DuaneMorris

Dietary Supplements, Combination Products, and Veterinary Medicine

SDRAN RAC Exam Review Course

Wednesday, August 13, 2014

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Our Topics Today

- Dietary Supplements
- Combination Products
- Veterinary Medicine

DIETARY SUPPLEMENTS

What We Will Cover on Dietary Supplements

- Basics
- New Dietary Ingredients
- Claims Allowed
- GMPs and Other Regulatory Requirements
- Adverse Events

The Basics

- **Pre-1994 – dietary supplements regulated as foods**
- **1994 – Dietary Supplement Health Education Act (DSHEA)**
  - Defined "dietary supplement" (D.S.)
  - Defined "dietary ingredient"
  - Required ingredient and nutrition labeling
  - Delineated the claims and nutritional support statements that could be made
  - Gave FDA power to promulgate D.S. GMP regulations
  - Required that any D.S. ingredient that was not on the market on the date of enactment (October 15, 1994) had to be subject to a New Dietary Ingredient (NDI) notification

Definition of D.S. – Part 1

- **Section 201(ff) of the Act -- The term "dietary supplement" -**
  - (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
    - (A) a vitamin;
    - (B) a mineral;
    - (C) an herb or other botanical;
    - (D) an amino acid;
    - (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
    - (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

AND …

Definition of D.S. – Part 2

- **Section 201(ff)(2):**
  - …means a product that -
    - **(A)(i)** is intended for ingestion in a form described in section 411(c)(1)(B)(i); or
    - "(ii) complies with section 411(c)(1)(B)(ii);
    - **(B)** is not represented for use as a conventional food or as a sole item of a meal or the diet; and
    - **(C)** is labeled as a dietary supplement;
  - ***411(c)(1)(B)(i)*** -- is intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form
  - ***411(c)(1)(B)(ii)*** -- if not intended for ingestion in such a form, is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet.

AND …

Definition of D.S. – Part 3(A)

- **Section 201(ff)(3)**
  - ***does*** -
    - (A) include an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f);

AND …

Definition of D.S. – Part 3(B)

- **Section 201(ff)(3)**
  - ***B) does not include*** – **<u>"Prior Market" Clause</u>**
    - (i) an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or
    - (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,

  which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act.

The Basics

- Except for purposes of section 201(g), a dietary supplement shall be deemed to be a food within the meaning of this Act.
  - ***In other words***, it can be a drug also if it meets the drug definition
- Premarket approval/clearance – not required, unless "new dietary ingredient" …

New Dietary Ingredients (NDI)

- **If a dietary ingredient was not marketed before October 15, 1994 and (a) not present in the food supply or (b) chemically altered even if present in the food supply or as a pre-DSHEA dietary ingredient), must notify FDA before marketing**
- **Notice:**
  - Goes to Office of Nutritional Products, Labeling & Dietary Supplements (ONPLDS)
  - At least 75 days before introducing NDI into interstate commerce

NDI Notice -- Contents

- **Name and address of manufacturer or distributor**
- **NDI name, including Latin binomial name of any herb or other botanical**
- **Description of products that contain the NDI + level of NDI in the product**
- **History of use or other evidence NDI is safe**
- **Process**
  - Get a filing date from FDA
  - 75 days after filing date, can go to market – BUT, that does not mean FDA agrees the NDI is safe
    - FDA can object
- **New draft guidance – July 2011 – for comment**

http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm

Labels and Labeling

- **Basics**
  - Statement of identity
  - Net quantity of contents
  - Ingredient list
  - Address of mfr., packer or distributor
  - Nutritional facts box

Labeling Claims

- **Nutrient content claims**
  - 21 CFR 101.13 – General Principles
  - Types of claims governed:
    - "Good source," "More" and "High Potency"
    - "Light" or "Lite"
    - Caloric claims
    - Sodium content
    - Fat, Fatty Acid and Cholesterol content

Health Claims

- **Possible for dietary supplements**
- **Petition process – for an allowable health claim – 21 CFR 101.70**
- **Standard for allowable claim: "significant scientific agreement"**
- **Examples:**
  - Calcium and osteoporosis
  - Sodium and hypertension
  - Fiber and cancer
  - Folate and neural tube defects (e.g., spina bifida)

