RAPS
REGULATORY AFFAIRS PROFESSIONALS SOCIETY

Preparing for the RAC Exam - Module 1

Strategic Planning, Design and Development

Wednesday, 8 March 2006

12:00 pm – 1:30 pm Eastern
11:00 am – 12:30 pm Central
10:00 am – 11:30 am Mountain
9:00 am – 10:30 am Pacific

Module 1 Agenda

Strategic Planning & Design for Drugs/Biologics and Devices

- RAC exam
  - Content and format
  - Proven methods for efficient study
  - Test taking strategies
- Practice questions
  - Review best answer
  - Discuss rationale / supporting content
- Opportunity to ask questions
- Additional references and definitions for you to study later

Audience Poll Question

We'd like to know who is in our audience today.

Please indicate whether you primarily work in Drugs, Biologics or Devices.

A → Drugs

B → Biologics

C → Devices

RAC Exam Content

- US laws, regulations, policies and guidelines
  - Pharmaceuticals
  - Biologics
  - Medical Devices
  - Biotechnology
- GCPs, GMPs, GLPs
- Key submissions (IND, NDA/BLA, IDE, PMA, etc.)
- Chemistry, Manufacturing and Controls
- Agency interactions
- Post approval requirements

References to CFRs, etc are provided within and at end of presentation

Test Format

- Information cut-off:
  - November exam: covers regulations in effect as of December 31 of the prior year
  - April exam (2006): same cut-off as prior November exam, ie. December 31, 2004 cut off for April 2006 exam
- 100 Questions in 2 hours
- Multiple Choice
  - Recall
  - Application
  - Analysis

Test Format

Types of multiple choice questions:

- 1 **best** answer and 3 incorrect responses
- Questions asking for the exception
- Questions with seemingly all good choices
  - Look for key word (eg, IND, IDE, NDA, PMA) to determine context
  - Look for key words like first, except, not
  - Don't over think, go with **best** answer

Best Study Practices

- Process of preparation is invaluable
- Divide and conquer
- Organize
  - By topic (eg, devices, GMPs)
  - Tabular (eg, reporting requirements)
- Presentations in a group setting
- Round table focused discussion (small groups)

Best Study Practices

- Individual study
  - Assess and prioritize your weakest area(s)
  - Study plan based available calendar time
  - Study in blocks of time
- RAPS Self Assessment Examination
  - Read the source references provided in the answer key
- Register for the exam
- Make up your own questions

Best Study Practices

Active vs Passive Study

- Learning requires the expenditure of energy
  - Incorporate multiple senses (hear, see, say)
  - Repetition
- Study (Flash) Cards
- Mnemonics
  - Organize material by finding the key words in each point, and arranging the letters into a sense or nonsense word according to first letter
- Association is key to memory

Adapted from: Ann Algier, Everything You Need To Know About Learning

Exam Day

- Be well rested
- Positive state of mind
- Know exact location of test facility (will be provided via mail and email approximately 2 weeks prior to the exam)
- Arrive on time (no later than 8:30am for registration)
- Bring #2 pencils, registration, photo ID
- Eat breakfast before (no food or drink allowed in test room)
- Exam administered by independent testing service

Taking the Test

- Use your time wisely
  - Target 25 questions every 30 minutes
  - Can skip and return
- Read the question and all the choices completely before marking your response
- Look for key words: “first”, “except”, “not”
- Can write on test booklet
- Choose the **best** answer
- Answer all the questions, no penalty for wrong answers

Process for Scoring Exams

- Exams scored by independent agency
- Statistical reports and item analysis as part of test-quality assurance
- Passing point or cut score determined via Modified Angoff Technique
- 0 to 99 point scaled score with 75 as passing point (different from the number of questions answered correctly)
- Exam revised periodically with new questions
- Equating procedure “equalizes” different versions for level of difficulty to ensure candidates are judged against same passing standard

Practice Question #1

In which situation is an IND not required?

