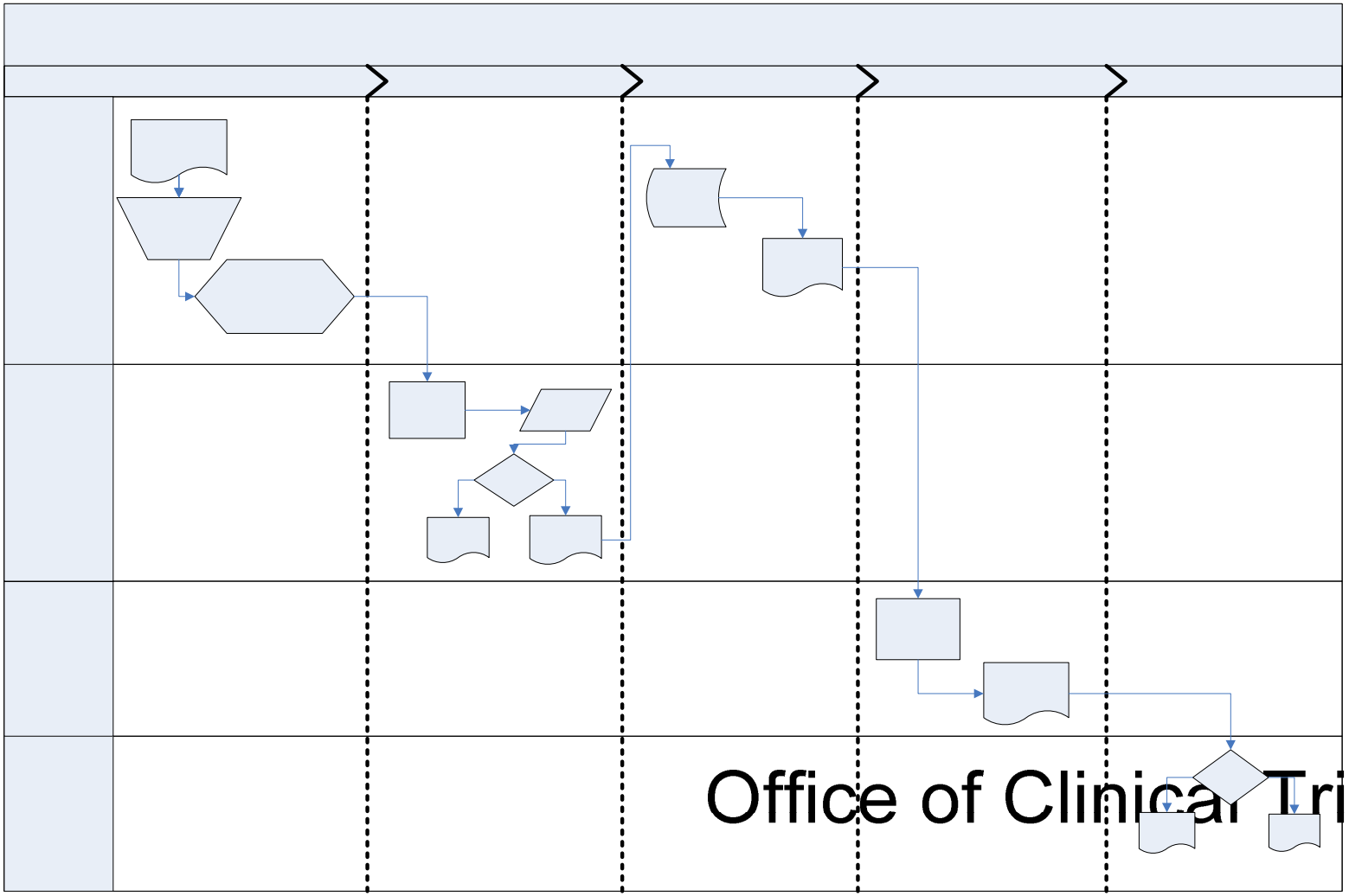
A/Manager – Clinical Division: Group I
Dr. Felix Omara

Manager – Clinical Division: Group II
Mr. Yadvinder Bhuller



A/Unit Head – Submission Management Unit
Mr. Yadvinder Bhuller

CURRENT PROCESS



WHAT ARE THE ISSUES?

