All You Ever Wanted to Know About Regulatory Writing

AMWA North Central Chapter

Saturday, April 30, 2011 10:30 to 12 noon
followed by optional lunch at nearby restaurant

Presenter
Dr. Joy Frestedt
President and CEO
Frestedt Incorporated

Masonic Cancer Research Building
MCRB conference room
University of Minnesota
425 East River Parkway (East River Road)
Minneapolis, MN 55455
What, exactly, is regulatory writing and how is it changing?
Is this a field you might want to get involved in, and would you be qualified?
How are changes at the FDA and in the regulatory environment itself impacting your work today, and how will they impact the many Minnesota medical device companies?
Agenda

- Background/Frame of reference
- What is Regulatory Writing?
  - Definitions and Job Examples
- US Regulatory Pathways
  - Drugs & Devices
- International Regulatory Pathways
  - EU & Canada
- How is the regulatory field changing?
- How does one get into regulatory writing?
  - Essential skills and knowledge
Background/Frame of Reference

- Dr. Frestedt
- Frestedt Incorporated
- Virtual CRO
- Clinical Trial Expertise
Joy Frestedt, PhD, RAC, CCTI
President & CEO of Frestedt Incorporated
- www.frestedt.com
- a virtual network with 70 experts meeting client needs
  - regulatory, clinical and quality affairs.
30 years scientific, clinical and regulatory experience in the health care, pharmaceutical and medical device industries
- Orphan Medical, AstraZeneca, Mayo Clinical Trial Services, Johnson and Johnson Medtronic, and CNS Therapeutics
Ph.D. in Pathobiology; University of Minnesota Medical School.
Member ASCO, AAPS, ACRP and currently Chair of the Ethics Committee for the Regulatory Affairs Professionals Society
# Frestedt Incorporated

<table>
<thead>
<tr>
<th>CROs</th>
<th>Frestedt Inc</th>
<th>Independent Consultants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Delegate Control</td>
<td>• SCALABLE CONTROL</td>
<td>• Single Resource</td>
</tr>
<tr>
<td>• Varied Expertise</td>
<td>• KNOWLEDGE NETWORKS</td>
<td>• Narrow Expertise</td>
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<tr>
<td>• Large Projects</td>
<td>• STRATEGIC PROJECTS</td>
<td>• Small Projects</td>
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Virtual CRO

- **Network of 70+ professionals** seasoned PhDs, MDs, MBA/MS/MAs, BS/BAs, and interns with the flexibility to provide...
- **Customizable, Collaborative and Creative solutions** to assist at any step along the way
- Supporting **clinical, quality and regulatory endeavors**

Your first call for help!
Clinical Trial Expertise

Project Management

Preparation
- SOP System design and implementation
- Feasibility assessment
- Literature search and summarization
- Investigator/Site selection

Protocol Development
- Biostatistical Analysis
- Objective/Endpoint evaluation
- Materials and Methods appraisal
- Informed Consent development

Start-Up and Execution
- Personnel Training
- Monitoring
- Data management
- Dietary analysis
- AE analysis and summarization

Closure
- Clinical Report writing
- Submission assistance
- Publication support

Collaborative Expertise utilizing a knowledge network of 70+
Clinical, Quality and Regulatory Professionals
PhDs, MDs, MBA/MS/MAs, BA/BSs and Interns
### Device and Pharma: Common Types of Clinical Trial Documents

<table>
<thead>
<tr>
<th>Pre-Study</th>
<th>Study</th>
<th>Post-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protocol</td>
<td>• Protocol Amendments</td>
<td>• Final Study Report</td>
</tr>
<tr>
<td>• Investigator’s Brochure</td>
<td>• Monitoring Visit/ Summary Reports</td>
<td>• Regulatory Body Submission</td>
</tr>
<tr>
<td>• Investigator’s Agreement</td>
<td>• Interim/Annual Reports to IRB/EC</td>
<td>• Serious/Adverse Events</td>
</tr>
<tr>
<td>• Case Report Forms</td>
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<tr>
<td>• Informed Consent</td>
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</table>
What is Regulatory Writing?
Regulatory Writing Is...