A) You intend to conduct a clinical trial with an investigational new drug

B) You intend to conduct a clinical trial with an approved drug to support a marketing application for a new indication

C) You intend to collect blood samples from subjects to look for biomarkers or pharmacogenetic information

D) You intend to conduct a clinical trial using 2 of your approved drugs in a new combination

Investigational New Drug Application (IND)

- IND application (21 CFR Part 312):
- Provides an exemption from premarketing approval requirements and allows you to legally ship drug for the purpose of conducting clinical investigations of that drug
- Applies to all clinical products subject to section 505 of the FD&C Act or to licensing provisions of the PHS Act
- An IND goes into effect
  - 30 days after FDA receives the IND unless FDA notifies sponsor that the proposed investigation(s) are subject to a clinical hold OR
  - Earlier, if so notified by FDA in writing

Practice Question #2

In the clinical development plan for an investigational anti-hypertensive drug, which of the following studies would typically be conducted first:

A) 1 month repeat dose toxicology study

B) Single dose escalation PK study in healthy volunteers

C) Multiple dose PK study in healthy volunteers

D) Single dose escalation study in hypertensive patients

Phases of Drug Development (study later)

Preclinical

- Pharmacology:
  - Animal pharmacology: whether drug affects the disease or symptoms in animal models
  - Safety pharmacology: whether drug adversely affects certain organs (eg, heart, lungs, brain)
- Toxicology: studies dose range for toxic effects
- Pharmacokinetics (drug absorption, distribution, metabolism, elimination)
- Pharmacodynamics (measurable effects like blood pressure)

Phase I/First in human/Phase IB

- Typically healthy volunteers, sometimes patients (eg, 25 to 70)
- Establish safe dosing range, usually single dose then multiple dose
- Pharmacokinetics, pharmacodynamics, drug metabolism
- Drug-drug interaction
- Age, food, gender, impaired organ function effects?
- Establish effect in humans (proof of concept)

Phases of Drug Development (study later)

Phase II

- Patients (eg, 35 to 200)
- Dose ranging, dose response
- Safety, efficacy

Phase III

- Performed in patients (eg, 100s to 1000s)
- Establish dose response
- Safety and efficacy
- Establish risk/benefit

Practice Question #3

A sponsor must report an unexpected, fatal or life-threatening experience believed to be associated with an unapproved drug/biologic:

A) to FDA, investigators and IRBs within 7 calendar days

B) to FDA and investigators within 7 calendar days

C) to FDA within 14 calendar days

D) to FDA and investigators within 7 working days

IND Safety Reports (21 CFR 312.32)

- Sponsors are responsible for review of safety information relevant to the safety of the drug
- IND Safety reports (calendar days)
  - 7 Day IND Safety Reports: serious and unexpected adverse drug experience associated with the use of the drug in clinical studies that was fatal or life- threatening
  - 15 Day IND Safety Reports: Any adverse experience associated with the use of the drug that is both serious and unexpected
- Reporting responsibilities
  - Sponsor reports to FDA and investigators
  - Investigators report to respective IRBs

Serious: adverse reaction that results in death, hospitalization, significant disability, congenital anomaly, or medically important per investigator

Unexpected: adverse reaction, where the specificity or severity is not consistent with current investigator brochure

Practice Question #4

Which of the following is a covered study as defined under Financial Disclosure regulations:

A) Phase I dose escalation study

B) Phase I/II Pharmacokinetic Study

C) A large open label safety study conducted at a large number of study sites

D) Phase III pivotal study

Financial Disclosure by Clinical Investigators

- Goal of financial disclosure is to minimize investigator bias in clinical studies due to excessive payment, royalty, or proprietary interest in the product.
- Covered study: Study for a drug or device submitted in a marketing application or reclassification petition that FDA relies upon to to establish the product is effective or any study in which a single investigator makes a significant contribution to the demonstration of safety.
- Not covered studies (typically): Phase I tolerance or PK studies, large open label safety studies at multiple sites, most clinical pharmacology studies.