STAGE 1: RECEIPT	
ISSUE	**SOLUTION**
Providing no or the incorrect contact name for the courier/delivery person. Providing the incorrect address on the package.	Ms. Connie Diotte (Assistant to the A/Director) is the contact person for the courier/delivery person. Her name should **ONLY** be included on the courier slip as a contact person for the individual who delivers your CTA. Note: Ms. Jenny Charron is no longer with the OCT.
Providing the incorrect name on the cover letter that accompanies all CTAs (e.g. addressing the cover letter for a CTA, CTA-Amendments (CTA-A), or CTA-Notifications (CTA-N) to Ms. Connie Diotte).	The name of the A/Director of OCT (i.e. Dr. John Patrick Stewart) should appear on the cover letter for CTAs, CTA-As and CTA-Ns.
The date the submission is received may not be the same date the submission is stamped. **Example**: CTAs received after 1 pm on Friday are date stamped for Monday. Why? The priority on Friday is to ensure there is no outstanding issue for CTAs already in Stages 2 to 5 (see previous slide) and that all the relevant files have been closed and sent to storage.	Ensure that the delivery of CTAs occurs in the morning, especially on the day before the weekend/holiday.
The OCT has no control on the type and volume of submissions it will receive on a daily basis.	

WHAT ARE THE ISSUES?

STAGE 2: SCREENING	
ISSUE	**SOLUTION**
The application is incomplete. **Examples**: - Missing or incorrect signatures on the HC 3011 form; - Missing relevant appendices of the HC 3011 form; - Missing the relevant electronic documents; - Missing cross-reference letters; - Sponsor and/or contact not identified; - Sponsor and/or contact's coordinates not clearly identified; - Missing DMF or extra volumes (joint reviews).	Please ensure that you are aware of all the requirements prior to sending the CTA (see clinical trials e-manual for more information) **AND** have **submitted a complete package**. Please feel free to contact us **after you have read the information in the e-Manual** and require additional clarification. YOUR GOAL SHOULD BE TO HAVE YOUR CTA SPEND THE LEAST AMOUNT OF TIME AT SCREENING.
The sponsor can not be located or has decided to go on holidays (e.g. Christmas).	Please ensure that the contact for the CTA is always available. PLEASE DO **NOT** SUBMIT CTAs WHEN YOU KNOW THAT NO ONE WILL BE AVAILABLE (FOR AN EXTENDED PERIOD) FROM YOUR END TO RESPOND TO CLARIFAX QUESTIONS

WHAT ARE THE ISSUES?

STAGE 2: SCREENING	
ISSUE	**SOLUTION**
Sponsor "name" change when it is not a 'legal' change (e.g. switching back and forth from "Inc" to "Ltd" to "Limited" depending on who is preparing the CTA for the OCT).	Please provide the legal name for the sponsor and then do not change it, unless it is a legal change (e.g. a merger). **KNOW YOUR NUMBERS & USE THEM APPROPRIATELY:** **FILE #:** "**9427**-COMPANY CODE-PRODUCT CODE **C**", where "C" is for clinical trials. This number is assigned by Health Canada's Record Management Division and is used for **internal filing purposes**. **CONTROL #:** This is **unique** for each CTA and CTA-A, is assigned by the OCT and should be used as the **primary number**, in conjunction with the file number, when communicating with the OCT.
Balance between providing guidance (internally and externally) vs. screening submissions.	Please refer and read the relevant documents, especially the clinical trials e-manual prior to sending your inquires to the OCT.

WHAT ARE THE ISSUES?

