

The Consumer Healthcare Products
Association and FDA present

The OTC Drug Seminar Series

Working Within the OTC Drug
Monographs

Co-sponsorship Agreement

Consumer Healthcare Products Association
(CHPA)
and
FDA

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Iris Khalaf, FDA

Karen Lechter, FDA

Lorna Totman, CHPA

Mitchell Weitzman, FDA

Purpose

To promote a better FDA and industry understanding of the unique challenges in the present and future OTC healthcare environment

FDA-CHPA Seminar Series

**OTC Monographs
Challenges for the Future
October 2, 2003**

OTC Monographs Challenges for the Future Planning Committee

- **June Austin – Regulatory Affairs, Procter & Gamble**
- **Dora Monserrate – Regulatory Affairs, GSK**
- **Mitch Weitzman- Regulatory Counsel, Regulatory Policy I, FDA**
- **Matthew Holman – Team Leader, OTC Drug Products, FDA**
- **Lynn Smith – Product Development, Pfizer**
- **Fred Hyman – Medical Officer, Dermal/Dental Drug Products, FDA**
- **Bill Nychis – Deputy Director, New Drugs and Labeling Compliance, FDA**
- **James Angello – Clinical and Medical Affairs, Pfizer**

OTC Monographs Challenges for the Future

09:00 am – 09:10 am	Welcome - David Hilfiker
09:10 am – 09:20 am	Introduction, Review of Agenda and Seminar Objectives – June Austin
09:20 am – 09:40 am	The History and Relevance of the OTC Drug Review – Mitch Weitzman/ Matthew Holman
09:40 am – 10:10 am	Issues that rise when products vary in some way from an OTC drug monograph and why these issues are important – Lynn Smith and Fred Hyman
10:10 am – 10:30 am	Break
10:30 am – 11:05 am	Challenges the FDA faces with the OTC monograph process – Bill Nychis
11:05 am – 11:20 am	Challenges the Industry faces with the OTC monograph process – Dora Monserrate
11:20 am – 11:50 am	OTC Monograph Case Studies – Jim Angello and Dora Monserrate
11:50 am – 12:00 pm	Closing Remarks – Mark Gelbert

OTC Monographs Challenges for the Future Seminar Objectives

- **To review the intent of the OTC drug monograph process for marketing generally recognized safe and effective drug products (GRASE).**
- **To discuss the utility of the process for today's innovations assuming GRASE criteria can be met.**

Case Study #1

Consider cost, time, & exclusivity

New Population

Facts:

- Consumers with dry scalp think they do not need dandruff shampoo - will not buy it
- Active ingredient does treat dry scalp

Issue: TFM requires “dandruff” in statement of identity

What are the options?

History of the OTC Drug Review: What It Is and Why It Came To Be

**Mitch Weitzman – Office of Regulatory
Policy, FDA**

**Matthew Holman – OTC Drug Products,
FDA**

Outline

- **The Mechanisms By Which OTC Drug Products are Regulated**
- **Legal and Regulatory History**
- **Overview of OTC Drug Review**
- **Using OTC Drug Monographs to Market Products of Present Day**

The Mechanisms By Which OTC Drug Products Are Regulated

NDA

- Drug product-specific
- Not generally recognized as safe and effective (GRASE)
- Pre-market approval

OTC Drug Monograph

- Active ingredient-specific
- GRASE
- No pre-market approval

Legal and Regulatory History of OTC Drug Products

1938

Food, Drug, and Cosmetic (FD&C) Act

- All new drugs must demonstrate safety

1951

Durham-Humphrey Amendment

- Provided specific standards for determining what drugs must be limited to Rx use.
- Reduced previous marketplace confusion
- Made OTC the default status of a drug product

Legal and Regulatory History of OTC Drug Products

1962

Kefauver-Harris Amendment

- All new drugs must demonstrate effectiveness as well as safety.
- FDA began Drug Efficacy Study Implementation (DESI) for all Rx and OTC drugs.
 - 420 OTC drug products under NDAs
 - Hundreds of thousands of non-NDA OTC drugs

Legal and Regulatory History of OTC Drug Products

1972

OTC Drug Review

- Advisory Panel convened for each therapeutic category of OTC drug products.
- Focus on active ingredients for each category.
- Results in the promulgation of a regulation- an OTC drug monograph.
- OTC drug monograph establishes conditions under which an OTC drug is GRASE and not misbranded.

Reasons for OTC Drug Review

- **Limited resources**
- **Created efficiencies**
- **Does not compromise the standards of safety and effectiveness applicable to NDAs**

What is included in an OTC Drug Monograph?