Reference 21 CFR Part 54

Practice Question #5

Your company is developing a product to treat a serious and life threatening disease. A clinically meaningful, well-established primary endpoint will be used in the pivotal studies. Which regulatory strategy might you select prior to commencing Phase 3 studies?

A) Request Special Protocol Assessment

B) Request Fast Track Designation

C) Request Priority Review

D) Approval under Subpart H, Accelerated Approval of New Drugs for Serious or Life Threatening Illnesses

Development Strategies

Fast Track Designation

- Treatment of serious and life-threatening illness with potential to meet unmet medical need
- Periodic meetings/communication with FDA are encouraged; however, non-fast track products have same access to meetings (eg, Pre-IND, End of Phase II, Pre-NDA/BLA)
- May qualify to submit portions of marketing application (rolling or continuous application)

Priority Review: 6 month review of marketing application

- The drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease, for example:
  - enhancement of patient compliance
  - elimination or substantial reduction of a treatment-limiting drug reaction
  - evidence of safety and effectiveness of a new subpopulation
- Do not need Fast Track Designation to request priority review

Development Strategies

Subpart H (21 CFR 314.500) Approval based on surrogate endpoint or clinical effect

- Serious or life-threatening diseases
- New therapy provides benefit over existing
- Requires postmarketing study(ies) to verify clinical benefit

Special Protocol Assessment

- Animal carcinogenicity protocols
- Product stability protocols
- Clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim
- Submit at least 90 days prior to starting the study
- 45 day review by FDA

Reference: Guidance for Industry, Special Protocol Assessment

Practice Question #6

As a regulatory affairs professional, you are responsible for developing the content of an information package for a Type B meeting with FDA. Your primary objective is to:

A) Reach consensus on content from contributing team members

B) Ensure content is sufficient to support meeting objective(s) and questions to FDA

C) Provide appropriate preclinical summary

D) Provide appropriate clinical summary

Meetings with FDA

Type A:

- Immediately necessary for otherwise stalled drug development program (critical path)
- should be scheduled within 30 days of request

Type B:

- Pre-IND; End of Phase 1; End of Phase 2; Pre-IND/BLA meetings
- should be scheduled within 60 days of receipt of request

Type C:

- Any meeting other than Type A or B.
- Should be scheduled within 75 days of receipt of request for meeting.

Reference: Guidance for Industry, Formal Meetings with Sponsors and Applicants for PDUFA products

Practice Question #7

You, a regulatory affairs professional, are assessing the information to be submitted in support of a marketing application for a new dosage form for a listed drug. You lack right of reference to one key preclinical report. Which type of application will you prepare for submission?

A) 505 (b) (1)

B) 505 (b) (2)

C) 505 (j)

D) PMA

Types of New Drug Applications

Section 505 of the Food, Drug, Cosmetic Act describes three types of new drug applications:

(1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1))

- New Drug Application (NDA)
- BLA Biologics Licensing Application (BLA)

(2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has **not obtained a right of reference** (section 505(b)(2))

(3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j))

- Abbreviated New Drug Application (ANDA)

Practice Question #8

If FDA were to invoke the Application Integrity Policy, which of the following is a possible outcome?

A) Defer review of pending application(s)

B) “File” a marketing application at the 60 day review

C) Grant a waiver or deferral for pediatric clinical study

D) Approve a marketing application

Application Integrity Policy (AIP)

- AIP focuses on the integrity of data and information in applications submitted for Agency review and approval
- Provides ability to withdraw approval of or refuse to approve applications in cases where
  - Application contains fraudulent data
  - Application contains "untrue statement of material fact" ie, a false statement, misstatement, or omission of a fact
  - Wrongful act has occurred ie, any act that may subvert the integrity of the review process
  - Any of these examples may be a pattern or practice that may occur in one or more applications

Reference: Compliance Policy Guide CPG 7150.09

Practice Question #9

Which of the following supplements to an approved NDA/BLA must be approved by FDA prior to distributing product made using the change?

