

Health Canada's Clinical Trial Inspection Program

Oversight of clinical trial activities across Canada is accomplished by the Health Products and Food Branch (HPFB) Inspectorate division of Health Canada (HC). This division of HC aims to provide a national compliance and enforcement program for drugs, natural health products, and medical devices, through inspections, compliance verification, establishment licensing, and regulation of laboratory functions. The main objective of the clinical trial inspection program is to ensure that the generally accepted principles of good clinical practices (GCP) are met, to validate the quality of the data generated, and to verify compliance to Division 5 of the Food and Drug Regulations. Sites could be selected for inspection according to the following criteria:

- number of clinical trials conducted at the site;
- number of subjects enrolled in the specified clinical trial;
- status of the specified clinical trial;
- number of serious unexpected adverse drug reactions at the clinical trial site; and/or
- compliance history of the sponsor and/or site and/or drug(s) involved in the specified clinical trial.

In 2009, a total of 55 inspections were conducted, whereas 60 to 65 inspections have already been conducted between January and March of 2010. It should be noted that the Inspectorate has stopped inspecting Research Ethics Boards (REBs).

The trial Sponsor and Clinical Site are typically notified by HC at least 5 days prior to an inspection; however, unannounced inspections may also occur if deemed necessary (*i.e.*, depending on the compliance history of the site or Sponsor). Based on inspections conducted between 2002 to 2010, 9.2% of site deficiencies were due to Good Manufacturing Practices (GMP) noncompliance (*e.g.*, drug transportation conditions were not monitored) and 38.5% of the deficiencies were noted in the quality systems and procedures which include:

- contract between the sponsor and the site expired;
- protocol amendments not submitted to the REB in a timely manner (*e.g.*, protocol dated February 2008 but submitted to the REB on December 2008), *etc.*

If a non-compliant rating is assigned on the Final Exit Notice, inspection findings will be discussed within the relevant review Directorate, and this may result in clinical trial suspension or cancellation.

Additional information on clinical trial site inspections as well as an overview of a typical inspection can be found on the following Health Canada website: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/insp_strat-eng.pdf.

NEWS RELEASE: Ashuren has been acquired by Intertek

We are pleased to announce that Ashuren Health Sciences, formerly part of Ciba Expert Services, has been acquired by Intertek. With over 25,000 employees, Intertek is a leading provider of quality and safety solutions to a wide range of industries around the world. The complementary strengths of Ashuren and Intertek will give each company the opportunity to better serve its respective clients.

In light of this change, staff at Ashuren want to assure you that Ashuren will continue to deliver the consulting services you have come to rely on, on a business-as-usual basis.

Most importantly, our professional team of consultants and administrative support staff, who have served your business needs and protected your company's interests in the past, remain in place and committed to you and your interests.

If you have any questions, or would like additional information about our services, please call or email your normal contact at Ashuren. Otherwise we can be reached at:
info@ashuren.com.

Ask Us!

Question:

Are finalized toxicology study reports required when filing an IND in the United States? What is the process for filing toxicology study reports to a CTA in Canada?

Answer:

Per FDA guidance documents, finalized study reports are not required when filing an initial Investigation New Drug (IND) application in the United States (US). Also, they are not required to be submitted in a Canadian Clinical Trial Application (CTA). However, the following discussion outlines the Food and Drug Administration (FDA) and Health Canada's current thinking.

FDA Requirements

The 1995 FDA Guidance "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products" provided initial recommendations regarding the submission of individual toxicology study reports. It stated that if final, fully quality-assured individual reports are not available at the time of IND submission, Sponsors can submit the IND with an integrated summary based on unaudited draft reports. Even though the FDA does not clarify whether study reports should be submitted with the initial IND, the FDA has become accustomed to seeing study reports in the original application and therefore most sponsors submit them, either as audited/unaudited drafts or as final reports. Once reports are fully finalized, which is expected to occur within 120 days of submission of the IND application, the reports may be submitted to the IND. If these are not submitted, they should be available to FDA upon request. In recent years, if there are no major changes to the findings, some

Sponsors are opting to provide a summary of the minor changes to the report in an IND serial submission, without providing a copy of the final study report. However, based on recent correspondence, FDA has noted that Sponsors generally should submit final, quality-assured reports within the 120 days, particularly if there are changes in the findings. Therefore, Ashuren recommends submitting the draft reports with the initial IND so that the FDA can do a thorough bottom-up review of the IND. The decision to submit reports finalized within the 120-day post-application period will depend on the types of changes between the draft and final reports. In addition to submissions to the IND, all finalized nonclinical study reports must be submitted with the New Drug Application (NDA) prior to final registration of the product.