Health Claims -- FDAMA

- ***Basis* – a published authoritative statement of a "scientific body of the United States with official responsibility for public health protection or research directly related to human nutrition …"**
  - National Academy of Sciences
  - NIH
  - CDC
- ***Process***
  - 120 days notice – then can make claim

Health Claims – "Qualified"

- **Result of Pearson v. Shalala – lawsuit over First Amendment right to make truthful commercial speech**
  - FDA cannot reject a health claim that ***might*** be misleading unless agency ***also*** finds that no disclaimer would eliminate the potential misconception
  - Examples:
    - "supportive but not conclusive data" shows omega-3 fatty acids may reduce risk of coronary heart disease
    - Antioxidants and cancer
    - Nuts and heart disease

Nutrient Content & Structure/Function Claims

- **Can apply to claims relating to how the D.S:**
  - helps address a classical nutrient deficiency disease (e.g., Vitamin C and scurvy); or
  - helps affect or maintain the normal, healthy structure or function of human body
    - but can't be disease claim – or it's a drug
    - FDA -- regulations and guidance on acceptable structure/function claims
  - helps with the "general well-being" supported by consumption

– ***Must bear disclaimer***: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Limits on Structure/Function Claims

- **21 CFR 101.93(g)(2) – ten criteria that are barred; include**
  - Effects a specific disease or disease class
  - Effects the characteristics signs or symptoms of a specific disease
  - Effects an abnormal condition linked to a natural state if the abnormal condition is uncommon or can cause significant harm
  - Effects a disease via:
    - Name
    - Contains a non-dietary ingredient that is a drug
    - Citation to articles that refer to diseases
    - Using "disease" unless general statement on disease prevention
    - Treats, prevents or mitigates an adverse event linked to disease therapy

Supporting Structure/Function Claims

- **Must have data to substantiate the claim**
- **Don't have to submit data to FDA, but you do have to inform FDA 30 days before making any nutritional support claims**
- **Must meet FTC standard – *"competent and reliable scientific evidence"***

  "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."

- **Literature reprints – if done in their entirety, are not considered "labeling"**

Other D.S. Regulatory Requirements

- **Registration – mandatory -- with FDA – 21 CFR 1.232**
- **GMPs**
  - June 2007 – Final Rule published; codified at 21 CFR 111
  - Examples of requirements
    - facility cleaning and pest control
    - maintaining, cleaning and sanitizing equipment
    - QC operations, including material review and disposition decisions
    - Lab operations
    - Manufacturing operations
    - Complaints
  - Guidance issued
  - Failure to meet GMPs – product is adulterated under § 402(g) of Federal Food, Drug, and Cosmetic Act

Adverse Events

- **Labeled maker, distributor or packer must submit serious adverse events to FDA within 15 business days of learning**
  - Adverse event – "any health-related event associated with the use of a dietary supplement that is adverse"
  - Serious – an event that results in:
    - Death
    - Inpatient hospitalization
    - Persistent or significant disability
    - Incapacity
    - Congenital anomaly or birth defect
    - Medical or surgical intervention … to prevent one of the above results
- **"At a Glance" on AEs – issued in 2011 –** http://www.fda.gov/downloads/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/UCM267417.pdf

COMBINATION PRODUCTS

What We Will Cover

- A Brief History of Combination Product Regulation
- Primary Mode of Action (PMOA) – The Key Lynchpin to FDA's Regulatory Regime for Combination Products
- The Request for Designation (RFD) Process
- GMPs
- Post-Market Safety Reporting
- How Many Applications to File?
- User Fees

What Is a Combination Product?

- As defined in 21 CFR § 3.2(e), the term *combination product* includes:
  - A product comprised of *two or more regulated components*, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise *combined or mixed and produced as a single entity*;
  - Two or more *separate products packaged together in a single package* or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
  - A drug, device, or biological *product packaged separately* that according to its investigational plan or proposed *labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use*, indication, or effect and where upon approval of the proposed product the *labeling of the approved product would need to be changed*, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
  - Any investigational drug, device, or biological *product packaged separately* that according to its proposed labeling is for *use only with another individually specified* investigational drug, device, or biological product *where both are required to achieve the intended use*, indication, or effect.