A) Make change(s) to comply with USP

B) Change in the technical grade of an excipient, same specifications and use

C) Add a warning statement to prescribing information

D) Process change outside the validated range

Supplements and Changes to an Approved Application

Applicant must notify FDA about each change in each condition established in an approved application, the magnitude of the change dictates type of supplement

- “Prior Approval Supplements” require FDA approval before implementing the change, eg, relax limits for a specification
- “Changes Being Effected” notifies FDA of the specific change, eg, add or strengthen a warning or precaution in prescribing information
- “Changes Being Effected in 30 days” notifies FDA of the specific change at least 30 days prior to distributing product made using the change, eg,
- Minor changes to be described in an Annual Report, eg, change made to comply with an official compendium

Reference 21 CFR 314.70

Practice Question #10

Which of the following products would not be regulated by CDER?

A) Therapeutic proteins

B) Vaccines

C) Chemically synthesized small molecules

D) Monoclonal antibodies

Product Jurisdiction

CDER is responsible for:

- Naturally occurring substances from mineral or plant sources
- Certain products produced by bacteria/fungi
  - Disaccharidase Inhibitors and HMG-Co A Reductase Inhibitors
- Chemically synthesized molecules
- Hormones
- Antibiotics
- Monoclonal Antibodies for in-vivo use
- Cytokines, growth factors, enzymes, immunomodulators, and thrombolytics
- Therapeutic proteins extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies

Practice Question #11

Which of the following devices would be regulated by CBER?

A) Warming device

B) Blood pressure cuff

C) HIV diagnostic test kit

D) Capillary blood collection tube

Product Jurisdiction

CBER is responsible for:

- Viral-vectored gene insertions (gene therapy products)
- Products composed of human or animal cells
- Allergen patch tests
- Allergenics
- Antitoxins, antivenins, and venoms
- *In vitro* diagnostics
- Vaccines, including therapeutic vaccines
- Toxoids and toxins intended for immunization
- Blood, blood components, and related products

Practice Question #12

You are developing a combination product and believe the primary mode of action will designate the product as a drug as opposed to a device. Your first course of action is to:

A) Develop written rationale describing the product, mode(s) of action, and proposed classification as a drug

B) Submit a formal request for designation to the Office of Combination Products

C) Call the CDER review division

D) Check the FDA website for information, eg, other combination/similar products

Product Jurisdiction

Is it a drug? Device? Combination? Who decides?

Intercenter Agreements

- between CDER and CBER (10/91)
- between CBER and CDRH (10/91)

Recent Announcements from CBER and CDER (check websites)

If unclear or dispute: Formally request designation in writing

21 CFR Part 3

Establishment Registration

- Establishments involved in the production and distribution of medical devices intended for marketing or leasing (commercial distribution) in the US are required to register with the FDA. This process is known as establishment registration.
- Registration provides FDA with the location of medical device manufacturing facilities and importers. The regulations for establishment registration are provided in 21 CFR 807.
- No registration fee is required.
- Registration of an establishment is not an approval of the establishment or its devices by FDA. That is, it does not provide FDA clearance to market.
- Misbranding by Reference to Establishment Registration Number: Title 21 of the Code of Federal Regulations, Section 807.39, states, "Registration of a device establishment or assignment of a registration number does not in any way denote approval of the establishment or its products. Any representation that creates an impression of official approval because of registration or possession of a registration number is misleading and constitutes misbranding."

Practice Question #13

For a medical Device, what is NOT a responsibility of the US Agent for a Foreign Establishment?

A) Report adverse events under the Medical Device Reporting regulation

B) Assisting FDA in communications with the foreign establishment,

C) Responding to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and

D) Assisting FDA in scheduling inspections of the foreign establishment.

