Rx to OTC: A Scripted Talk

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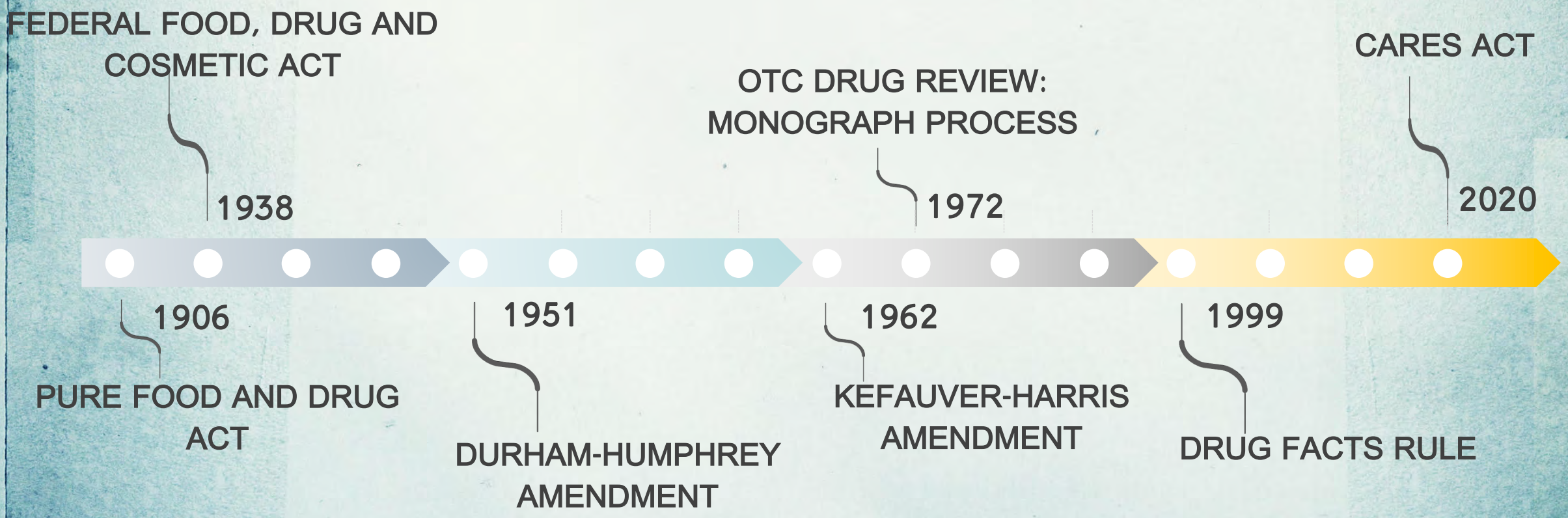
The Journey


1906
PURE FOOD AND DRUG ACT
1938
FEDERAL FOOD, DRUG AND COSMETIC ACT
1951
DURHAM-HUMPHREY AMENDMENT
1962
KEFAUVER-HARRIS AMENDMENT
1972
OTC DRUG REVIEW: MONOGRAPH PROCESS
1999
DRUG FACTS RULE
2020
CARES ACT

OTC Definition

- Drug product that
  - Has been marketed over a period
  - Has shown good safety profile
  - Has low potential for misuse or abuse *AND…*
  - Benefits consumers for self medication through proper labeling with approval by the Health authorities for over-the-counter use

OTC Drug Requirements

- Safety and efficacy standards
  - Consumers must be able to:
    - Self-select
    - Self-diagnose
    - Self-treat
    - Self-manage
- Good manufacturing practices
- Standardized labeling format
  - “Drug Facts”
- Available to consumers without a prescription
- Low abuse potential
- Benefits of availability outweigh risks

Drug versus New Drug?

- OTC Monograph
- OTC New Drug Application (NDA)

Drug Monograph History

- OTC drug review established in 1972 to evaluate the safety and effectiveness of OTC drug products
- Advisory Review Panels
- Developed by a three-step monograph process
- Set of regulations by therapeutic class for drug ingredients that are Generally Recognized as Safe and Effective (GRASE)
- Active Ingredient categories
  - Category 1: GRASE
  - Category II: not GRASE
  - Category III: cannot determine if safe and effective

What is GRASE?