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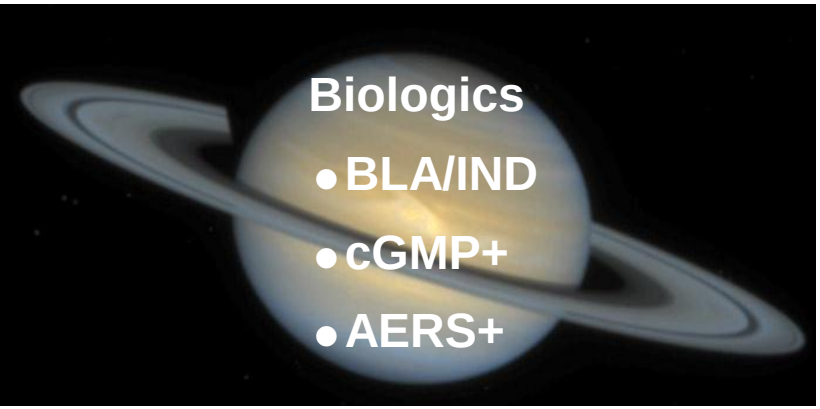
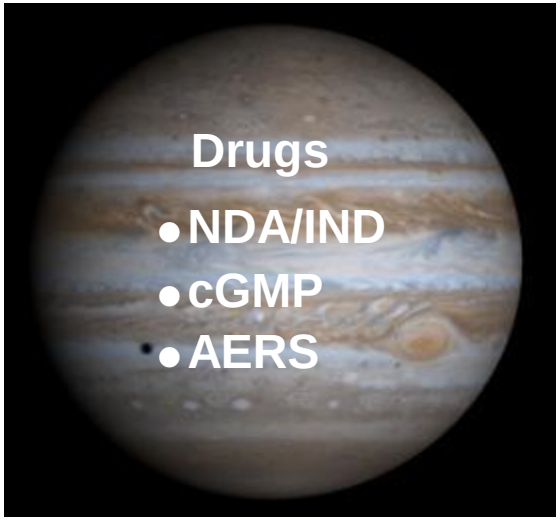
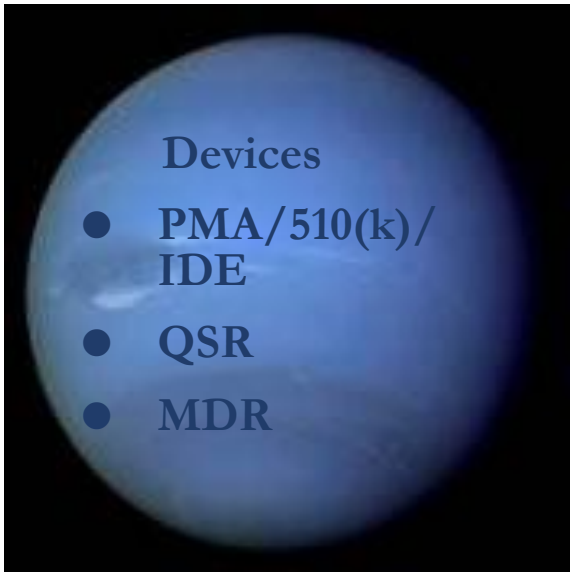
The Combination Galaxy







A Brief History of Combinations

- **Safe Medical Device Act of 1990 -- combination products first statutorily recognized**
  - Required assignment to lead center based on Primary Mode of Action ("PMOA")
  - Implemented by Chief Mediator and Ombudsman
- **Office of Combination Products ("OCP")**
  - Created by Medical Device User Fee and Modernization Act (MDUFMA) – 2002
  - OCP given broad oversight responsibilities covering the regulatory life cycle of combination products.
    - Coordinate reviews among FDA Centers
    - Ensure consistency among similar reviews

Section 503(g) of the Act

- **FDA is required to assign a combination product to a lead Center based on its "primary mode of action"**
- **PMOA was not defined in the statute or regulations**
- **For some products, PMOA is difficult to identify**
  - Early in development (just don't know)
  - Products that have two (or more) completely different modes of action, neither of which is subordinate to other

PMOA -- Determining Which Center Leads

- ***PMOA*** **= Primary Mode of Action; not defined in statute, but in regulations**
  - Final Rule – 8/25/2005; 70 Fed. Reg. 49848
    - *http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf*
- ***Mode of Action*****: the means by which a product achieves an intended therapeutic effect or action 21 CFR 3.2(k)**