US Agent, Foreign Establishments

- All foreign establishments must notify FDA of the name, address and phone number of their United States agent
- Agent must either reside in the U.S. or maintain a place of business in the U.S. The US agent cannot use a post office box as an address. The US agent cannot use an answering service. The agent must be available to answer the phone or have an employee available to answer the phone during normal business hours. The Official Correspondent for registration may also be the US agent for the establishment, but this is not required.
- If FDA is unable to contact the foreign establishment directly or expeditiously, FDA may provide information or documents to the US agent, and such an action shall be considered equivalent to providing the same information or documents to the foreign establishment. The US agent has no responsibility to report adverse events under the Medical Device Reporting regulation (21 CFR Part 803), or to submit Pre-market Notifications [510(k)] (21 CFR Part 807, Subpart E)

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Practice Question #14

Which Congressional Act provided Statutory Authority to FDA to regulate medical devices?

A) Safe Medical Devices Act of 1990 (SMDA)

B) Medical Device User Fee and Modernization Act of 2002 (MDUFMA)

C) Federal Food, Drug, Cosmetic Act (FDC Act)

D) Medical Device Amendments of 1976 (MDA)

Regulatory History

Statutory authorities

- Biologics Control Act (1902)
- Federal Food, Drug, Cosmetic Act 1938, PL 75-717, as amended (FDC Act)
- Medical Device Amendments of 1976 (MDA)
- Safe Medical Devices Act of 1990 (SMDA)
- [Medical Devices Amendments of 1992]
- [FDA Export Reform and Enhancement Act of 1996]
- FDA Modernization Act of 1997 (FDAMA)
- Medical Device User Fee and Modernization Act of 2002 (MDUFMA)

Regulatory History

- Federal Food, Drug, Cosmetic Act (FDC Act) contained no specific authorities for devices
- Prior to 1976, devices regulated under general control provisions of FDC Act, e.g., . . .
  - Prohibitions against adulteration and misbranding
  - Compliance with good manufacturing practices
  - Labeling
  - Registration/Listing
  - Record keeping

Regulatory History

- Medical Device Amendments of 1976 (MDA): <u>fundamental regulatory paradigm</u>
  - Classification of devices based on level of control necessary and sufficient for safety and effectiveness
  - Requirements for Registration of Establishments and Listing of Devices
  - Requirements for Premarket Notification [510(k)], when applicable

Regulatory History

Fundamental paradigm (cont)

- Requirements for Premarket Approval (PMA), when applicable [with alternatives for Product Development Protocol (PDP) or Humanitarian Device Exemption (HDE)]
- Provisions and requirements for conducting clinical studies under Investigational Device Exemptions (IDE)
- Provisions for reclassification and exemptions from premarket notification

Practice Question #15

Which of the following is NOT a key Medical Device submission which directly leads to marketing permission from FDA?

A) 510(k), Pre-market Notification, Part 807

B) HDE, Humanitarian Device Exemption, Part 814

C) Premarket Approval (PMA), Part 814

D) IDE, Investigational Device Exemptions, Part 812

Practice Question #16

At completion of review of a 510(k), FDA may take the following actions except:

A) Declare device substantially equivalent

B) Declare device not substantially equivalent

C) State a 510(k) is not required to market the device

D) Approve the device for market

Key Submissions in the Medical Device World

- Investigational Device Exemptions (IDE), regulations for clinical studies, Part 812
- Pre-market Notification [510(k)], Part 807, Subpart E
  - Classification via “substantial equivalence”
    - Intended use / indications for use
    - Technology / new types of questions
    - Specifications
    - Performance
- Pre-market Approval (PMA), Part 814
  - PDP and HDE