- Preparing documents for US and international authorities to review prior to approving products for sale on the market
  - Regulatory documents report the research conducted to demonstrate the product is safe and effective / performs as intended
  - Each country has different requirements
  - Many different types of documents need to be submitted depending on the product and the intended use
CSR, Clinical Study Report; PSURs, Periodic Safety Update Reports; IBs, Investigator Brochures; SmPCs, Summary of Product Characteristics; PIL, Patient Information Leaflet; PR, Public Relations

Senior Regulatory Medical Writer Full Time Permanent $90k+Bonus! …
…exp. medical writer to lead the writing effort and write regulatory documents. …specializing in Clinical Study Protocols… Amendments, Clinical Study Reports, Investigator brochures, Clinical Summaries …

Main job responsibilities include:
-Writing Protocols, CSRs, annual reports, IBs, INDs, NDAs, briefing books
-Minimal responsibilities to write abstracts, posters and manuscripts
-Work closely with the clinical team and other cross-functional teams
-Help to coordinate the efforts of the consultant writers and vendors

Requirements/Skills:
-3-6 years of medical writing experience; Minimum of B.S. degree
-Experience in leading NDA/BLA filings, EMEA filing experience a plus

Company offers extremely competitive compensation and generous benefits .. stock incentives. …Code: 1249305; Contact Information: Dandan Zhu - Real Staffing - New York - 23RD FLOOR 1270 AVENUE OF THE AMERICAS - NEW YORK 10020 - Tel: +1 212 707 8499
Regulatory CMC Writer: A pharmaceutical company here in the San Francisco bay area is looking for a CMC writer to join their team for 6 month contract.

Responsibilities: Prepare, coordinate and manage the chemistry, manufacturing and control (CMC) documents for regulatory submissions. This includes US and ex-US marketing and investigational applications. Provide a strong working knowledge of regulatory (US FDA, EMEA, Health Canada) guidelines and apply these guidelines to CMC projects and submissions.

Requirements: BS in science with MS in Pharmaceutical/Regulatory Sciences or equivalent experience. Minimum of 3-5 years of relevant experience in pharmaceutical industry required; Experience in the preparation of CMC sections of regulatory dossiers including INDs/ NDAs, IMPDs/CTAs and DMFs;...

Ref Code: 1249833; Contact Information: Rachel Riley, Real Staffing - San Francisco, C/O Regus One Market Street, San Francisco94105; Tel: +1 415 293 8190; Fax: +1 415 293 7719
Regulatory Documents

- Documents submitted to track and evaluate
  - Chemistry Manufacturing and Control of Drug
  - Design engineering of Medical Device
  - Ethical and procedural conduct of a clinical trial
  - Quality of the data produced
  - Compliance with protocol, SOPs, GLPs and GCPs
    - Principal Investigator
    - Site
    - Sponsor
    - IRB/EC

Standard Operating Procedures
Good Laboratory Procedures
Good Clinical Practices
Submission Pathways

- Start with Critical Documents
  - Literature Searches
  - Reports and Summaries
  - Data Analysis Compilation
  - Supplemental Information

- Prepare for submission (paper or electronic)
- Each country has their own process and requirements
- Drugs and Devices have different paths and requirements - require different documents
US Regulatory Pathways

Drugs and Devices
FDA Organization (in part; 1-11-11)

CDER
- National Center for Toxicological Research (Dr. William Slikker)
- Office of Foods (Michael Taylor)
- Center for Drug Evaluation and Research (Dr. Janet Woodcock)

Commissioner (Dr. Margaret Hamburg)

Office of International programs (Dr. Murray Lumpkin)

CDRH
- Center for Devices and Radiological Health (Dr. Jeffrey Shuren)
- Center for Biologics Evaluation and Research (Dr. Karen Midthun)

## Drug Development Path

<table>
<thead>
<tr>
<th>Stages</th>
<th>Identify</th>
<th>Pre Clinical</th>
<th>File IND</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>File NDA</th>
<th>Phase IV Post Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>1-2</td>
<td>3.5</td>
<td>0.5-1</td>
<td>1-2</td>
<td>2-4</td>
<td>4-6</td>
<td>1.5</td>
<td>varies</td>
</tr>
<tr>
<td>% INDs approved</td>
<td></td>
<td></td>
<td># IND Submitted 2007 = 2589; 2008 = 2039</td>
<td>70%</td>
<td>30%</td>
<td>27%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>% NCEs Approved</td>
<td></td>
<td></td>
<td>5000 Compounds Tested</td>
<td>5 Compounds in clinical trials</td>
<td>1 Compound approved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Population</td>
<td>Literature</td>
<td>Laboratory and Animal Studies</td>
<td>Summary and Proposal</td>
<td>20-100 Healthy</td>
<td>100-300 Disease</td>
<td>1000-3000 Disease</td>
<td>Indication based on population tested</td>
<td>varies</td>
</tr>
<tr>
<td>Purpose</td>
<td>Identify new products</td>
<td>Assess Safety and Biological Activity</td>
<td>Ensure testing show safety and efficacy</td>
<td>Dose Finding and Safety</td>
<td>Develop Safety, Efficacy and Indication</td>
<td>Verify Safety &amp; Efficacy during use as indicated</td>
<td>Must be safe and effective</td>
<td>Safety Surveillance - Long-Term</td>
</tr>
</tbody>
</table>