- Drug is not considered a new drug ONLY when is generally recognized as GRASE
- In order to conclude GRASE determination, drug must satisfy three criteria
  - 1st particular drug must have undergone adequate, well-controlled clinical investigation to establish safety and efficacy
  - 2nd Investigations must be published in scientific literature and available to experts
  - 3rd experts must agree, based on the current studies that the product is safe and effective for its intended use

Phases of OTC Review

- 1st phase: Advanced Notice of Proposed Rulemaking (ANPR)
  - Multiple advisory panels created
    - Example: antacid panel, antimicrobial panel, etc
  - Followed by Public Comment Period
- 2nd phase: Tentative Final Monograph
  - FDA evaluation of information including panel finding, public comments and additional new data
  - Agency publishes tentative findings as Tentative Final Monographs
  - Followed by Public Comment Period
- 3rd phase: Final Monograph
  - FDA publishes final rule → Final monograph establishing standards and labeling in each OTC drug category

"A Recipe/Rule Book"

- What is included in a monograph
  - Preamble
  - Acceptable ingredients and combinations
  - Uses (indications)
  - Dosage and formulations
  - Warnings
  - Direction for use
  - Consistent with final monograph-GRASE

Monographs Pros/Cons

- No dossier required prior to marketing
- Lighter regulatory requirements
  - No annual products reports
  - No periodic safety reports
- Less CMC constraints
- Quicker time to market
- No clinical study requirements
- No exclusivity
- Limited to ingredients/indications/dosage forms obtained in monograph

Why monograph reform?

- Prior process was a protracted, multistep rulemaking process to establish and/or amend monographs
- Legal liability with delay in finalizing monographs
- Innovation is rarely possible (new combinations, new product formulations)
- Competitors can immediately implement monograph revisions
- Previous delay in safety updates

Monograph reform goals

- Improve the process by replacing rulemaking with administrative orders
- Improve efficiency, timeliness, and predictability
- Facilitate innovation
- Establish process to rapidly address safety issues
- Finalize pending monographs
- Provide FDA with user fees to support OTC monograph drug activities

Coronavirus Aid, Relief, and Economic Security Act

- Signed into law on March 27, 2020
- To aid response efforts and economic impact of COVID-19
- Additionally, includes statutory provisions that reform and modernize OTC monograph drug regulation
- Replaces rulemaking processes with administrative order process for issuing, revising and amending OTC monographs
- Provides FDA authority to assess and collect user fees dedicated to monograph drug activities
  - Provide additional resources to help agency conduct regulatory activities in timely manner

Timeline Monograph Reform

- First three years devoted to current external mandates, safety activities, and OTC monograph reform implementation and infrastructure development
- Year 4 and 5: FDA expects to have established effective review capacity to begin to have timelines and performance goals for review activities to create a steady state of monograph review program

Before and After CARES

WHAT STAYS CONSTANT

- Ingredient based review
- Active ingredients grouped by therapeutic category
- GRASE determination
- Drugs complying with OTC monographs and other applicable requirements may be marketed without FDA approval
- Process includes public comment period

NEW FEATURES

- Administrative order process
- OTC Monograph order request (OMOR)
- Clarification of status of existing OTC monograph drugs (including previous TFM and ANPR)
- Process for minor changes in dosage form
- Exclusivity period for certain OTC Monograph drugs
- OTC monograph user fees
- Formal meetings with FDA and Sponsors

Administrative order process

- Replaces rulemaking process
- Gives FDA authority to issue administrative order that adds, removes, or changes GRASE conditions for OTC monograph
- Expediated safety process
- Either industry or FDA can initiate the administrative order process
  - A request by industry to initiate the administrative order process is called an OTC Monograph Order Request (OMOR)

User Fees

- Over the counter monographs order requests (OMORS)
  - Tier One OMOR: $507,201
  - Tier two OMOR: $101,404
  - *Due upon submission of OMOR*
- Establishment Fees
  - Charged to the owner of an OTC monograph drug facility engaged in the manufacturing or processing of an OTC drug in a finished dosage form- regardless whether they had an OMOR
  - Annual fee per geographical location
  - For 2022
    - Monograph Drug Facility (MDF) fee: $24,178
    - Contract Manufacturing Organization (CMO) fee: $16,119

Why Fees?