STAGE 2: SCREENING	
ISSUE	**SOLUTION**
7-day target: Interpretation of the term "healthy". **Example**: Dose determination study where the sub-population is required to be dependent on a drug/substance. The sponsor considers this to be a "healthy human" study subject to the 7-day target because other then the dependence/addiction aspect, the participants are "healthy" (i.e. "they will be screened to ensure that they do not have any underlying disease/condition").	From a drug development perspective, if the sub-population that is being proposed in the trial is the same/similar to the sub-population that will eventually use the drug product once it is on the market, then classifying these studies as "Phase I-Healthy Human studies" just to have them reviewed under the 7-day target is inappropriate.
The 7-day target is not a regulatory default. That is, all CTAs are subject to the 30-day default, but the OCT attempts to do certain submissions within 7-days. This is primarily based on the fact that the pharmacological and safety profile of the drug that are subject to the 7-day target/review period is well established.	The 7-day target was designed primarily for bioequivalency trials where a generic is being compared to an innovator. While the OCT attempts to meet the 7-day target for other, Phase I – Healthy Human trials, depending on the volume of the submission and the evidence available to date for the drug product (i.e. NCE vs. product on the market), the CTA may go into the 30-day default. Do **NOT** schedule your start date on day 8.

WHAT ARE THE ISSUES?

STAGE 4: ASSESSMENT	
ISSUE	**SOLUTION**
The application is incomplete. **Examples:** -The Investigator's Brochure (IB) is not up-to-date and/or the addendum to the IB does not provide the relevant evidence required to support the protocol; -Rationale for study design and dose and sub population selection not provided or is inadequate (i.e. not scientifically sound); - Certificate of Analysis (CoA) is not provided; -- The Quality Overall Summary is incomplete.	Please ensure that you are aware of all the requirements prior to sending the CTA (see clinical trials e-manual for more information) **AND** have **submitted a complete package**. Please provide the relevant, scientific rationale to support your study and it's parameters. Please provide the CoA with the CTA since this greatly facilitates the Quality review of your submissions. Currently, there is a separate QOS template for Phase I CTAs, but one template for Phase II and III. Thus, the requirements for a Phase I are clear, but there seems to be some confusion with respect to the Phase II vs. III requirements. The OCT's Quality Division is in the process of revising the QOS templates in order to also separate the Phase II requirements from the Phase III. In the interim, the sponsor should recognize that the requests for additional information is primarily based on the fact that the level of evidence required to assess a drug product in Phase II is not the same for a Phase III trial.
preCTA meetings: As a sponsor, you can always request to have a preCTA meeting with the OCT. This is particularly useful when the proposed trial involves a New Chemical Entity (NCE) and these meetings can also be used as an educational/training session for 'new' staff that have joined your team.	

WHAT ARE THE ISSUES?

STAGE 4: ASSESSMENT	
ISSUE	**SOLUTION**
Joint reviews with Medical Device Bureau (MDB) [OCT is the Lead]. Note: Unlike *Division* 5, the medical device regulations do NOT have a 30-day default.	It is recommended to get the ITA approved first and then submit the approval letter in Section 1.2.11 (Other Application Related Information) of the CTA. The cover letter of the CTA should also clearly state that the MDB has reviewed and authorized the sale of the medical device component for this trial.
Responses to clarifax: Sending clarifax responses that do not address the question is not only inappropriate, but can also significantly delay the review process and/or result in a negative, regulatory decision.	Please contact us immediately if the clarifax question is not clear. Please provide a response to the clarifax that is scientifically sound and is supported by the relevant references.
Not including minutes from meetings/discussions that have occurred with TPD's Review Bureau.	This information should not only be captured in the cover letter, but the minutes should be included in Section 1.2.11 (Other Application Related Information) of the CTA.
Changing recommendations/record of decision that were agreed upon during a preCTA when filling the CTA.	Any changes to the official/final records of a meeting must be discussed with the OCT prior to submitting the CTA in order to determine the appropriate mechanism for sending this information. All preCTA minutes and slides should be included in Section 1.2.11 (Other Application Related Information) of the CTA.

WHAT ARE THE ISSUES?