### CRO SERVICES

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Early/Late Phase Development</th>
<th>Pre/Peri/Post approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory</td>
<td>Plan</td>
<td>File/Negotiate</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Define/Specify NCE</td>
<td>Analyze NCE in human matrixes - Phase 2b/3a and Phase 3b/4a</td>
</tr>
<tr>
<td>Safety</td>
<td>Drug metabolism and safety</td>
<td></td>
</tr>
<tr>
<td>Non-Clinical</td>
<td>Toxicology, Imaging and Research models</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Laboratory Based Biotechnology &amp; Core Labs (hematology, cardiac/cardiac safety, immunology, etc.)</td>
<td></td>
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<tr>
<td>Bioanalytical</td>
<td>Bioanalytical Chemistry</td>
<td></td>
</tr>
<tr>
<td>Health Economics</td>
<td></td>
<td>Reimbursement and Outcomes Research</td>
</tr>
</tbody>
</table>

June 2011 issue of ACRP Journal The Monitor
US-FDA-CDER Regulations

- Center for Drug Evaluation and Research
  - 21CFR200 General
  - 21CFR201 Labeling
  - 21CFR208 Medication Guides
  - 21CFR211 cGMP for finished pharmaceuticals
  - 21 CFR312 Investigational New Drug (IND) Application
  - 21 CFR314 Applications for FDA approval to market a new drug
    - New Drug Application (NDA)
    - Abbreviated New Drug Application (ANDA) [generics]
  - 21 CFR 316: Orphan Drugs
Drug: Examples of Regulatory Forms

- **Investigational New Drug Forms (IND)**
  - [FDA 1571](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm) Investigational New Drug Application
  - [FDA 1572](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm) Statement of Investigator

- **New Drug Application Forms (NDA)**
  - [Form FDA-356h](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm) Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
  - [Form FDA-3397](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm) User Fee Cover Sheet

- **Abbreviated New Drug Application Forms (ANDA) for Generic Drug Products**
  - [Form FDA-356h](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm) Application to Market a New Drug, Biologic or An Antibiotic Drug For Human Use

- **Orphan Drug Products (for rare diseases and disorders)**
  - No form, but prescribed format for application

IND Application Requirements

- FDA Form 1571 & 1572 (Investigator signs 1572)
- Table of Contents
- Introductory Statement
- General Investigational Plan

- Investigator’s Brochure
- Protocols and Amendments- IRB Approved
- Informed Consent forms- IRB approved
- Advertisements- IRB Approved

- Chemistry, manufacturing, control data and EIS
- Pharmacology/Toxicology data
- Laboratory Accreditations
- Test article accountability records
- Previous human experience
- Additional information
NDA Application Requirements

1. Index
2. Labeling (check one) Draft Labeling Final Printed Labeling
3. Summary (21 CFR 314.50 (c))
4. Chemistry section
   A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
   B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA’s request)
   C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
15. Establishment description (21 CFR Part 600, if applicable)
16. Debarment certification (FD&C Act 306 (k)(1))
17. Field copy certification (21 CFR 314.50 (l)(3))
18. User Fee Cover Sheet (Form FDA 3397)
19. Financial Information (21 CFR Part 54)
ANDA Application Requirements

- **Generic drug applications** are termed "abbreviated."

- Generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

- Must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug).
Orphan Drug Application Requirements

- **Format for application:**
  - “How to apply for designation as an orphan drug”
  - Subpart C: Designation of an Orphan Drug 316.20
  
- **Content and Format of a request for an orphan drug:**
  - Sponsor requests rare disease designation
  - Name and Address of sponsor
  - Description of rare disease/condition
  - Description of the drug and the scientific rationale
  - If a variation of a previous orphaned drug—how it differs
  - If only for a subset of the diseased population, why it is appropriate
  - Summary of regulatory status and marketing history
  - Documentation with appended authoritative references demonstrating:
    - For <200,000 people in the US
    - Costs of research can’t be recovered with sales
    - Information previously provided to the FDA
# Pharma: Specialized Documents

## Drug Master Files (DMF)
- Submission to the FDA used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs to others who wish to refer to the work done by the sponsor without access to the work.