PMOA …

- ***Primary mode of action*** is the single mode of action of a combination product that provides the *most important therapeutic action* of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.
- **Three types of modes of action:**
  - Biological product
  - Device
  - Drug
- **Combination products typically have more than one identifiable mode of action**

Source: 21 CFR 3.2(m)

Final PMOA Rule: Constituent Parts

- **A constituent part of a combination product has a:**
  - ***Biological product mode of action*** if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings…
  - ***Device mode of action*** if it meets the definition of device…, it does not have a biological product mode of action, and it does not achieve its primary intended purposes through chemical action within or on the body….and is not dependent on being metabolized for the achievement of its primary intended purposes
  - ***Drug mode of action*** if it meets the definition of drug…and it does not have a biological product or device mode of action.

Factors Impacting PMOA

- Proposed use(s) or indication(s)
- How it achieves its overall intended therapeutic effect(s)
- Relative contribution of each component toward the overall intended therapeutic effect
- Duration of the contribution of each component towards the intended therapeutic effect
- Data or information that describes and supports the mode of action

The PMOA Decision Tree – "Assignment Algorithm"

- **If unable to determine most important therapeutic action with reasonable certainty, FDA will use the "assignment algorithm" at 21 CFR 3.4(b).**
- **Two major factors, considered in order:**
  - **Consistency:** is there an agency component that regulates other combination products presenting similar questions of S & E with regard to the combination product as a whole?
  - **Safety and Effectiveness:** which agency component has the most expertise related to the most significant S&E questions presented by the combination product?

Assignment Algorithm – Additional Factors

- Intended use/indication(s)
- Overall therapeutic effect(s)
- Does a device component incorporate a novel or complex design or have potential for significant failure modes?
- Is drug component a new molecular entity or formulation?
- Has a generic version of drug been approved?
- Is biological component a particularly fragile molecule?

Assignment Algorithm – Additional Factors …

- How well understood are the components on a comparable basis? Is one more risky?
- Which components raise greater risks?
- Have any components been approved/cleared?
- Is there a new indication, route of administration, or significant change in dose or use of component?

Not Sure of PMOA -- Requests for Designations (RFD's)

- **Voluntary Formal Process under 21 CFR Part 3**
- **Seeks to determine:**
  - Regulatory Identity or Classification
  - Assignment of Lead Center
  - *Collateral issue* -- clarification of regulatory pathway
- **If don't seek RFD and submit for marketing, FDA may stay review clock while making designation determination**

RFD's …

- **When to file RFD:**
  - Before filing any application for investigational or marketing authorization
  - As soon as enough info exists for FDA to make a decision
- **Can meet with OCP before filing RFD -- not required**
- **Regulation – 21 CFR 3.7**
- **Guidance on How to Write a RFD**
  - Federal Register – Monday, April 18, 2011 – 76 Fed. Reg. 21752
  - *http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf*
- **Format – follow descriptions in 21 CFR 3.7(c)(1)-(3)**
- **Electronic filing – allowed, but not required**
- **15-page limit (with attachments)**

RFD Contents – 13 Sections

- Contact Information
- Product Name
- Description of Product
- Prior Approvals and Agreements
- Chemical, Physical or Biological Composition
- Development Work & Testing
- Manufacturing Information
- Proposed use or Indications
- Modes of Action (*all*) and Primary Mode of Action
- Schedule and Duration of Use
- Dose and Route of Administration
- Related Products
- Other Relevant Information
- Sponsor's Recommendation on PMOA/classification and Center with jurisdiction

RFD's …

- **Guidance – drills down on the 13 sections**
- **Some Key Points from the Guidance:**
  - State how you think your product should be assigned and why
    - State the basis for your assertion why your selected PMOA is most important therapeutic action for the product
    - Assignment Algorithm -- if you cannot determine, "with reasonable certainty," the PMOA, must use assignment algorithm (Slides 12 - 14)
      - Even if you are sure, should address anyway
  - Appropriate to file an RFD even if you believe that the product is NOT a combination product, but uncertainty remains

RFD's – OCP Process

- OCP reviews RFD's for completeness w/in 5 work days
- If complete, OCP sends acknowledgement letter to sponsor, and copy of RFD's to three Center liaisons
- Center recommendations due to OCP in 21 days
- Consultation among OCP, Centers and Office of Chief Counsel
- Decision reached, response letter prepared, necessary clearances obtained
- Decision must issue within 60 calendar days; ***if not YOUR recommendation wins!!***