- **GRASE active ingredients**
 - dosage strength
 - dosage form
- **Labeling requirements**
 - indications
 - directions for use
 - warnings
- **Final formulation testing**

Drug Facts	
Active ingredient	Purpose
Benzoyl peroxide 10%	Acne treatment cream
Uses ■ treats acne ■ dries up acne pimples ■ helps prevent new acne pimples	
Warnings	
For external use only	
Do not use ■ on broken skin ■ on large areas of the body	
When using this product	
■ apply to affected areas only ■ avoid unnecessary sun exposure and use a sunscreen	
■ do not use in or near the eyes ■ this product may bleach hair or dyed fabrics	
■ using other topical acne drugs at the same time or right after use of this product may increase dryness or irritation of the skin. Only one drug should be used unless directed by a doctor.	
Stop use and ask a doctor if too much skin irritation or sensitivity develops or increases	
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.	
Directions	
■ clean the skin thoroughly before applying ■ cover the entire affected area with a thin layer 1 to 3 times daily	
■ because too much drying of the skin may occur, start with 1 application daily, then gradually increase to 2 to 3 times daily if needed or as directed by a doctor	
■ if bothersome dryness or peeling occurs, reduce application to once a day or every other day	
■ if going outside, use a sunscreen. Allow benzoyl peroxide to dry, then follow directions in the sunscreen labeling.	
Other information store at 20-25°C (68-77°F)	
Inactive ingredients aluminum hydroxide gel, bentonite, carbomer-940, dimethicone, glyceryl stearate SE, isopropyl myristate, methylparaben, PEG-12, potassium hydroxide, propylene glycol, propylparaben, purified water	

21 CFR Part 330: Overview of OTC Drug Review

- 1. Advisory review panel**
- 2. Advance Notice of Proposed Rulemaking (ANPR)**
- 3. Tentative Final Monograph (TFM)**
- 4. Final Monograph (FM)**

OTC Drug Review



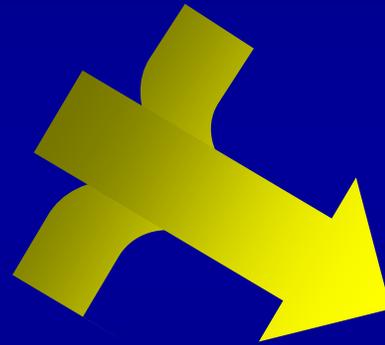
Advisory Review Panel



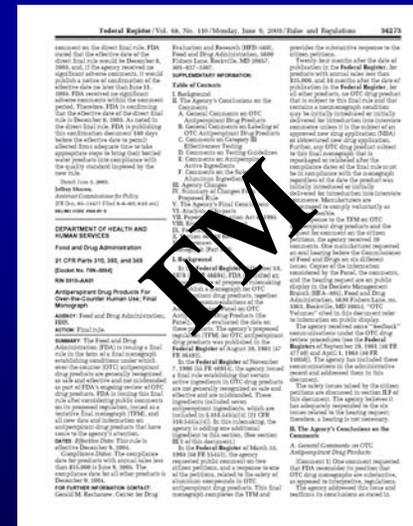
- **Category I: GRASE**
- **Category II: not GRASE**
- **Category III: cannot determine if safe and effective**

OTC Drug Review

Comments



Data



Comparison of OTC Drug Monograph System and NDA

OTC Drug Monograph

- no pre-approval
- no PDUFA user fee
- no exclusivity
- long process
- ingredient-based
- public process

NDA

- pre-approval
- PDUFA user fee
- exclusivity
- short clock
- drug product-based
- confidentiality

Both procedures are driven by scientific data

Using OTC Drug Monographs to Market Innovative Products

- Citizen Petition
- Time and Extent Application
- NDA deviation

Citizen Petition

- **21 CFR 10.33**
- **Can be used to amend OTC drug monograph at any stage**
- **Limited to conditions marketed prior to 1975**
 - “conditions”: active ingredient, dosage form, indication, etc.

TEA

- **21 CFR 330.14**
- **February 2002**
- **Can be used to amend OTC drug monograph**
 - U.S. marketing experience after OTC drug review began
 - OTC drugs with marketing experience outside the United States
- **Meets “material extent” and “material time” requirements of §201(p)**

TEA

- **Can be used for**
 - active ingredient or botanical substance
 - dosage form
 - dosage strength
 - route of administration
- **Marketed for ≥ 5 continuous years in the same country and in sufficient quantity**

Flexibility Introduced into OTC Drug Monograph System: TEA

**Step 1: Submission of TEA & publication of Federal Register notice of eligibility
-call for data**

Step 2: FDA reviews safety and efficacy data to determine GRASE

NDA Deviation

- **21 CFR 330.11**
- **Allows certain data submitted to OTC drug monograph to be the basis of an NDA**
 - **only data relating to deviation is required**
 - **deviations: active ingredient dose, dosage form, indication, etc.**

Summary

- **OTC Drug Review began in 1972 as innovative approach to determine the safety and effectiveness of OTC drugs.**
- **OTC Drug Review is a long, complex public process.**
- **Citizen Petition and TEA are procedures for amending an OTC drug monograph.**
- **NDA deviation is another useful avenue to bring innovative OTC drug products to market.**

Issues That Arise When Products Vary in Some Way From an OTC Drug Monograph

Why These Issues Are Important

Lynn Smith – Pfizer

Fred Hyman – Dermal/Dental Drug Products

Issues that arise when products vary in some way from an OTC drug monograph

- What makes an OTC drug fall outside of the monograph?
- What is the process for approving these new drugs?
- What are the challenges of keeping monographs current?
- How are consistent review standards maintained within the context of different drug approval routes?