## Chemistry Manufacturing and Controls (CMC)
- Ensure quality of drug substance and drug product
  - Nomenclature, structure, and drug substance properties
  - Manufacturing
  - Characterization
  - Control of drug substance
  - Reference standards
  - Container closure system
  - Stability
Pharma: Specialized Documents

Periodic & Annual Reports

- Distribution Data
- Adverse Events
- Changes to Labeling
- Stability Data
- Changes to Official Compendia
- Additional Tests
- Narrowing of Specifications
**Device Development Path**

<table>
<thead>
<tr>
<th>Stages of Process</th>
<th>Design</th>
<th>Bench</th>
<th>File IDE</th>
<th>V&amp;V</th>
<th>File PMA</th>
<th>Post Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-1</td>
<td>1-2</td>
<td></td>
<td>0.5-3 varies</td>
</tr>
<tr>
<td>Test Population</td>
<td>Literature</td>
<td>Lab, Animal, Cadaver Studies</td>
<td>Summary and Proposal</td>
<td>1-5 Case Studies</td>
<td>20-100</td>
<td>Indication will be based on population tested</td>
</tr>
<tr>
<td>Purpose</td>
<td>Identify new products</td>
<td>Assess Safety and Biological Activity</td>
<td>Ensure testing show safety and efficacy</td>
<td>Verify Design</td>
<td>Validate Safety, Efficacy and Indication For Use</td>
<td>Must be safe and effective</td>
</tr>
</tbody>
</table>

**CRO SERVICES**

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Physician interaction; Usability Testing; Safety and Efficacy</th>
<th>Pre/Peri/Post approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory</td>
<td>Prepare info, file submissions/amendments, negotiate</td>
<td>File/Negotiate Report</td>
</tr>
<tr>
<td>Safety</td>
<td>Mechanical issues, Failure Modes; Product complaints</td>
<td>Post market surveillance</td>
</tr>
<tr>
<td>Non-Clinical</td>
<td>Bench testing; re-engineering; animal/cadaver testing</td>
<td>Design changes</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Engineering labs- packaging, stability, shelf life</td>
<td></td>
</tr>
<tr>
<td>Bioanalytical</td>
<td>Biocompatibility - toxicology</td>
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</tr>
<tr>
<td>Health Economics</td>
<td>Reimbursement and Outcomes Research</td>
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</tbody>
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US-FDA-CDRH Regulatory Paths

- Under the Office of Device Evaluation in CDRH
  - Premarket Approval (PMA) Applications
    - PMA supplements
  - Product Development Protocols (PDP)
  - Humanitarian Device Exemptions (HDE)
  - Investigational Device Exemptions (IDE)
    - IDE Amendments and Supplements
  - Premarket Notifications (510(k))
US-FDA-CDRH Regulations (in part)

- 21CFR801 Labeling
- 21CFR803 Medical Device Reporting
- 21CFR807 Establishment Registration/Device Listing
  - Subpart E Premarket Notification Procedures 510(k)
- 21CFR812 Investigational Device Exemptions (IDE)
- 21CFR814 Premarket Approval (PMA)

- 21CFR820 Quality System Regulation (QSR)
  - Good Manufacturing Practices (GMP)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm
Device Regulatory Process

Class II b

De Novo 513(g)

PMA?

Devices: Class I

- Subject to general controls
  - Establishment and Device listing
  - Labeling
  - Compliance with FDA’s quality system regulations (QSR)

- Most Class I
  - Exempt from 510(k) premarket notification
  - In some cases exempt from compliance with QSR other than minimal record keeping and reporting requirements
**Devices: Class II**

- Subject to general and special controls
  - Listing, Labeling & Compliance with QSR
  - Performance standards
  - Post-market surveillance

- Most Class II
  - Require 510(k) submission

- Some Class II
  - require clinical data
  - ?PMA
Class III devices are:
- Life sustaining/Life supporting
- Implantable devices
- New devices – not found to be substantially equivalent to legally marketed devices