Key Submissions in the Medical Device World

- Investigational Device Exemptions (IDE), regulations for clinical studies, Part 812
  - IDE content requirements
  - FDA refuse to accept policy and other practices
  - Requirements of companion regulations [e.g., Institutional Review Boards (IRB), Informed Consent (IC), Financial Disclosure (FD)]
  - Records and reporting
  - Safety - reliability of design and manufacturing; biocompatibility; animal studies for safety and functionality
- Among content requirements:
  - Report of investigations
  - Investigational plan with protocol
    - Device description
    - Indication(s) for Use
    - Considerations for control
    - Statistical hypotheses, sample size, and analysis plan
    - Risk analysis
  - Manufacturing information

Key Submissions in the Medical Device World

IDE (cont)

- Special provisions for device studies
  - Exemptions from IDE regulations
  - Non-Significant Risk (NSR) device studies
  - Allowances for changes in protocol or device during conduct of study (per FDAMA)
- Types of studies (per policy or practice)
  - Feasibility or pilot study
    - Usually 1 center and 5-10 patients
    - May have few centers and few patients at each center
  - Confirmatory study for 510(k)s
  - Pivotal or definitive study for PMAs
    - Study design and sample size scientifically justified

Key Submissions in the Medical Device World

IDE (cont)

- Statutory review time, 30 days
- Likely review time, 30 days (iterative, 74% on first review @ 28 days, FY 2004)
- Agency decision

  -Approval

  -[Conditional approval with conditions]

  -Disapproval, with deficiencies identified

  -Withdrawal of approval (or proposed withdrawal of approval)

Practice Question #17

From a pre-clinical viewpoint, which of the following constitute pre-clinical activities in medical device development?

A) Animal use testing to validate the design of your device

B) Bench testing to verify that your design performs as designed

C) Biocompatibility/Toxicity testing

D) Functional/Safety/Performance testing

E) All of the above

NSR and SR

- IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

- The IDE regulations describe two types of device studies, "significant risk" (SR) and "non-significant risk" (NSR).

NSR and SR

- An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and

  (1) is an implant; or

  (2) is used in supporting or sustaining human life; or

  (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or

  (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

- An NSR device investigation is one that does not meet the definition for a significant risk study.
- For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study (21 CFR Part 50).

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Practice Question #18

With respect to a Non-Significant Risk device clinical trial, which of the following is NOT required before starting the trial?

A) Informed consent of trial participants

B) IRB approval of the trial

C) Financial disclosure by investigators

D) Submission of the trial protocol to FDA for approval

Key Submissions in the Medical Device World

- Premarket Notification [510(k)], Part 807, Subpart E
  - Classification via “substantial equivalence”
    - Intended use / indications for use
    - Technology / new types of questions
    - Specifications
    - Performance
  - Disclosures and Statements
    - 510(k) Summary or Statement
    - Truthful and Accuracy Statement
    - Class III Summary
    - Financial disclosure

Key Submissions in the Medical Device World

- 510(k) (cont)
  - "New 510(k) Paradigm" (policy and practice)
    - Traditional 510(k)
    - "Special 510(k): Device Modifications"
    - "Abbreviated 510(k)"
  - No pre-clearance QSR inspections, except for pre-amendments class III devices; otherwise on biannual basis

Key Submissions in the Medical Device World

- 510(k) (cont)
  - Traditional or Abbreviated 510(k)
    - Statutory review time = 90 days
    - Likely review time, 85 -100 days ±
    - 3rd party review 34% faster than FDA only review (also, no user fee to FDA)
  - Special 510(k)
    - Statutory review time = 30 days
    - Likely review time, 10 - 30 days
      - FY 2004 average 30 **FDA days**

Key Submissions in the Medical Device World

- 510(k) (cont)
  - Agency decision
    - Substantially equivalent (SE), proceed to market
    - Not substantially equivalent (NSE), device retained in class III and requires PMA
    - Unable to determine, deficiencies identified
  - ODE received 3,110 original 510(k)s, as well as 1,787 510(k) supplements (responses to hold letters, the receipt of which restart the 90-day review clock), and 1,408 510(k) amendments (additional information received while the 510(k) is under review, the receipt of which does not affect the review clock) in FY 2004.