What makes an OTC drug fall outside of the monograph?

Active Ingredients

- OTC Drug Monograph specifies which active ingredients are allowed.
 - Dosage Strength
 - Monograph drugs may have an acceptable range, or may have several distinct acceptable concentrations

Skin Protectant Monograph: Acceptable range for Dimethicone is 1 – 30%



Sodium Fluoride Rinses 0.02% and 0.05% solutions at pH7



What makes an OTC drug fall outside of the monograph?

Active Ingredients

- OTC Drug Monograph specifies which active ingredients are allowed.
 - Dosage Strength
Monograph drugs may have an acceptable range, or may have several distinct acceptable concentrations
 - **Complexes of the drug**
Cough-Cold Monograph: Phenylephrine bitartrate under consideration.

What makes an OTC drug fall outside of the monograph?

Inactive Ingredients

- Although the OTC Drug Monograph provides no formal guidance as to the choice of inactives, all inactives must be:
 - safe
 - suitable in the amount administered
 - must not interfere with the drug's effectiveness
 - must not interfere with tests, assays for the product's identity, strength, quantity and purity.

What makes an OTC drug fall outside of the monograph?

Inactive Ingredients

- Some monographs require final formulation testing to determine that the active ingredient efficacy is not affected by the inactives.
 - USP dissolution testing for internal analgesics
 - UV testing for sunscreens
 - USP in vitro ANC testing for antacids

Other considerations:

- Inactives that are “active”
Actives that are “inactive”

Original A&D Diaper Ointment label listed vitamins A & D as actives

Aspirin + Caffeine
Caffeine=adjuvant that
boosts effect of aspirin



What makes an OTC drug fall outside of the monograph?

Dosage Forms

- In some monographs, specifics of the dose form are detailed, while in others, the dose form is less defined.
Anticaries monograph: dosage forms are very specific - paste, powder, liquid
Cough & Cold Monographs: dosage form is not specified for oral nasal decongestants & antihistamines.
- OTC Drug Industry continues to develop novel delivery forms that will differentiate new products in the marketplace – these may fall outside of the monograph.

e.g. Rid Mousse

What makes an OTC drug fall outside of the monograph?

Dosage Forms

Rid Mousse



- The delivery form specified in the pediculicides final monograph is a “non-aerosol dosage formulation”.
- Manufacturer wished to bring a mousse form to the marketplace.
- Mousse particle size of concern to FDA; believed would have an impact on drug delivery and efficacy.
- NDA deviation was submitted and approved.

What makes an OTC drug fall outside of the monograph?

Dosage Forms

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Cough & Cold Monographs: dosage form is not specified for oral nasal decongestants & antihistamines.
- OTC Drug Industry continues to develop novel delivery forms that will differentiate new products in the marketplace – these may fall outside of the monograph.
- Often not clear if a minor change e.g. viscosity, takes the drug out of the monograph.
 - At what point does the shift from a gel to lotion to cream require more data for marketing?

What makes an OTC drug fall outside of the monograph?

Indications

- A new indication for an existing monographed drug would require an NDA or NDA-deviation prior to marketing.



New Claim for Antihistamines:

- Indications allowed in the Cough-Cold Monograph: Temporarily relieves runny nose and sneezing, itching of the nose and throat, and itchy, watery eyes due to hay fever or upper respiratory allergies.
- If manufacturer wanted to include a hives or urticaria claim, they would have to file an NDA or NDA deviation.



What is the process for approving new drugs that fall outside of the monograph?

New NDA

- Safety and efficacy support through pivotal trials
- Additional expense of user fee is generally required
- Mandated time frame for definitive regulatory decision
- Exclusivity may be granted
- Submission is confidential

Comments

- **Process is resource intensive – revenue opportunity needs to be significant. HOWEVER:**
 - ✓ 3-Yr exclusivity may be granted
 - ✓ Application is confidential
 - ✓ Short time for regulatory decision

What is the process for approving new drugs that fall outside of the monograph?

NDA Deviation

- Similar to NDA in most respects. Generally, NDA deviations supplement published scientific data.
- There must be a final monograph, not TFM.
- User fee required. Submission is confidential
- Exclusivity may be granted.

Comments

- There is still the expense of the clinical studies to support the deviation from the NDA plus the user fee. **HOWEVER:**
 - ✓ 3-Yr exclusivity may be granted
 - ✓ Application is confidential
- Not an unattractive option for Industry. To date – an under utilized pathway.

What is the process for approving new drugs that fall outside of the monograph?

Citizen's Petition

- Generally relies on data to supplement the existing monograph.
- New clinical data that is submitted usually does not require the same rigor as pivotal clinical trial for an NDA.
- Can be submitted to a TFM in addition to a FM.
- There is no fee. Process is public.
- No exclusivity is granted. There is no mandated time for a decision.

Comments

- Where clinical data is required, it usually does not require the same rigor as pivotal trials required for an NDA. HOWEVER:
 - ✗ No exclusivity
 - ✗ No confidentiality
 - ✗ No mandated timeframe
- Risk of competitive knock-offs

What is the process for approving new drugs that fall outside of the monograph?