Subject to general and special controls

Most Class III
- Require PMA
- Most stringently regulated

Unless marketed prior to May 28, 1976 (Pre-amendment devices)
Device: 510(k) Requirements

- Description of the new device
  - Photographs
  - Engineering drawing
- Labeling
  - Draft promotional materials
- Identification of predicate device(s)
- Narrative and tabular comparisons
- Predicate device’s intended use, indications
- Technological characteristics
- Principles of operation
- Software documentation
- Sterility information
- Biocompatibility information
- Statement or declarations of conformance to applicable standards and guidance documents
- Summaries of any performance testing
- Administrative requirements
  - Truthfulness and accuracy statement
  - 510(k) summary
  - Payment of a user fee
Device: IDE Application

- 21 CFR Part 812
- Clinical study protocol
- Non significant risk (NSR) investigated device
  - Requires IRB approval
  - Informed consent
  - Need not obtain FDA approval before study begins
- A significant risk device study
  - Potential for serious risk to health, safety or welfare to the subjects
  - Intended as an implant
  - Used in supporting or sustaining human life
  - Substantial importance in diagnosing, curing, mitigating or treating a disease
  - Prevents impairment of human health
  - Potential for serious risk to health, safety or welfare of a subject
Device: PMA Requirements

- Complete description of the device
- Complete description of the components
  - Photographs
  - Engineering drawings of the device
- Detailed description of the methods, facilities and controls used to manufacture
- Prepared labeling, advertising literature, any training material
- Software documentation
- Sterility information
- Biocompatibility information
- Extensive clinical trials
- Animal studies
- Bench tests
- Published and unpublished literature
- Bibliography of all published reports known concerning the device’s safety or effectiveness
Device: Specialized Documents

Risk Management
- Part of Clinical evaluation report
- Assesses the potential for adverse events from use, device or procedure

Failure Mode and Effect Analysis (FMEA)
- FAILURE: Identify potential defects in the process, design or product based on past experiences with similar items
- EFFECT: analysis of the consequences of the failures
European Commission (EC):

- Core of 3 Medical Device Directives (MDD)
  - Directive 90/385/EEC: Active Implantable Medical Devices
  - Directive 93/42/EEC: Medical Devices
  - Directive 98/79/EC: In Vitro Diagnostic Medical Devices

- Technical Revision/Amendment of MDD
  - Directive 2007/47/EC

- Clinical Trials
  - 2001/20/EC: GCP for conduct of clinical trials on medical products for human use

- Guidance documents

Europe: Regulatory Approval Process - Medical Devices

Determine the classification of your device according to the Canadian Medical Devices Regulations (CMDR)

Class I
- MDEL only needed if you sell Class I devices directly and not through an established Canadian distributor.

Class II
- Implement ISO 13485:2003 quality system to meet Canadian requirements.

Class III
- Have ISO 13485 quality system audited by a Registrar that is CMDCAS accredited by Health Canada (HC) and receive ISO 13485:2003 certificate.

Class IV
- Submit MDEL application** and pay fees to HC
- Submit MDL application* and ISO certificate, fees. Pay fees to HC.

Submit MDL application plus ISO certificate and Premarket Review Document**. Pay fees to HC.

Prepare Medical Device Establishment License (MDEL) application.

Submit MDL application. STED format required for Class III and IV submissions.

Prepare Medical Device License (MDL) application accepted or rejected by Health Canada.

Medical Device License (MDL) application accepted or rejected by Health Canada.


Approved device applications posted Health Canada website.

You are now approved to sell your device in Canada. Annual fees will be assessed and payable to Health Canada.

How Is The Regulatory Field Changing

- US
- International
Overview of Laws and Guidelines for Clinical Research Management

Pharmaceutical
- US FDA CFR312
- EU (EMEA)
- ICH-GCP E6

Medical Devices
- US FDA CFR812
- EU (MDD)
- ISO 14155
US 510K Process is Changing

- 25 Proposed changes to the process
- 85% of devices are substantially equivalent to devices on the market
- Small percentage of devices require clinical data to support application

US 510K Proposed Changes

- **De Novo Process:**
  - A new effort to streamline the review process for innovative products with a lower risk to patient safety through a process called the "de novo" process

- **Clinical Data:**
  - New guidance for industry to clarify when clinical data should be submitted to increase the predictability of new devices and transparency within the FDA approval process

- **Knowledge Experts:**
  - The creation of a new group of experts who can use their knowledge and experience to help the FDA address emerging scientific concerns and facts regarding new medical device technologies