RFD's – Process …

- **Request for Reconsideration**
  - Submit within 15 calendar days
  - Cannot exceed 5 pages in your reconsideration submission
  - No new information (if you do, FDA will consider it a new RFD)
  - FDA response within 15 calendar days
  - FDA has been known to change a decision upon reconsideration
- **Effect of RFD Letter – designated FDA Center can only be changed without your consent to protect the public health or another compelling reason.**
  - *Source*: 21 CFR 3.9(b)

Jurisdictional Decisions -- Examples

- **Breath Test Combinations**
  - http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103134.htm
- **Heparin Catheter Lock-Flush Solutions**
  - Federal Register of 8/17/2006 -- http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-13509.htm
  - Summary -- http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103161.htm
- **Metered Dose Inhalers, Spacers and Other Accessories**
  - http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103179.htm
- **Drug/Biologic Combinations**
  - http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm119233.htm

Which GMP Rules Apply?

- **What has FDA said?**
  - Guidance on GMPs for Combination Products
    - *http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm*
    - Sets forth broad framework for application of cGMP to combination products
  - Proposed Rule on GMPs for Combination Products
    - September 23, 2009 – 74 Fed. Reg. 48423
    - *http://edocket.access.gpo.gov/2009/pdf/E9-22850.pdf*

Final Rules on GMPs

- **January 22, 2013 – 78 Fed. Reg. 4307**
  - https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products
- **FDA: "The final rule is largely identical to the proposed rule." 78 Fed. Reg. @ 4308.**
- **Creates 21 CFR Part 4**
- **Effective date:** 180 days after promulgation – July 22, 2013

GMPs …

- **Assumptions underlying final GMP rule:**
  - During and after components combined, both sets of cGMP regulations apply (whether a single entity product or co-packaged products)
  - However, compliance with both sets of regulations can generally be achieved by using either regulation and agency does not see need for parallel systems
- **Two options under final rule**
  - Parallel systems -- satisfy all requirements for both systems
  - ***"Streamlined Approach"*** – full compliance with one system, plus compliance with designated parts of other system [where other system is not your usual system] ***IS*** full compliance with all of second system

Streamlined – Drug "Dominant"

- **Must meet all drug GMP rules, plus these device Quality System rules:**
  - 820.20 – Management Responsibility
  - 820.30 – Design Controls
  - 820.50 – Purchasing Controls
  - 820.100 – Corrective and Preventive Action (CAPA)
  - 820.170 – Installation
  - 820.200 – Servicing
    - ***21 CFR 4.4(b)(1)***

Streamlined – Device "Dominant"

- **Must meet all device Quality System rules, plus these drug GMP rules:**
  - 211.84 – Testing and approval or rejection of components, drug product containers, and closures
  - 211.103 – Calculation of yield
  - 211.132 – Tamper-evident packaging for OTC drugs
  - 211.137 – Expiration dating
  - 211.165 – Testing and release for distribution
  - 211.166 – Stability testing
  - 211.167 – Special testing requirements
  - 211.170 – Reserve Samples
    - ***21 CFR 4.4(b)(2)***

GMPs – Issues Addressed in Final Rule

- **What governs in investigational stage?**
  - Phase 1 – drug component exempt from drug GMPs
  - Device component – exempt, except design controls in all phases
- **Does it apply to already approved combination products?**
  - Yes; the rule does not change what applies, but creates a system for understanding how to apply the distinct GMP rules
- **Defined "convenience kits" –**

  " … only kits that solely include products that are: (1) Also legally marketed independently and (2) included in the kit as already packaged and with the same labeling as for independent marketing.