TEA

- This process allows for an “eligible” submission to be considered for inclusion in a monograph.
- There is no fee.
- There is no timeframe.
- There is no exclusivity.

Comments

- ✓ An attractive option to industry, one we would like to see more fully utilized.

Challenge of Keeping the Review Process Current and Consistent

- **Changes Over Time**
 - The monograph process may be lengthy.
 - Science evolves.
 - Healthcare standards change.
- **Consistency Between Monograph Process and Alternatives**
 - The monograph is a review of active ingredients.
 - The NDA process requires rigorous pivotal trials.

Why are Changes Over Time Important?

- Panel Report to Tentative Final Monograph may span 1-18 years.
- Tentative to Final Monograph can require an additional 1-10 years.
- There is great variation in the process.
- The length of time adds significant complexity to industry and government.
 - The Agency must protect the public health.
 - Industry must manage the risk of marketing drugs that are at the ANPR or TFM phase.



All Good Things Take Time

Risk to Product Development

- **The Agency must protect the public by removing drugs that are either unsafe or ineffective.**
- **Uncertainty about acceptance of active ingredients will affect future marketing decisions.**
- **Labeling, dosing, formulation testing, and other aspects of the Final Monograph can change after the time of panel report.**

Changing to Meet the Monograph

- **FDA encourages manufacturers to remove non-Category 1 ingredients prior to the final monograph publication.**
- **Ingredients may be removed for efficacy or safety concerns.**
- **Ingredients or claims may be added prior to final monograph publication.**

Removal and Reformulation of Drug Ingredients

- Some products are reformulated for efficacy reasons, e.g. tooth desensitizers.



Safety Concerns

- Some ingredients have not been generally recognized as safe.
 - Phenolphthalein-containing laxatives
 - Antihistamine methapyrilene



Adding New Indications

- New data submitted after the TFM can result in acceptance of active ingredient.
- Example: Antiperspirants were given additional claims after the TFM was published.



Changing Patterns

- As the science or standards of care evolve during this lengthy process, some aspects of the monographs can be dated upon publication.
- Example – Anticaries Monograph
 - Dental decay pattern has changed.
 - Many more areas incorporated fluoridation.
 - Fluoride became ubiquitous in the food supply.

Changing Patterns (cont)

- **Some products require amendment after publication of the FM.**
- **Example – Pediculicides**
 - **The Final Monograph was published in 1993.**
 - **In 2002, the Agency proposed amending the label to include more explicit directions for use.**

Statistical Considerations

- **As Biostatistics becomes more sophisticated, (i.e., tests of non-inferiority and equivalence), differences in sample sizes and methods of statistical testing may result.**

Keeping up with Changing Science

- An already published monograph can be updated to reflect changing technology and standards of care.
 - Proposal to Amend
 - Comments
 - Amendment
- Agency or Industry initiated

Maintaining Consistency Between the Monograph and NDA Process

- **Demonstration of safety and efficacy should require similar evidence and standards for approval, regardless of process.**

Differences Between the Monograph and NDA Processes

- **Process**

- The Monograph reviews an entire class of drugs.
- The Monograph reviews just the active ingredients.
- The NDA process reviews the individual drug product in total.

Consistency Between Monograph and NDA Processes

- **Data Required**
 - The monograph is generally a review of literature and smaller trial results.
 - The monograph reviews data from many different products simultaneously.
 - The NDA requires two or more pivotal clinical trials.
 - In most cases, only data from the to-be-marketed formulation is valid for the NDA.

Monograph vs. NDA (cont)

- **Labeling**

- Each label is individually crafted for each drug under NDA review.
- Monographs use class labeling.

- **Dosage**

- Dosage will only reflect what is tested for an NDA.
- A range of dosages is often given in a monograph.

Colgate's Total Toothpaste

- This drug was reviewed as an NDA.
- Concurrently, the antigingivitis panel report was being developed.



Summary

- **Deviations from currently marketed drugs such as dosage, indications, or labeling may require a submission process rather than the monograph for drug approval.**
- **Alternate routes may be resource intensive and therefore not viable marketing options.**
- **Changing science and improvement in healthcare standards bring challenges to the table for any method.**

Summary (cont)

- Insuring safe and effective drugs may be effected through changes, when necessary, to the monograph itself, or reformulation of products.
- FDA and Industry share the burden of maintaining current and consistent standards in the drug review process.
- None of the challenges are insurmountable.