STAGE 4: ASSESSMENT	
ISSUE	**SOLUTION**
The PCERT and/or other CTA related documents (e.g. the protocol) is inaccessible (i.e. locked/password protected PDFs). These documents are used by the Assessment Officer to generate the final report for the manager. This involves modifying the PCERT by entering the relevant comments, including additional information from the protocol and/or IB. Having these documents 'locked' significantly delays this process. In addition, having the PCERT 'locked' defeats the purpose of having the sponsor prepare this template as a requirement for the CTA.	If you are submitting these documents as PDF files, please provide them in an editable format or provide the OCT with the password in the cover letter. Currently, the Screening Officer's are requesting for this information at Stage 2, which does delay the submission from going into the next stage.
PSEAT has not formally replaced the PCERT. This is causing significant delays since the Assessment Officer uses the PCERT in order to generate the PSEAT.	The OCT encourages more sponsors to use of the PSEAT in order to not only validate these templates, but also help facilitate the review process.
The sponsor can not be located or has decided to go on holidays (e.g. Christmas).	Please ensure that the contact for the CTA is always available.
PLEASE DO NOT SUBMIT CTAs WHEN YOU KNOW THAT NO ONE WILL BE AVAILABLE (FOR AN EXTENDED PERIOD) FROM YOUR END TO RESPOND TO CLARIFAX QUESTIONS.	

WHAT ARE THE ISSUES?

STAGE 5: DECISION	
ISSUE	**SOLUTION**
The 30-day default The inability to put a CTA on 'hold' or to 'stop-the-clock' in situations where the sponsor needs additional time in order to provide the appropriate response to the OCT was not identified as an issue by stakeholders at the Phase I and II *Division 5* consultations. However, this continues to be a significant problem and results in several, unnecessary withdrawal requests. In addition, from OCT's perspective this is not the best utilization of resources.	Stakeholders are requested to reflect on the potential benefits of having *Division* 5 revised such that it incorporates this type of flexibility, where it provides the regulatory authority for the OCT to 'stop-the-clock' under pre-defined situations. Comments related to this request or to the 30-day default time-frame should be sent directly to: clinical_trials_regulatory_review@hc-sc.gc.ca
Balancing the all the relevant duties/responsibilities assigned to a manager, including providing the final decision to the sponsor.	Please refer and read the relevant documents, especially the clinical trials e-manual prior to sending your inquires to the OCT.

Recently the OCT suffered from a serious IT/server issue that resulted in their inability to have access to DSTS and their emails. This had a significant impact on the CTA process.	The OCT is in the process of creating an in-house Business Continuity Plan (BCP) Team in order to be more proactive under such situations.

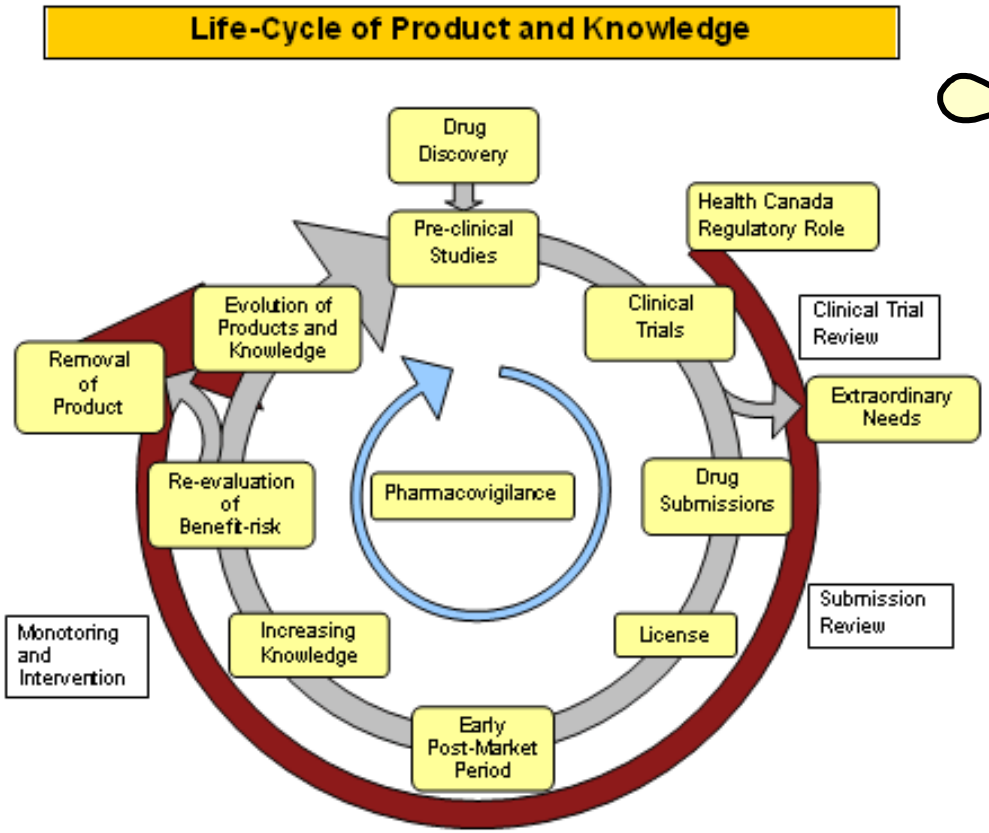
WHAT ARE THE ISSUES?