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Practice Question #19

The establishment, performance and auditing of a human-use clinical device trial requires conformance with all of the following except:

A) 21 CFR 50 Protection of Human Subjects

B) 21 CFR 56 IRB

C) 21 CFR 807 Establishment Registration

D) 21 CFR 812 IDE Exemptions

Key Submissions in the Medical Device World

- Premarket Approval (PMA), Part 814
  - 37 original, 565 supplements in FY 2004
  - Content requirements (regulation)
  - Modular submissions (optional; For FY 04 ODE received a total of 21 PMA shells and 65 modules.)
  - Disclosures
    - All studies relevant to device
    - Conformance with IDE, IRB/IC/FD, QSR, GLP regulations and consensus standards
    - Financial disclosure

Key Submissions in the Medical Device World

- PMA (cont)
  - Reliance on “valid scientific evidence” (statute)
  - Demonstration of “safety and effectiveness” for the intended use(s) (statute)
  - Demonstration of “clinical utility” (policy)
  - Usually, presentation at device advisory panel meeting (statute and policy)
  - Pre-approval audit of clinical sites
  - Pre-approval inspection of manufacturing facility
  - Conditions of approval

Key Submissions in the Medical Device World

- Humanitarian Device Exemption (HDE)
  - Alternate path to satisfying PMA requirement (statute),
    - 9 filed in FY 2004
  - Two steps: (1) obtaining Humanitarian Use Device (HUD) status from FDA Office of Orphan Products Development and (2) obtaining approval of HDE application from CDRH under Part 814, Subpart H
  - Limitations imposed: labeling, cost, IRB approval

Key Submissions in the Medical Device World

- Product Development Protocol (PDP)
  - Alternate path to satisfying PMA requirement (statute)
  - Consultation with FDA staff and device panel with agreement on protocol and criteria for approval (statute)
  - Not used much (one filed in FY 2004);
  - Phased approach with segmented reviews (statute)
  - No implementing regulations

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Question and Answer

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Thanks!
Keep Studying!
Good Luck!

After the exam,
put it out of your mind, go do something fun
Results by mail in 4 to 6 weeks
Remember to recertify once every 3 years

Code of Federal Regulations

The FDA's portion of the Code of Federal Regulations (CFR), Title 21, interprets the Federal Food, Drug and Cosmetic (FD&C) Act, Public Health Service Act (Section 351 and 352) and related statutes.

Title 21 of the CFR contains most of the regulations pertaining to food, medical devices, drugs and biologics.

Final regulations published in the Federal Register (Final Rule) are collected in the CFR which is divided into 50 titles which represent broad areas subject to Federal regulations.

Regulations have the weight of law.

Sources of Information
Title 21 of Code of Federal Regulations

Part 3 Product Jurisdiction

Part 7 Enforcement Policy (and Recalls)

Part 11 Electronic Records & Signature

Part 50 Protection of Human Subjects

Part 54 Financial Disclosure

Part 56 Institutional Review Boards

Part 58 Good Laboratory Practices

Part 99 Off Label Dissemination

Part 201 Labeling

Part 202 Prescription Drug Advertising

Part 203 Marketing

Part 207 Registration

Part 208 Medication Guides

Part 210 cGMP

Part 211 cGMP

Part 312 Investigational New Drug Application

Part 320 Bioequivalence and Bioavailability

Part 314 Applications for FDA Approval to Market a New Drug

Part 600 Biological Products Part 312 Investigational New Drug Application

Part 320 Bioequivalence and Bioavailability

Part 314 Applications for FDA Approval to Market a New Drug

Sources of Information
Title 21 of Code of Federal Regulations

Part 600 Biological Products

Part 601 Biological Product Licensing

Part 606 cGMP for Blood and Blood Components

Part 607 Establishment Registration and Product Listing for Manufacturers of Human Blood and Blood Components

Part 610 General Biological Products Standards Part 606 cGMP for Blood and Blood Components

