

Reproductive and Developmental Toxicology Terminology: Out with the Old, in with the New

As guidance documents are revised and updated, the terminology used to describe studies can also change. The table below describes the old and new terminology used to describe reproductive and developmental toxicity studies in different regulatory jurisdictions including the United States, Japan, and the European Union.

ICH Stage	US FDA Guideline	UK and EEC Guides	Japanese Guideline	OECD, US EPA OPPTS, and US FDA Redbook
A: Premating to conception	Segment I	Segment I	Segment I	Multigeneration One-generation
B: Conception to implantation	Segment I	Segment I	Segment I	Multigeneration One-generation Developmental toxicity
C: Implantation to closure of the hard palate	Segment I Segment II	Segment I Segment II	Segment II	Multigeneration One-generation Developmental toxicity Developmental neurotoxicity
D: Closure of the hard palate to the end of pregnancy	Segment I Segment II Segment III	Segment I Segment II	Segment II	Multigeneration One-generation Developmental toxicity Developmental neurotoxicity
E: Birth to weaning	Segment I Segment III Pediatric	Segment I Segment II Segment III	Segment II Segment III	Multigeneration One-generation Developmental toxicity Developmental neurotoxicity
F: Weaning to sexual maturity	Pediatric	Segment I Segment II	Segment III	Multigeneration Developmental neurotoxicity Developmental Immunotoxicity

EEC=European Economic Community; EPA=Environmental Protection Agency; FDA=Food and Drug Administration; ICH=International Conference on Harmonisation; OECD=Organization for Economic Cooperation and Development; OPPTS=Office of Prevention, Pesticides & Toxic Substances; US=United States (Reference: Adapted from Principles and Methods of Toxicology, 5th edition. W. Hayes (Ed.) (2008). pp. 1662.)

Regulatory Highlights

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

FDA

- [Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information](#) (10/16/2009)
- [Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance Production and Process Controls](#) (11/19/2009)
- [Residual Solvents in Drug Products Marketed in the United States](#) (11/24/2009)
- [Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims](#) (12/8/2009)
- [M3\(R2\) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals](#) (01/2010)

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We will be attending the
49th Annual Society of Toxicology (SOT) Conference
Salt Lake City, UT
March 7-11, 2010

If you would like to meet with Ashuren representatives during this event please email us at: info@ashuren.com

About Us:

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:

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Regulatory Highlights

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Health Canada

- [Guidance for Industry: Preparation of Drug Submissions in the Electronic Common Technical Document \(eCTD\) Format \(11/04/2009\)](#)
- [Requirements for Efficacy Claims against the 2009 \(H1N1\) Pandemic Influenza A Virus for Hard Surface Disinfectant Drug Products \(12/02/2009\)](#)
- [Guidance Document - Human-Use Antiseptic Drugs \(12/03/2009\)](#)
- [Mandatory Problem Reporting for Medical Devices \(GUI-0059\) \(12/11/2009\)](#)
- [Voluntary Problem Reporting for Medical Devices \(GUI-0060\) \(12/11/2009\)](#)
- [Notice - Guidance for Industry: Preparation of a Premarket Review Document in Electronic Format for a Class IV Medical Device Licence Application \(12/15/2009\)](#)

EMA

- [Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis \(11/30/2009\)](#)
- [Guideline on Xenogeneic Cell-Based Medicinal Products \(01/12/2009\)](#)
- [Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension \(02/12/2009\)](#)
- [Guideline on Validation of Analytical Methods Used in Residue Depletion Studies \(12/22/2009\)](#)

ICH

- [S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals Step 4 \(12/18/2009\)](#)

For a complete listing of new guidances or hard copies of any of these documents, please visit the respective agency website, or contact us at info@ashuren.com.

Ask Us!

Question: What are the major Chemistry, Manufacturing, and Controls (CMC) documentation differences between conducting a clinical trial in Canada vs. the United States (US)?

There are many differences. In Canada, each clinical protocol is submitted as a new Clinical Trial Application (CTA). In the US, once the initial Investigational New Drug (IND) application has been filed, all subsequent protocols are submitted under the same IND number (as long as the patient population and indication are identical).

How does the CMC documentation fit into this? Depending on whether the product is classified as a drug or biologic, a CTA may require the submission of just a Module 2.3 (drug) or both a Module 2.3 and a Module 3 (specifically for a biologic). In the US, the FDA is moving toward the CTD format and therefore prefer all CMC information to be provided in Module 3.

How does the Clinical Phase impact the CMC? For a drug in Canada, the CTA requires the Module 2.3 Quality Overall Summary (QOS) to be in a specific template. There are 3 different templates, one for each clinical phase, i.e., Phase I, II or III (refer to http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qual_cta_dec-eng.pdf). Sponsors should use the appropriate QOS template. For a biologic, Health Canada has several guidance documents available (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/index-eng.php>) where the general CTD guidance for Module 2.3 and Module 3 is followed. In the US, similar CMC information is required for both drugs and biologics, however there are no templates.

Here's the major difference: For a new protocol in Canada, depending on the clinical phase, a complete CMC information package must be submitted with each CTA. However, if there are multiple CTAs, for example Phase I, CMC information should be cross-referenced to the previous CTA QOS-Phase I using the control and file numbers for the submission. When moving on to Phase II the QOS_Phase II template should be used; as cross referencing to the previous Phase I information is not accepted. The same applies for Phase III. Therefore, quality information can only be cross-referenced if it was previously submitted in the same phase or higher phase (e.g., an approved Phase III CTA can be cross-referenced in a new Phase II CTA). In the US, as the product moves from one clinical phase to the next, the appropriate CMC updates are continuously provided as CMC Information Amendments to the active IND.

If you have any further questions or require more clarifications, please feel free to contact Ashuren at info@ashuren.com.

Please note, the FDA is now accepting electronic INDs. Stay tuned for a future issue of our 'Ask Us' section entitled "The Perks and Pitfalls of Going Electronic".

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



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