- **"Words are, of course, the most powerful drug used by mankind."**

Rudyard Kipling

- **Contact Information: Fred Hyman**
 - **Phone: (301) 827-2020**
 - **E-mail: hymanf@cder.fda.gov**

OTC Drug Monographs Challenges for the Future Compliance

**William G. Nychis –New Drugs and Labeling
Compliance, FDA**

Outline

- **OTC Drug Marketing in the United States**
- **Compliance policy toward OTC drugs**
- **Has the OTC Drug Review been successful?
Does it meet today's and will it meet
tomorrow's needs?**

Regulation of OTC Drugs-A Brief History

- **1906 - Federal Food and Drugs Act**
- **1938 – Federal Food, Drug, and Cosmetic Act (FFDCA)**
- **1951 – Durham-Humphrey Amendment**
- **1962 – Kefauver-Harris Drug Amendments**
- **1966 – DESI Review of Rx and OTC Drugs**
- **1972 – OTC Drug Review**
- **1972 – Drug Listing Act**

Regulation of OTC Drugs Prior to the Review

- **FDA regulated OTC drug marketing usually through litigation, an expensive and protracted process.**
- **New OTC drugs routinely came on the market without agency knowledge or concurrence.**
- **If companies changed formulation and/or labeling, a new case needed to be developed.**

Intent of the OTC Drug Review

- **Replace costly product by product review with a review of the estimated 200 active ingredients in the thousands of OTC drugs marketed.**
- **Rulemaking provides an equitable and effective method for reviewing OTC drugs and bring industry-wide compliance.**

Marketing Status of Ingredients Recommended for OTC Use

- **Products which were “deferred” to the review could stay on the market pending completion of the category.**
- **FDA encouraged drug manufacturers to reformulate and/or re-label their marketed OTC drug products to bring them into conformity with current medical knowledge and experience.**

40 FR 56675 at 56676, December 4, 1975 – Marketing Status of Ingredients Recommended for OTC Use/Proposed Rulemaking and Enforcement Policy

Continued Marketing of OTC Drugs During the OTC Drug Review

- **OTC drugs not subject to a final rule may continue to be marketed under a firm's own responsibility without risk of regulatory action if certain conditions are met.**

68 FR 7951 at 7954/5, February 19, 2003, OTC Ophthalmic Drug Products for Emergency First Aid Use; Proposed Amendment for Final Monograph for OTC Ophthalmic Drug Products

Preapproval for OTC Drug Not Required for products subject to a final monograph

- **Labeling and formula must meet final rule**
- **Product must also comply with all other labeling requirements of the Act**
- **Must be manufactured under CGMP**
- **Firm must register and list product**
- **OTC timed release dosage forms are regarded to be new drugs – require NDA**

Compliance Follow-up for Products Subject to a Final Rule

- **When a final rule is published, most companies comply with the final rule. Companies are given either six months or a year to bring their products into compliance.**
- **For those that do not, we follow-up with for cause inspections.**
- **Companies that market “legal” products create a level playing field for everyone.**
- **Self-regulation works to the advantage of government, industry, and the consumer.**
- **Final rules include “negative monographs” included in 21CFR310.**

Risk Management

- **Limited resources**
- **Maximize public health impact by targeting actions that have impact**
- **Factors considered include:**
 - **Direct health hazard**
 - **Indirect health hazard (serious diseases)**
 - **Impact on NDA approval and OTC monograph processes**
 - **Effects beyond the immediate action**
 - **Media attention and consumer impact**

Dietary Supplement Health and Education Act 1994 (DSHEA)

Section 201(ff) of the Act defines “dietary supplement:”

- a vitamin**
- a mineral**
- an herb or other botanical**
- dietary substance . . . increasing total dietary intake**
- a concentrate, metabolite, constituent, extract, or combination of any ingredient described above**

DSHEA Definitions (cont):

“Dietary supplement” means a product that:

- is intended for ingestion in pill, capsule, tablet, powder, or liquid form**
- is not represented for use as a conventional food or sole item of meal or diet**
- is labeled as a “dietary supplement”**
- may include products such as approved new drugs under specified circumstances**

Claims permitted under DSHEA:

- **May make claims to affect the structure and function of the body.**
- **Cure, mitigation, prevention, or treatment of disease not permitted by DSHEA.**
- **Products regulated as drugs in the past may now be considered dietary supplements if they meet DSHEA.**

Impact of DSHEA on OTC Drug Review

- **Structure function claims for orally ingested products under the OTC drug review may now be considered dietary supplement claims under certain conditions.**
- **January 6, 2000 Federal Register defines what types of statements that may be made concerning the effect on the structure or function of the body.**

DSHEA: Structure/Function Claim Examples (January 6, 2000 FR)

- **Antacid to relieve upset stomach, occasional acid indigestion.**
- **Antiemetics for prevention and treatment of nausea, vomiting, or dizziness associated with motion.**
- **Sleep-aids for the relief of occasional sleeplessness.**
- **Stimulants to help restore mental alertness when experiencing fatigue or drowsiness.**

Questions Regarding DSHEA should be addressed to:

**Center for Food Safety and Applied Nutrition
Office of Nutritional Products and Dietary
Supplements (HFS-800)
5100 Paint Branch Road
College Park, MD 20740**

ICA Between CDER and CFSAN

ICA Between CDER and OCAC

- **CFSAN designation as the lead center for certain products for which labeling includes disease claims if such products also conform to each of the elements of the dietary supplement definition in section 201(ff) of the FFDCA.**
- **OCAC/CFSAN and CDER have concurrent jurisdiction for products positioned as cosmetics but include structure/function and/or disease claims.**

Drug/Cosmetic Products

Cosmetic Definition:

Section 201(i) of the Act

Drugs/Cosmetics

- **Antiperspirants/deodorants – stop perspiration (drug) and cover up odor (cosmetics)**
- **Dandruff shampoos – treat dandruff (drug) and cleanse the hair and scalp (cosmetic)**
- **Sunscreen/Suntan Preparations – prevent sunburn (drug) and moisturize while tanning (cosmetic)**
- **Fluoride toothpastes – prevent cavities (drug) and clean teeth or freshen breath (cosmetic)**
- **Skin Protectants – heal cuts (drug) and moisturize skin (cosmetic)**

Questions about cosmetic products

- **Contact the Office of Cosmetics and Colors,
Linda Katz, MD., Director**
- **VERB Room 1110 (HFS-100)**
- **1110 Vermont Ave. Washington, DC 20502**

Questions regarding OTC Drugs Contact:

**OTC Compliance Team (HFD-312)
Division of New Drugs and Labeling Compliance
Office of Compliance
Center for Drug Evaluation and Research
Montrose Metro II
11919 Rockville Pike
Rockville, MD 20852**

Telephone (301) 827-8930

Summary

- **The OTC Drug Review assures safe, effective, and affordable OTC drugs are available to the American consumer.**
- **Without the OTC Drug Review, an NDA/ANDA submission and approval scheme would make OTC drugs much costlier.**
- **While the OTC Drug Review went on, products deferred to the review could stay on the market, while unsafe and/or ineffective products were removed from the market.**

Summary (cont)

- **New products can be brought on the market through several avenues available to the OTC drug industry.**
- **Agency resources for OTC drug compliance compete with other Agency priorities including counterterrorism and counterfeit drug issues.**

OTC Monographs Challenges for the Future Industry

Dora Monserrate – GlaxoSmithKline

James Angello - Pfizer

Industry's Challenge

- **What does the monograph process mean to us**
- **Business needs and public health service**
- **Effect on decisions**
- **Decision making tool**
- **Case studies**
- **Industry and FDA looking to the future**

What it provides Industry

Guides product development and marketing

- Innovative regulation
- With USP, it creates standards for safety, efficacy, and labeling
- Standard labeling levels the playing field
- Preserves brand name and identity
- Easy entry for new products (brand name and generic)
- Refresh existing product line

Business Needs and Public Health Service

Product innovation, essential for growth and survival

- **Science updates basic knowledge**
- **Consumer unmet needs**
- **Consumer concerns about health**

Various regulatory environments

- **Harmonization can help global challenges**
- **TEA process**

Effect on Decisions

Exclusivity

- Recover cost of additional studies
- Business development need for protected product

Cost and Time Considerations for OTC products

- Potential new products are abandoned
- Compare Monograph, NDA, NDA Deviation, and DSHEA regulatory routes

Which regulatory path?

	<u>Time</u>	<u>Cost</u>
NDA	5 - 7 yrs.	\$ 50 – 300 MM
NDA Deviation	3 – 5 yrs.	\$ 20 MM
Monograph	18 – 24 mo.	\$ 400 K
DSHEA	18 – 24 mo.	\$ 400 K

What are the commercial needs?

- **Strongest possible claim**
 - scientific support
 - clinical benefit
- **Superiority**
 - scientific support
 - benefit to consumers
- **Fill market gap (unmet consumer need)**
- **Exclusivity**
- **Speed to market**

Impact of Development Decisions

Real-Time Audience Exercise to See the Effect of Submission Route on Development Decisions

Outline

- *Case Summary* - Assume the goal is to provide adequate efficacy and safety information to obtain a new indication for “Hives/Urticaria” for an already marketed antihistamine product with an older original approval date (say a first generation antihistamine approved more than 25 years ago with a limited existing data package).
- Review of cost and revenue assumptions for this potential new indication
- *Group Exercise: determine **select** research and development requirements for the following three submission routes:*
 - (1) Petition to the Monograph
 - (2) NDA Deviation
 - (3) Full IND/NDA
- *Rate each potential submission item as: “Probably Required”, “Possibly Required” or “Probably Not Required” for each submission route (by majority vote)*
- In real-time see the financial revenue and cost analysis unfold for this potential new OTC antihistamine indication
- Conclude with unveiling the 10-year financial impact and group vote on whether any of the three submissions would result in a viable project proposal for an OTC industry group.