POST-DECISION PHASE	
ISSUE	**SOLUTION**
CTSI forms are not provided in a timely manner or the data is entered in appropriately.	The OCT is currently revising the CTSI form such that it provides additional guidance for the sponsor on how to fill these forms correctly. In the interim, it is important for the sponsor to recognize that the CTSI form not only provides information on the site, but also on the QI and the REB Approval. In addition, the OCT has assigned a clerk to specifically bring issues to the attention of the manager (e.g. the same name appears as the QI and for the contact person from the REB) and also to the sponsor. The goal is to have forms that are complete prior to entering the information into the internal database.
Re-submission of CTAs that were 'withdrawn without prejudice' without providing any information as to why the CTA was withdrawn in the first place.	When re-submitting a CTA, the sponsor should clearly identify in the cover letter that this is a re-submission and then also provide the relevant information on how the issues identified during the original review have now been addressed. This information should be included in Section 1.2.11 (Other Application Related Information) of the CTA. The OCT will then attempt to sent the CTA to the original reviewers in order to facilitate the review process.

WHAT IS HC DOING?

Registration & Disclosure

OCT Restructure



GGPs

Division 5 Review

CONTACT INFORMATON

(CURRENT OCT MANAGERS)

OCT – Clinical Division: Group I **Types of CTAs:** Hematology/Oncology, Immunology; Allergy, Respiratory, Infection and Rheumatology	Dr. Felix Omara A/Manager felix_omara@hc-sc.gc.ca 613.941.4774
OCT – Clinical Division: Group II **Types of CTAs:** Gastrointestinal, CNS, Cardio-Renal, Metabolism, Endocrinology and Reproductive Medicine	Mr. Yadvinder Bhuller Manager yadvinder_bhuller@hc-sc.gc.ca 613.941.0570
OCT – Quality Division	Dr. Rajkumar Kumarathasan A/Manager rajkumar_kumarathasan@hc-sc.gc.ca 613.941.6059
OCT – ADR	Dr. Hoda Eid A/Manager hoda_eid@hc-sc.gc.ca 613.941.1622
OCT – Submission Management Unit	Mr. Yadvinder Bhuller A/Unit Head

REFERENCES

Clinical Trials e-Manual	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro_e.html
Review of the Regulatory Framework for Clinical Trials	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/index_e.html
Registration and Disclosure of Clinical Trial Information	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/enreg-clini-info/index_e.html
The Progressive Licensing Framework	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/proglic_homprog_concept_e.html
Notice – Release of Draft Good Guidance Practices Manual for comment	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/ggp_notice_bpld_avis_com_e.html
Other/Relevant Information related to Clinical Trials	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/index_e.html http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/qtqtc/index_e.html
Government Electronic Directory Services	http://direct.srv.gc.ca/cgi-bin/direct500/TE?FN=index.htm

Questions?

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