Note, to clarify when the clock starts for the "120-day period", the FDA released a Q & A document. The FDA indicated that it measures the 120-day period "based on the Agency's receipt (date of receipt stamped on the IND submission) of the *integrated summary report [sic]* including the toxicology information".

Health Canada Requirements

Health Canada does not want toxicology study reports to be submitted with any CTA. All nonclinical data should be summarized in the IB which is submitted initially with the original CTA and then updated on an annual basis. However, all finalized nonclinical study reports must be submitted with the New Drug Submission (NDS) prior to final registration of the product.

Submit your regulatory and/or toxicology questions to info@ashuren.com for your chance to get them answered in our next issue!

Did you know that the EMEA has changed its name?

The European Medicines Agency has dropped its use of the EMEA acronym. As of December 8th 2009, the regulatory body that oversees drug approvals in Europe will no longer call itself EMEA. Since many drug companies use the same acronym to describe the joint market of Europe, the Middle East and Africa, the overlap was a source of confusion.

Going forward, the Agency (as it will be known for short) will go by its full name. There are no plans to adopt "EMA" as a new acronym unless it becomes widely used by the public and makes sense to formalize. The new identity shift will manifest itself on the organization's Website, e-mail addresses, formal communications and in its visual branding.

Read the full press release here: <http://www.ephra.org/a/3754>

Regulatory Highlights

Please find below a list of selected guidances of interest that have recently been released by various international agencies:

FDA

- [Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions \[04/02/2010\]](#)
 - [Annex 7: Dissolution Test General Chapter \(PDF-93 KB\)](#)
 - [Annex 9: Tablet Friability General Chapter \(PDF-84 KB\)](#)
- [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format \[03/22/2010\]](#)
- [S9 Nonclinical Evaluation for Anticancer Pharmaceuticals \[03/05/2010\]](#)
- [M3\(R2\) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals \[01/20/2010\]](#)

Health Canada

- [QT/QTc Interval Prolongation: Guidance for Product Monograph Content \[03/31/2010\]](#)
- [Guide for the Analysis and Review of QT/QTc Interval Data \[03/31/2010\]](#)

- [Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics \(SEBs\) \[03/05/2010\]](#)
- [Natural Health Products- Labelling Requirements Checklist \[03/18/2010\]](#)
- [The Natural Health Products Regulatory Review Action Plan-Phase I \[03/09/2010\]](#)
- [Guidance for Industry - Preparation of Veterinary Abbreviated New Drug Submissions - Generic Drugs \[03/01/2010\]](#)

European Medicines Agency

- [Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials \[3/11/2010\]](#)
- [Draft Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus \[02/10/2010\]](#)
- [Guideline on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis \[01/02/2010\]](#)
- [Guideline on the Investigation of Bioequivalence \[01/29/2010\]](#)
- [Guideline on selection of test materials for genotoxicity testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products \[01/18/2010\]](#)



At Ashuren, we are a team of experienced professionals that specialize in scientific and regulatory consultancy. Our focused team of consultants provides strategic advice on:

- Regulatory Affairs
- Product Development Programs
- Submission Preparation and Review
- Toxicology
- GLP Monitoring and Compliance
- Clinical Planning

If you have any questions, comments, or require further information in regards to any information provided in this document, please do not hesitate to contact:

Ratinder Brar
at rbrar@ashuren.com
or 1-877-244-4844
www.ashuren.com

Contact Information...

United States

1319 Lake Forest Circle
Hoover, Alabama
35244

1011 US Highway 22
Suite 200
Bridgewater, New Jersey
08807-2950

Canada

2233 Argentia Road
Suite 308
Mississauga, Ontario
L5N 2X7

Europe

Branksome Chambers
Branksomewood Road
Fleet, Hampshire, UK
GU514JS

Asia

160-0002
Matsuda Bld. Finesis
6-29-20, Shinjuku
Shinjuku-ku, Tokyo