Impact of Development Decisions

Real Time Audience Exercise to See the Effect of Submission Route on Development Decisions

Revenue Assumptions

- *This new indication will generate \$20MM in incremental gross sales in the first year regardless of the submission route*
- *Petition to the monograph route will see declines in sales following the first year due to swift use of claim by competitors.*
- *The NDA deviation to the monograph or IND/NDA routes will see 5% incremental growth up to year three (effect of exclusivity) and 2.5% growth in subsequent years (typical growth of an OTC product)*

<i>Annual Sales After Launch</i>	<i>Petition to Monograph</i>	<i>NDA Deviation to the Monograph</i>	<i>IND/NDA</i>
Year 1	\$20MM	\$20MM	\$20MM
Year 2	15% Decline	5% Growth	5% Growth
Year 3	10% Decline	5% Growth	5% Growth
Year 4	5% Decline	2.5% Growth	2.5% Growth
Year 5	2.5% Growth	2.5% Growth	2.5% Growth
Year 6	2.5% Growth	2.5% Growth	2.5% Growth
Year 7	2.5% Growth	2.5% Growth	2.5% Growth
Year 8	2.5% Growth	2.5% Growth	2.5% Growth

Impact of Development Decisions

Real Time Audience Exercise to See the Effect of Submission Route on Development Decisions

Marketing Cost Assumptions

- *Marketing costs will be identical for each submission route*
- *The indication will require \$10MM in launch costs in the first two years*
- *A \$5MM incremental will be spent in subsequent years for advertising and promotion*
- *Cost of advertising and promotion will rise 5% annually*

Marketing Costs	Petition to Monograph (\$MM)	NDA Deviation to the Monograph (\$MM)	IND/NDA (\$MM)
Brand Launch Year 1	\$10.0	\$10.0	\$10.0
Promotion Costs Year 2	\$10.0	\$10.0	\$10.0
Promotion Costs Year 3	\$5.0	\$5.0	\$5.0
Promotion Costs Year 4	\$5.3	\$5.3	\$5.3
Promotion Costs Year 5	\$5.5	\$5.5	\$5.5
Promotion Costs Year 6	\$5.8	\$5.8	\$5.8
Promotion Costs Year 7	\$6.1	\$6.1	\$6.1
Promotion Costs Year 8	\$6.4	\$6.4	\$6.4

Impact of Development Decisions

Real Time Audience Exercise to See the Effect of Submission Route on Development Decisions

Cost of Goods Assumption

- *No additional cost for manufacturing and distributing since the product is already marketed in our example.*

Time-to-Market Assumptions

- *Petition to the Monograph is estimated as a 3-year program from project initiation to new claim launch*
- *NDA Deviation to the Monograph is estimated as a 4-year program from project initiation to new claim launch*
- *IND/NDA is estimated as a 6-year program from project initiation to new claim launch*

Case Study #1

Consider cost, time, & exclusivity

New Population

Facts:

- Consumers with dry scalp think they do not need dandruff shampoo - will not buy it
- Active ingredient does treat dry scalp

Issue: TFM requires “dandruff” in statement of identity

What are the options?

Case Study #1: Options

<u>Option</u>	<u>Why Yes</u>	<u>Why No</u>
NDA	<ul style="list-style-type: none"> ▪ confidential ▪ exclusivity? 	<ul style="list-style-type: none"> ▪ time and money ▪ full documentation
NDA Deviation	<ul style="list-style-type: none"> ▪ confidential ▪ exclusivity? ▪ limited documentation 	<ul style="list-style-type: none"> ▪ time and money
Petition Monograph	<ul style="list-style-type: none"> ▪ likely to be accepted ▪ limited documentation 	<ul style="list-style-type: none"> ▪ unspecified time ▪ no exclusivity
No submission – omit “dandruff”- market at risk	<ul style="list-style-type: none"> ▪ Speed to market ▪ No safety risk ▪ Low regulatory risk – re- label at FM stage 	

Case Study #1: Outcome

- No submission - market at risk
- Consumer need for desired product filled
- Product relabeled at final monograph stage
- Target population continues to buy product
- Competition copies concept



Case Study #2

Consider cost, time, & exclusivity

New Indication

Facts:

- Science unveils another benefit of a Category I ingredient
- Doctors are convinced that it has a benefit in reducing the risk of a particular disease and they recommend it for that purpose

Issue: indication is not in a final monograph

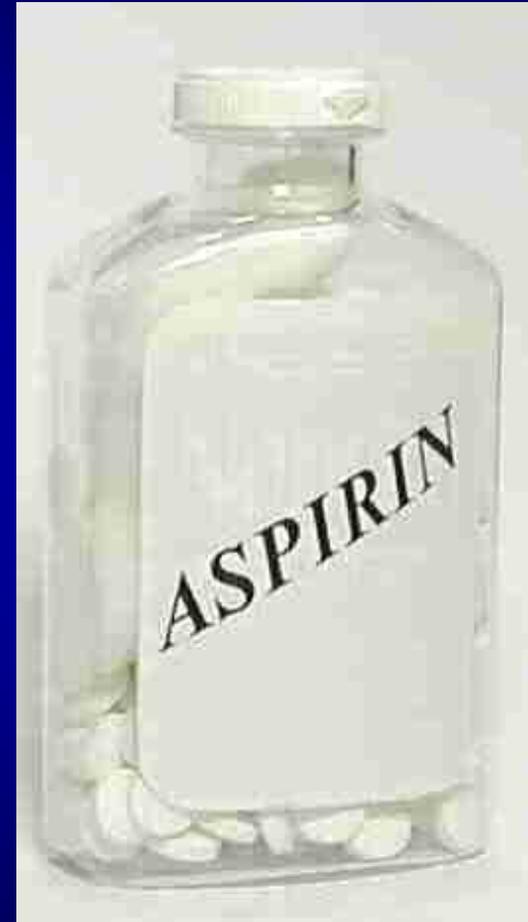
**Which options will
optimize the public health benefit?**