GMPs – Issues Addressed in Final Rule

- **What if two provisions (QSR v. Drug GMP) appear to clash?**
  - follow the one more "specifically applicable to the constituent part" (if you can figure that out) – 78 Fed. Reg. at 4314
- **What happens while a constituent part is being made at a separate facility?**
  - all CGMP provisions applicable to that constituent part (i.e., drug, device, or biologic) must be satisfied at that facility
    - and … when it is brought to another facility where it is combined with a different constituent part, then you have to meet the CGMPs that apply to both …
    - but … you can use the "streamlined" approach

GMPs – Issues Addressed in Final Rule

- **Design controls –**
  - to be addressed in guidance
  - "The design history file for a combination product … ***must address all design issues resulting from the combination of the constituent parts, regardless of whether***" the manufacturer picks a "drug dominant" or "device dominant" scheme (or full implementation of both) – 78 Fed. Reg. 4315
  - Examples:
    - document and provide objective evidence that the drug is appropriate for use with the device – e.g., why a particular drug will work with a drug-eluting stent
    - document that the device is appropriate for the drug -- e.g., that a syringe will not interact with the drug

GMPs -- Special Cases

- **Blood and blood component products – also must meet requirements of 21 CFR Part 606**
- **Human Cellular and Tissue-based Products (HCT/Ps) – Current Good Tissue Practices apply if product is also regulated as a drug, device or biologic**
  - Section 361 of Public Health Service Act – if HCT/P is combined with another article (other than water and certain other agents), it is a drug, device or biologic
  - 21 CFR 1271 will apply if the HCT/P is also part of a combination product, especially the Good Tissue Practice rules at 21 CFR 1271.145 et seq.

GMP Final Rule – Guidance Will Issue

- **FDA plans to issue a guidance on how to meet the new rule, especially relative to:**
  - design controls, including coming into compliance with pre-manufacturing design controls for products already being marketed
  - handling at multiple facilities or multiple manufacturers, including the duties of the "central managing facility" (*my term*)
  - conflicts between overlapping provisions of GMPs vs. QSR
  - batch release testing

Post-Marketing Safety Reporting

- **Initially – a "concept paper"**
  - *http://www.fda.gov/oc/combination/adeventconpaper.pdf*
- **Federal Register, October 1, 2009; 74 Fed Reg. 50744**
  - *http://edocket.access.gpo.gov/2009/pdf/E9-23519.pdf*
- **Basic approach**
  - Generally will follow the reporting system applicable to the type of marketing application under which cleared (if single application) -- NDA/PMA or 510(k)/BLA
  - Assumption – the systems are "substantially similar"
  - But, there are five types of safety reports that are unique – have to see if one applies, in your scenario, to your combination product

The Five Unique Safety Reports

- **5-Day Report –** under Medical Device Reporting (MDR) Rule – when you learn of a reportable event associated with the device that necessitates remedial action to "prevent an unreasonable risk of substantial harm" to public health
- **30-Day Device Malfunction Report –** under MDR, get info that "reasonably suggests" the device has malfunctioned and, if malfunction were to recur, the device or a similar device you market would be likely to cause or contribute to death or serious injury

The Five Unique Safety Reports …

- **15-Day Alert – for drugs and biologics –** reports of a serious and unexpected adverse event
  - *Note*: under MDR, "serious" events are reportable in 30 days, but MDR does not talk about unexpected, so 15-day Alert governs where a combination product containing a device has a serious ***and*** unexpected event if you can't determine which component caused the AE
- **3-Day Field Alert –** for drugs only under 21 CFR 314.81(b)(1) – certain types of problems with drugs such as: bacteriological contamination, failure to meet specifications (e.g., stability) or labeling errors that could lead to product mix-ups
- **Expedited Blood Fatality Report –** if blood collection or transfusion is fatal, has to be reported in 7 days of the fatality

The Proposed Safety Rule in Action

- **If a single application covers the combination:**
  - Use reporting rules required under the particular application
  - As applicable under factual scenario, use one of Five Types
- **When two applications cover the combination:**
  - If you can reasonably conclude which component caused the adverse event, you can use that component's reporting system
  - If unclear which component caused AE, have to satisfy reporting requirement of all types of application
  - If other application is held by a third party, have to notify that person within 5 days of learning of event ***and*** also satisfy your reporting duties

How Many Applications?

- **Concept Paper on Marketing Applications for Combination Products**
  - *http://www.fda.gov/downloads/CombinationProducts/RequestsforComment/UCM108197.pdf*
- **Basics:**
  - PMOA does not ensure application status; but lead Center
  - Single application usually is sufficient
  - Exceptions
    - One component is already approved, but labeling will need to be changed
    - Biologics – legally can have separate apps. for components
    - When the components are "separate and complex" – e.g., a device in combination with a new molecular entity drug/biologic
    - Where needed to "apply mechanisms to ensure appropriate regulation or unique regulatory requirements" not available under one app.
      - Example: gene therapy

How Many Applications?...