Part 610 General Biological Products Standards

Parts 640 to 680 Blood

Part 803 Medical Device Reporting

Part 806 Corrections and Removals

Part 807 Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices (510k regulations)

Part 812 Investigational Device Exemptions for setting up Clinical Study

Part 812 Premarket Approval of Medical Devices

Part 820 Quality System Regulations

Subpart C: Design Controls

International Conference on Harmonization (ICH)

ICH Impact on Drug Development

- Regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions brought together to discuss scientific and technical aspects of product registration.
- Purpose to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration to reduce the need to duplicate the testing
- Objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development with regulatory obligations to protect public health.

Sources of Information

- International Conference on Harmonization (ICH) Guidance
  - E2A: Clinical Safety Data Management
  - E4: Dose Response Information to Support Drug Registration
  - E5: Ethnic Factors in the Acceptability of Foreign Data
  - E6: Good Clinical Practice
  - E8: General Considerations for Clinical Trials
  - E10: Choice of Control Group and Related Issues in Clinical Trials
  - M4: Organisation of Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use
- RAPS Fundamentals of Regulatory Affairs

Sources of Information

FDA Guidance Documents:

- General topics such as:
  - Formal Meetings with FDA
  - Special Protocol Assessments
  - Electronic submissions
  - Content and Format of IND
  - Providing Clinical Evidence of Effectiveness
  - Applications Covered by Section 505(b)(2)

Definitions

Device [Section 201(h)]: The term “device” (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is–

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

Definitions

Device (cont)

- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or . . .

- (3) intended to affect the structure or any function of the body of man or other animals, and which does **not achieve *its primary* intended purposes through chemical action** within or on the body of man or other animals and which is **not dependent upon being metabolized for the achievement of *its primary* intended purposes**.

Definitions

Valid scientific evidence [21 CFR 860.7(c)(2)]: Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device...

Definitions

Valid scientific evidence (cont)

from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required my vary . . .

Definitions

Safety and effectiveness [21 CFR 860.7]:

> . . . will consider (1) The persons for whose use the device is represented or intended; (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) The probable benefit to health from the use of the device weighted against any probable injury or illness from such use; and (4) The reliability of the device.

Definitions

Substantial equivalence [Section 513(i)]: . . . means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device

- (i) has the same technological characteristics as the predicate device, or . .
- (ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent contains information ... that demonstrates that the device is as safe and effective as a legally marketed device and
- (II) does not raise different questions of safety and effectiveness than the predicate device.

Definitions

Biological Product (21 CFR 600.3(h)): Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man

Biologics are substances derived from or made with the aid of living organisms

Definitions

What is a Drug?

- article recognized in the official USP, Homeopathic Pharmacopoeia of the US, or official National Formulary
- article intended for the use in the diagnosis, cure and mitigation, treatment or prevention of disease in man or other animals
- article intended to affect the structure or function of the body of man or other animals (other than food)
- article intended for use a a component of the above

Reference: Section 201(g)(1) of the Federal Food Drug and Cosmetic Act

Prepare for the RAC (US) Exam - Module 1: Strategic Planning & Design

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Dr. Chadwick was most recently Director, RA/QA for Gyrus Medical in Maple Grove, MN. Dr. Chadwick was responsible for developing regulatory strategy for emerging and marketed products within the company and for regulatory submissions/compliance, and the quality system. He has over 25 years of experience in the medical device industry in such areas as basic research and development, clinical research, and for the past 10 years, regulatory affairs/quality assurance. The scope of his experience includes the product areas of dermatology, periodontology, urology, cardiology, drug delivery and electrosurgery. Dr. Chadwick spent many years in research and development functions and managing clinical trials prior to transitioning into regulatory affairs. Dr. Chadwick received a BS in biology from Albright College and a PhD in anatomy and cell biology from the School of Medicine, University of Pittsburgh.

Prepare for the RAC (US) Exam - Module 1: Strategic Planning & Design

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