Case Study #2: Options

<u>Option</u>	<u>Why Yes</u>	<u>Why No</u>
NDA	<ul style="list-style-type: none"> ▪ confidential ▪ exclusivity? 	<ul style="list-style-type: none"> ▪ time and money ▪ full documentation
NDA Deviation	<ul style="list-style-type: none"> ▪ confidential ▪ exclusivity? ▪ limited documentation 	<ul style="list-style-type: none"> ▪ time and money
Petition Monograph	<ul style="list-style-type: none"> ▪ likely to be accepted ▪ limited documentation 	<ul style="list-style-type: none"> ▪ unspecified time ▪ no exclusivity
No submission - market at risk	<ul style="list-style-type: none"> ▪ speed to market 	<ul style="list-style-type: none"> ▪ safety risk?

Case Study #2: Outcome

- **Petition to revise the monograph**
- **Manufacturer was prepared to market new labeled product (first to market) as soon as FDA approved special changes related to indication**
- **Professional labeling approved and final**
- **Competitors copy the concept**
- **New indication associated with original brand**



Case Study #5

Consider cost, time, & exclusivity

Indication vs structure/function claim

Facts:

- single ingredient with history of use in food
- category I active ingredient in OTC drug monograph
- science unveils additional health benefit

Issue: unveiled benefit not a monograph indication

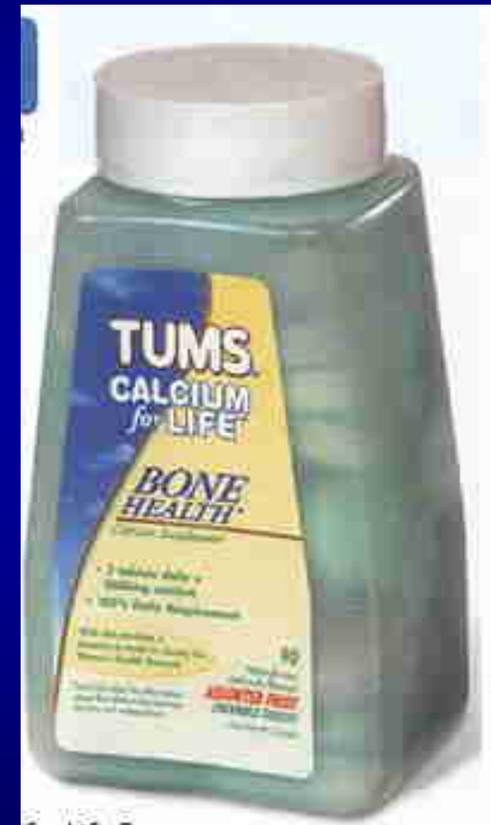
What are the options?

Case Study #5: Options

<u>Option</u>	<u>Why Yes</u>	<u>Why No</u>
NDA	<ul style="list-style-type: none"> ▪ New indication (prevention) ▪ confidential ▪ exclusivity? 	<ul style="list-style-type: none"> ▪ time and money ▪ full documentation
NDA Deviation	<ul style="list-style-type: none"> ▪ confidential ▪ exclusivity? ▪ limited documentation 	<ul style="list-style-type: none"> ▪ time and money
Petition Monograph	<ul style="list-style-type: none"> ▪ likely to be accepted ▪ limited documentation 	<ul style="list-style-type: none"> ▪ studies? ▪ unspecified time ▪ no exclusivity
DSHEA – structure/function claim	<ul style="list-style-type: none"> ▪ speed to market ▪ no additional cost ▪ perceived benefit ▪ no safety risk 	<ul style="list-style-type: none"> ▪ no special labeled indication

Case Study #5: Outcome

- Market dietary supplement (DSHEA)
- Structure/Function claims
- FDA Disclaimer
- Competitors copy the concept



Industry and FDA

Looking to the Future – What Regulatory Options Can Work for Both Industry and the FDA?

TEA

- New process - only one Notice of Eligibility
- Incentive to use this process?

Finalizing the Monographs

- Public meetings (Sunscreen Monograph)
- Current NDA Ingredient \Rightarrow Monograph ingredient
 - Appropriate time to switch? (e.g. clotrimazole)
- Testing procedures updated based on scientific advances

Industry and FDA Looking to the Future

NDA Deviation

- Undeveloped opportunity?
- Industry/FDA workshops?
- FDA Guidance document?

Foreign regulatory process

- How do they differ?

Summary

- **Monograph process is very useful**
- **Industry/consumer needs new products**
- **Science and consumer research updates data**
- **Decisions based on exclusivity, time, cost**
- **Regulatory paths are compared**
- **Risk management in practical application**
- **Other processes complement monograph process**
- **Industry and FDA have common goals**

Looking forward to the future of OTC Drug Monographs

FDA standards provide industry with parameters for what is safe and efficacious and the appropriate labeling.

FDA and industry need to partner in the conduct of studies that will provide FDA with new/updated information.

Closing Remarks