- ***You Might Want Two*** **– perhaps:**
  - To qualify for Waxman-Hatch Exclusivity
  - Orphan Drug Status
  - To protect proprietary data if 2 firms are involved
- **Complex decision tree suggested in concept paper on how these are handled**

User Fees – Can I Pay the Least Amount?

- **Guidance on User Fees for Combination Products – April 2005**
  - *http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147118.pdf*
- **Basics**
  - Depends on type and # of applications
  - If two applications submitted voluntarily, pay two fees
  - If two applications REQUIRED, still pay two fees
- **"Innovative Product Waiver" – consider seeking**

References

- **Combination Products Main Homepage**
  - http://www.fda.gov/CombinationProducts/default.htm
- **Frequently Asked Questions on Combination Products**
  - http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm
- **Jurisdictional Determinations –**
  - http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/default.htm
- **Guidance on Early Development Considerations for Innovative Combination Products (9/2006)**
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126054.pdf
- **Final Rule on "Primary Mode of Action" – 8/25/2005; 70 Fed. Reg. 49848**
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf

Additional References …

- **SMG 4011 – Intercenter Consultative/Collaborative Review Process**
  - http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM283569.pdf
- **Other Types of Combinations (e.g., Drug/Cosmetic)**
  - http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101464.htm
- **Examples of Combination Product Approvals**
  - http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm
- **Articles on Combination Products – at OCP site**
  - http://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm116639.htm

VETERINARY PRODUCTS

Basics

- **Center for Veterinary Medicine (CVM) – controls:**
  - New Animal Drug Application (NADA) process
    - Investigational
    - Full
    - Abbreviated
  - Medicated Feeds
  - Pet Food

Investigational New Animal Drug (INAD)

- Must be in place before shipping an investigational new animal drug
- Reviewed by Office of New Animal Drug Evaluation (ONADE)

New Animal Drug Application (NADA)

- **New animal drug – Section 201(v) of the Act:**

  … means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed,—

  (1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

  (2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions

- **Safety – in target animal and humans that might consume same animal**

NADA …

- Governed by Section 512(b) of Act and 21 CFR 514
- Basic sections:
  - Identification
  - Table of Contents
  - Labeling
  - Components & Composition
  - Manufacturing Methods, Facilities & Controls
  - Samples
  - Analytical Methods for Residues
  - Safety & Effectiveness Evidence
  - Applicant's commitment to market consistent with NADA
  - GMP Compliance
  - GLP Compliance
  - Environmental Assessment (unless Categorical Exclusion applies)
  - FOI Summary – of studies serving as basis for approval – FDA will release to public

NADA -- Requirements & Processes

- **Patent information – holder of approved NADA must "list" with FDA if claims drug or a method of use for drug**
- **FDA must publicize approvals monthly – "Green Book"**
- **Phased submission/review – allowed by CVM – leads to a "technical section complete" letter**
  - Administrative NADA – CVM then has 180 days
- **Expedited Review – ERS – advances in animal health or reduction of human pathogens**

MUMS – Minor Use/Minor Species

- Major species – horse, cattle, dog, cat, pigs, chickens, and turkeys
- Minor species – all others
- Minor use -- major species for indication that occurs infrequently and in only a small number of animals *or* in limited geographical areas *and* in only a small number of animals annually.

MUMS – Benefits and Procedures

- **"Conditional Approval" – can market after proving safe if reasonable expectation of effectiveness**
  - have 5 years to collect effectiveness data via annual renewals
- **"Indexing" – 21 CFR 516 – legally marketed drugs can be used for unapproved minor species**
  - reviewed by expert panels
- **Designation – if received, can get 7 years market exclusivity and other monetary benefits**

Generics – Abbreviated NADA (ANADA)

- **1988 – created by Generic Animal Drug and Patent Term Restoration Act (GADPTRA) – very similar to Waxman-Hatch Act for human drugs**
  - Bioequivalence – in at least one labeled species
- **Market exclusivity available for full NADAs**
  - 5 years – New Chemical Entity
  - 3 years – New studies –
    - substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence studies or residue depletion studies, except residue depletion studies for minor uses or minor species) required for the approval of the application and conducted or sponsored by the applicant

Animal Drug User Fee Act (ADUFA)