- **Decision Making:**
  - The establishment of a new Center Science Council of senior FDA experts within the agency’s medical device center to oversee the agency’s science-based decision making

- **Post-Market Surveillance:**
  - A commitment to continue and strengthen the monitoring of devices after they are introduced to the market. A public database will summarize and explain all FDA decisions regarding the approval of devices
US: 510(k) Possible Consideration

- Class IIb established – clinical data, manufacturing data, and or post market data would be needed to support clearance
- Seek statutory authority to expand regulation for off-label use
- Consolidate terms “indication for use” and “intended use”
- Define conditions disallowing device use as a predicate
- Issue regulation defining FDA’s authority to rescind 501(k)
- Seek greater authority to require post market surveillance as a condition of clearance
- Require manufacturers to keep 1 unit of a device available for the clearance process

US: Healthcare Reform

- Uncertain environment - ?future reimbursement issues
  - 2.3% Excise Tax - medical device sales after 1/1/2013
  - Transparency Requirements - physician payments
  - Comparative effectiveness - Patient centered outcome research
  - Fraud and Abuse - Anti-kickbacks and false claims
  - Coverage for Clinical Trial Costs - Health plans can no longer deny coverage for routine patient costs associated with clinical trials
  - Women’s Health - New Office of Women’s Health Issues
  - Medicare Payment Issues - Reduced reimbursement rate for imaging centers

EXAMPLE: ISO 14155:2011

ISO: 14155
2003
Part 1

28 Page General Guidance

ISO: 14155
2003
Part 2

16 Page Clinical Investigation Plan

ISO: 14155
2011

65 Page Detailed Content
### ISO 14155 Changes: Risk and QC

<table>
<thead>
<tr>
<th>Addition/Expansions</th>
<th>Changes Made or Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Mitigation</td>
<td>• Clinical Evaluation Report (required to justify the study design)</td>
</tr>
<tr>
<td></td>
<td>• Risk Analysis Report (required)</td>
</tr>
<tr>
<td>Quality Control</td>
<td>• Clinical Research Quality Management System (implied need)</td>
</tr>
<tr>
<td></td>
<td>• Data Monitoring Committees (discussion)</td>
</tr>
<tr>
<td></td>
<td>• Auditing (recommendations)</td>
</tr>
<tr>
<td>Addition/Expansions</td>
<td>Changes Made or Required</td>
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<tr>
<td>Study Documentation</td>
<td>• Essential Documents list (consistent with the ICH E6)</td>
</tr>
<tr>
<td></td>
<td>• Document and data control and electronic data systems (requirements)</td>
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<td></td>
<td>• Protocol (required content for Clinical Investigation Plan)</td>
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<tr>
<td></td>
<td>• Investigator’s Brochure (required content for medical device)</td>
</tr>
<tr>
<td></td>
<td>• Case Report Forms (suggested content and organization)</td>
</tr>
<tr>
<td></td>
<td>• Suspension or premature termination of a trial (procedures)</td>
</tr>
<tr>
<td></td>
<td>• Working with vulnerable populations (procedures)</td>
</tr>
</tbody>
</table>
How does one get into Regulatory Writing?

- Essential skills and knowledge
Getting into the Field

- Just do it
- Seek position with pharmaceutical, biotech or medical device company
- Generally requires advanced degree - MS, PhD, MD
- Strong computer/software skills
  - Documents, spreadsheets, presentation formats, templates, style guides, table formatting, and customized toolbars
- Knowledge of statistics
- Prefer experience in therapeutic area
Essential Skills and Knowledge

- Clinical study design and conduct
- Protocol Writing
- Case Report Form
- Informed Consent
- Investigator’s Brochures
- Clinical Study Reports
- Risk Management Plans/Reports
- Reading and interpretation of clinical data
  - Raw Data
  - Summary Tables

- Detail Oriented
- Need to be able to work within guidelines and forms
Essential Skills and Knowledge

- Regulations: US
  - GCP: Good Clinical Practices

- Regulations: International
  - ICH: International Conference on Harmonization
  - ISO: International Standards Organization
What, exactly, is regulatory writing and how is it changing?

Is this a field you might want to get involved in, and would you be qualified?

How are changes at the FDA and in the regulatory environment itself impacting your work today, and how will they impact the many Minnesota medical device companies?
QUESTIONS: Contact Information

- Dr. Joy Frestedt, PhD, RAC, CCTI
  President and CEO

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