- Increased FDA OMOR Review Capacity
  - Requires hiring and training new staff
- FDA will issue several final guidance to fully implement the use of OMORs
- IT platform:
  - Develop platforms for reviewing electronic submission, archiving review work, generating reports and cataloging monographs documents
  - Create and implement public facing IT dashboard
- Performance Goals
  - Year 4 (2024): 50% of OMOR submissions received will issue a final order by specified goal date
  - Year 5 (2025) 75% of OMOR submissions received will issue a final order by specified goal date

Innovation OMORs

Tier 1 (exclusivity) ($500,000)	Tier 2 (other) ($100,000)
New Ingredient*	Reordering of existing information in Drug Facts label
New Indication**	Standardization of the concentration or dose of a finalized ingredient
New Combination*	Ingredient nomenclature change to align with standards-setting organization
New Test Method**	Addition of information (either required or optional) to "Other Information" of the Drug Fact Label
New Route of administration or dose**	Modification of "Directions for Use" to be consistent with final order/guidance on minor dosage form changes
Any request not deemed to be Tier 2	
New Monograph Therapeutic category	

**To a monograph that has already has one or more ingredients that have already been found to be GRASE*
***to a monograph that already has one or more ingredients that been found to be Grace and the new indication applies to the GRASE ingredient*
****to a monograph that already has one more ingredient that have already been found to be GRAE and the round of administration applies to one or more of the GRASE ingredient*

Industry-Initiated order

- Requestor submits OMOR
- FDA files OMOR
- FDA issues proposed order
- Public comment on proposed order
- FDA issues final order

FDA-Initiated Order

- FDA issues proposed order
- Public comment on proposed order
- FDA issues final order

Expediated FDA Order

- Can be initiated when
  - Drug poses imminent public safety risk
  - Change in drug labeling, drug class labeling, or drug combination is expected to minimize unreasonable risk for serious adverse event
- FDA issues an interim order that becomes effective prior to public comment
  - Following public comment, the FDA will issue a final order

Exclusivity

- Exclusivity award for
  - Changes (other than safety) which are supported by new human data studies essential to the approval of the change
  - New active ingredients
- Human data: data from any testing with human subjects, including clinical trials of safety and effectiveness or pharmacokinetics or bioavailability studies
- The 18-month exclusivity period begins from the effective date of the order and the date the requestor may market the drug

OTC NDA

- The alternative regulatory option for legally marketing an OTC drug is the FDA new drug application (NDA) process
- If a product is not marketed in accordance with the requirement of the OTC monograph system, a product is not GRASE and will likely be considered a “new drug”
- All new drugs require FDA premarket approval
- Marketed after NDA approved
- Product specific

New Drug Application

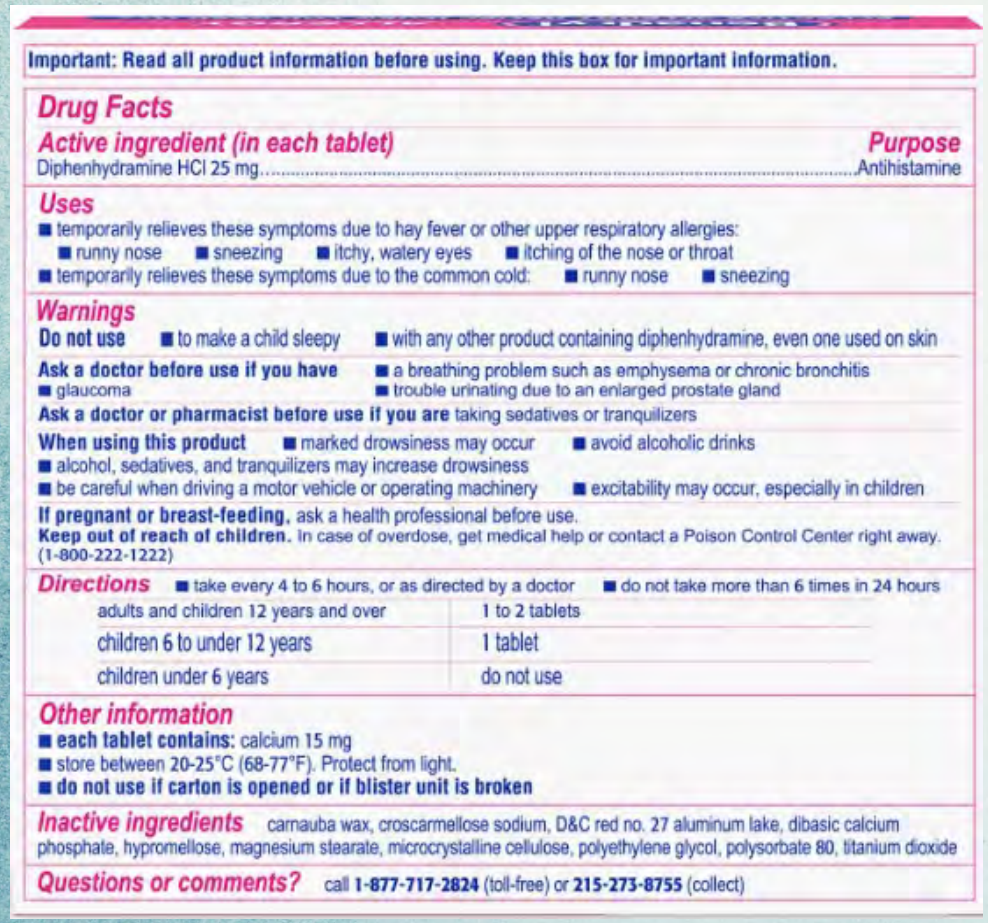
- Pathway through which drug sponsors formally propose that FDA approve a new pharmaceutical for marketing
- Required documentation
  - Clinical test results
  - Drug ingredients
  - Animal study results
  - Documentation of in-vivo drug behavior
  - Drug manufacturing, processing, labeling and packaging information