- **Initially put in place in 2003; thus, not on same reauthorization schedule as other user fees**
- **Waivers or reductions – may be possible:**
  - application submitted under MUMS – Minor Use/Minor Species solely for a MU or MS
  - small business
  - NADA solely to provide for AD's use in a "free-choice medicated feed"
- **Technically, do not apply to Abbreviated New Animal Drug Applications, but they have a separate law -- *AGDUFA***

Animal Feeds

- **Non-medicated – to meet animal's nutritional needs**
  - includes pet food
  - generally – no prior approval by CVM if made from approved food additives or GRAS (generally recognized as safe) ingredients
- **Medicated – to deliver drug to animal**
- **Dietary supplements marketed for animals – treated as food and not under DSHEA**
- **Three types:**
  - Type A Medicated ***Articles***
  - Type B Medicated Feeds
  - Type C Medicated Feeds

Type A Medicated Articles

- Mixtures of one or more drug substance(s) with appropriate vehicles
- Requires pre-approval of an NADA or ANADA
- Category I – require no withdrawal period at lowest use level in each species in which approved
- Category II – require a withdrawal at lowest use level in at least one species or regulated on a "no residue" basis or with a zero tolerance
- Intended solely to manufacture another Type A or a Type B or Type C Medicated Feed

Type B Medicated Feed

- Contains either a Type A Medicated Article or another Type B Medicated Feed, plus substantial quantity of nutrients (at least 25% of total weight)
- Used solely to manufacture another Type B Medicated Feed or a Type C
- Before being fed to animal, must be substantially diluted to produce a Type C Medicated Feed

Type C Medicated Feed

- **Contains an active drug component – intended:**
  - as complete animal feed; or
  - to be fed top-dressed; or
  - offered free choice in conjunction with other animal feed to supplement the animal's total daily ration
- **Produced by substantially diluting a Type A Medicated Feed, a Type B Medicated Feed, or another Type C Medicated Feed**
- **Medicated Feed cGMPs – 21 CFR 225**

Off-Label Use

- **Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA)**
  - Allows for veterinarians to use approved animal drugs for unapproved uses
    - can't result in violative residues in food-producing animals
    - consistent with regulations in 21 CFR 530
  - Allows for use of approved human drugs for animal uses under certain circumstances

Veterinary Devices

- **CVM has jurisdiction, but not significantly regulated**
  - Adequate directions for use in target species
  - Subject to adulteration and misbranding provisions of Act
  - QSR for human devices not applicable
  - Must meet other requirements such as laser standards
- **AliveCor – Vet app marketed before human use 510(k) cleared …**

Veterinary Biologics

- **Regulated by Center for Veterinary Biologics in Animal & Plant Health Inspection Service (APHIS) at USDA**
- **Under Virus-Serum Toxin Act (VSTA) of 1913**
  - Pure, safe, potent and effective biologics
  - Veterinary Biologics Establishment License
  - Veterinary Biologics Product License
  - Allows for a phased review of license applications

Questions?

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About Your Speaker

***Michael A. Swit, Esq.*, is a Special Counsel in the San Diego office of the international law firm, Duane Morris, LLP, where he focuses his practice on solving FDA legal challenges faced by highly-regulated pharmaceutical and medical device companies. Before joining Duane Morris in March 2012, Swit served for seven years as a vice president at The Weinberg Group Inc., a preeminent scientific and regulatory consulting firm in the Life Sciences. His expertise includes product development, compliance and enforcement, recalls and crisis management, submissions and related traditional FDA regulatory activities, labeling and advertising, and clinical research efforts for all types of life sciences companies, with a particular emphasis on drugs, biologics and therapeutic biotech products. Mr. Swit has been addressing vital FDA legal and regulatory issues since 1984, both in private practice with McKenna & Cuneo and Heller Ehrman, and as vice president, general counsel and secretary of Par Pharmaceutical, a top public generic and specialty drug firm. He also was, from 1994 to 1998, CEO of *FDANews.com,* a premier publisher of regulatory newsletters and other specialty information products for FDA-regulated firms. He has taught and written on many topics relating to FDA regulation and associated commercial activities and is a past member of the *Food & Drug Law Journal* Editorial Board. He earned his A.B., *magna cum laude*, with high honors in history, at Bowdoin College, and his law degree at Emory University.**