Regulation Comparison

OTC NDA	OTC MONOGRAPH
Pre-market approval-FDA	No premarket approval
Confidential filing	Public filing process
Drug-product specific	Active ingredient-specific by OTC drug category
User Fee	User Fee
Potential for marketing exclusivity (3 years)	Potential for marketing exclusivity (18 months)
Mandated FDA review timelines	Manufacturer responsible for ensuring product compliance without FDA mandated review (either pre- or post-market
May require clinical studies, including studies on label comprehension and actual use	Generally, does not require clinical studies
Approved labeling is unique to the drug	Labeling is defined by the monograph. Once marketed, FDA can review labeling at any time
Approved NDA is your “license” to market	Final monograph open to anyone
Trade name reviewed prior to marketing	No review of trade name prior to marketing. Once marketed, FDA can review trade name at any time

Label appearance

Benadryl® (OTC monograph antihistamine product) Label



Important: Read all product information before using. Keep this box for important information.

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Diphenhydramine HCl 25 mg ..... Antihistamine

Uses

- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
  - runny nose
  - sneezing
  - itchy, watery eyes
  - itching of the nose or throat
- temporarily relieves these symptoms due to the common cold:
  - runny nose
  - sneezing

Warnings

Do not use
- to make a child sleepy
- with any other product containing diphenhydramine, even one used on skin

Ask a doctor before use if you have
- a breathing problem such as emphysema or chronic bronchitis
- glaucoma
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product
- marked drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. (1-800-222-1222)

Directions

- take every 4 to 6 hours, or as directed by a doctor
- do not take more than 6 times in 24 hours

adults and children 12 years and over	1 to 2 tablets
children 6 to under 12 years	1 tablet
children under 6 years	do not use

Other information

- **each tablet contains:** calcium 15 mg
- store between 20-25°C (68-77°F). Protect from light.
- **do not use if carton is opened or if blister unit is broken**

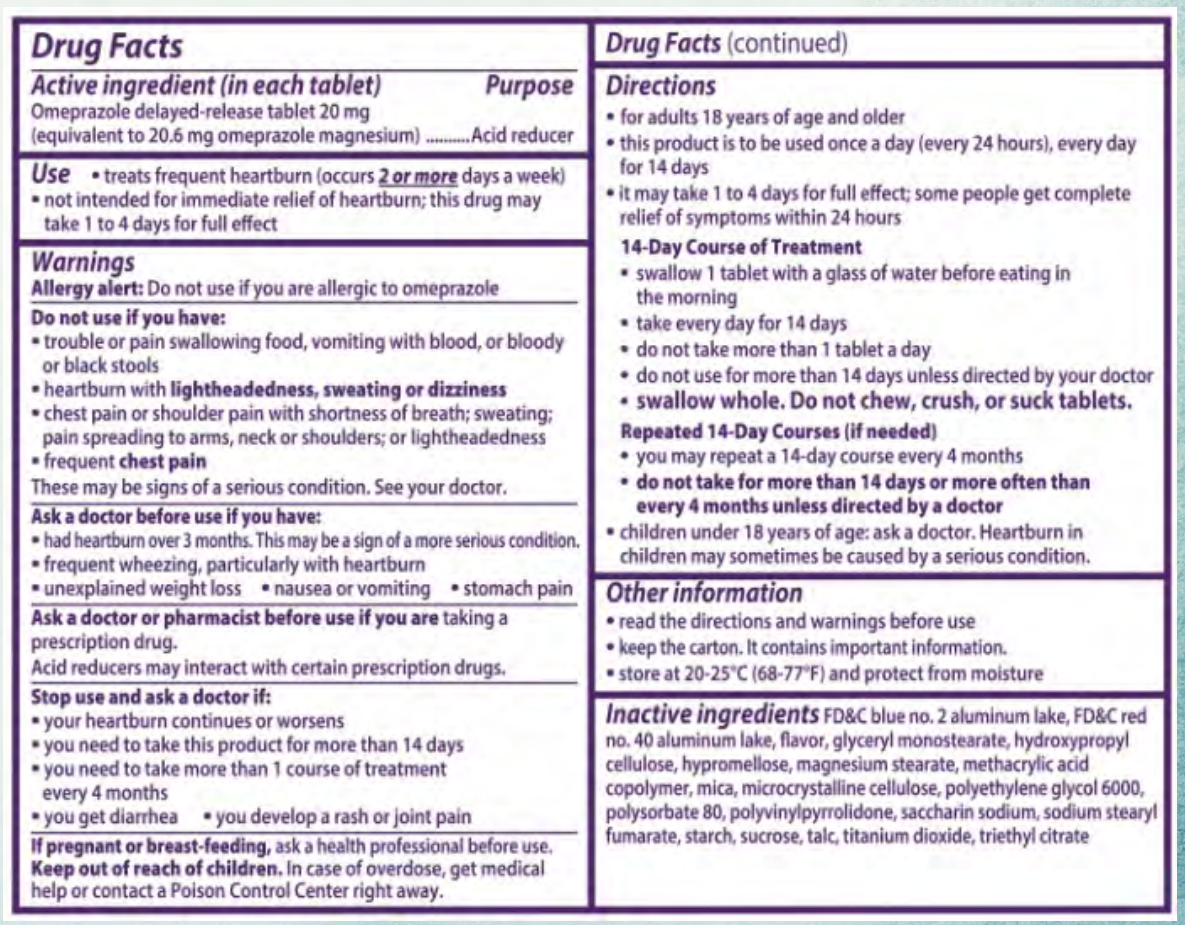
Inactive ingredients

carnauba wax, croscarmellose sodium, D&C red no. 27 aluminum lake, dibasic calcium phosphate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide

Questions or comments?

call **1-877-717-2824** (toll-free) or **215-273-8755** (collect)

Prilosec® (OTC NDA product) Label



Drug Facts

Active ingredient (in each tablet) — **Purpose**

Omeprazole delayed-release tablet 20 mg (equivalent to 20.6 mg omeprazole magnesium) ..... Acid reducer

Use

- treats frequent heartburn (occurs ***2 or more*** days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Warnings

Allergy alert: Do not use if you are allergic to omeprazole

Do not use if you have:
- trouble or pain swallowing food, vomiting with blood, or bloody or black stools
- heartburn with **lightheadedness, sweating or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**

These may be signs of a serious condition. See your doctor.

Ask a doctor before use if you have:
- had heartburn over 3 months. This may be a sign of a more serious condition.
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking a prescription drug.
Acid reducers may interact with certain prescription drugs.

Stop use and ask a doctor if:
- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months
- you get diarrhea
- you develop a rash or joint pain

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions

- for adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- it may take 1 to 4 days for full effect; some people get complete relief of symptoms within 24 hours

14-Day Course of Treatment
- swallow 1 tablet with a glass of water before eating in the morning
- take every day for 14 days
- do not take more than 1 tablet a day
- do not use for more than 14 days unless directed by your doctor
- **swallow whole. Do not chew, crush, or suck tablets.**

Repeated 14-Day Courses (if needed)
- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**
- children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition.

Other information

- read the directions and warnings before use
- keep the carton. It contains important information.
- store at 20-25°C (68-77°F) and protect from moisture

Inactive ingredients

FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, flavor, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, saccharin sodium, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate

Prescription

- FD&C Act: restricts drugs to prescription status only if the drug requires a learned intermediary
  - Because of toxicity, or potential for harmful effects, or the method of its use, or the collateral measures necessary for its use, it is only safe under the supervision of a practitioner licensed by law to administer such drug

Regulatory Pathway

- OTC NDA can occur via
  - RX to OTC switch
    - Complete versus partial switch
  - Direct to OTC NDA
    - No prior marketing as a prescription drug
  - NDA derivation
    - Drug product deviates from the OTC monograph
  - Generic (ANDA)

OTC NDA versus RX NDA

VARIABLE	OTC NDA	RX NDA
NDA FOCUS	For Rx-OTC switch-focus is on safety in the OTC population. For OTC NDA, focus is on safety and efficacy in the OTC environment	Safety and efficacy of the new chemical entity
END-USER STUDIES	Label comprehension Self selection	None
LABELING	Product label focuses on the information needed to assure the safe and efficacious use of the product to the consumer. There is no requirement for prescribing information	Prescribing information for HCP. Education guide for patient
USER FEES	May require a user fee	Requires user fees
ADVERTISING	FTC	FDA
FDA REVIEW LEAD	Lead: ONDP: reviews consumer studies, post marketing safety data, OTC labeling, regulatory issues Review division: subject matter experts review safety and efficacy data related to controlled clinical trials	Review division
MARKET EXCLUSIVITY	NCE exclusivity-5 years Tx to OTC switch-3 years if clinical data required to support the switch or new indication	NCE exclusivity: 5 years

Why Rx to OTC switches?

- Increased access and treatment utilization for the consumer
- Aging population will drive new healthcare needs
- Makes business sense
  - Product lifecycle extension
- Consumer use
  - Economic and cost-saving opportunities
  - Decreased health care resource utilization

US switch criteria

- Can the product be labeled adequately such that
  - The consumer can self-diagnose, self-treat and self-manage the condition?
  - The consumer can make the correct self-selection decision?
  - HCP not needed for the safe and effective use of the product?
- Does the product have an acceptable safety margin?
- Is the product safe when used according to the labeling?
- Does the product have a low potential for abuse/misuse?
- Do the benefits outweigh the risks?

Types of switches

EXISTING OTC CATEGORY	Established that consumers can self-diagnose, and self-treat the condition OTC options are currently being sold (ie allergy, laxative, etc) Usually minimal testing (if any is required)
NEW OTC CONDITION	Demonstrate that consumers can accurately self recognize and self diagnose the condition without masking or delaying treatment or other more serious conditions
FULL SWITCH	The full Rx NDA switches over, no population or indication is left behind
PARTIAL SWITCH	Some indicators or populations remain Rx

OTC Consumer Studies

- Label Comprehension Study
  - Does the consumer understand the Drug Facts Labeling
- Self Selection Study
  - Can the consumer identify if the drug applies based on their personal medical history?
- Actual Use Study
  - Can the drug be used according to label?
- Human Factors Study
  - Can the consumer understand and correctly use the drug?

Who Initiates the Switch to OTC?

- Holder of approved prescription NDA
- Other parties
  - Citizen petition
- FDA does not conduct studies to support Rx to OTC switches

Safety evaluation for OTC switches

- Candidates for switch assessed following may years of Rx use
  - Apply concept of incremental risk
  - In context of original RX label
  - Evolved understanding of initial safety topics through clinical trials, epidemiologic studies and marketing experience
- Extensive analysis of public and internal pharmacovigilance (PV)
- Published literature

FDA Approval

- Ultimately a judgement call is required
- Decision shared by two FDA divisions
  - Division of Non-Prescription Drug Products (DNDP)
  - Therapeutic Division
- Consumer behavior study results are rarely definitive
- Difficulty decision

Thank you for your time!

References

Drug Facts Labeling links:
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http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm150436.htm
Drug Facts Rule (21 CFR 201.66)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.66
Drug Registration and Listing Web page:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm
Monograph Reform Web Page
Monograph Reform is Here! - US Food and Drug Administration
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Small Business Assistance: Frequently Asked Questions on the Regulatory Process of Over-the-Counter (OTC) Drugs
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