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## WORKSHOP: EFFECTIVE RX-TO-OTC SWITCHING

# Benefit/risk decision-making as the final common pathway to OTCness

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## Introduction

### Premise:

The single most important principle to ensure that Rx-to-OTC switch will continue to expand self-care is the concept that switch is a testable hypothesis, defined by a data-driven benefit-risk decision.

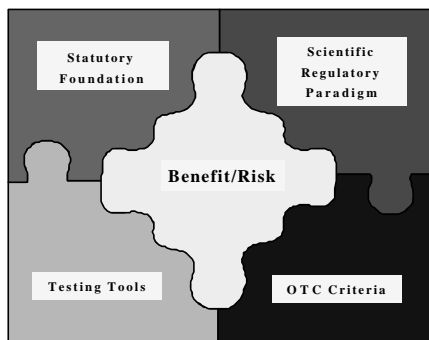
## Definition

- “OTCness is the widespread availability of safe and effective nonprescription medicines for responsible self care by the consumer ...
  - ... according to label directions,
  - ... pursuant to the applicable laws, regulations, and voluntary industry codes affecting manufacturing, packaging, labeling, distribution, and sales of quality products
  - ... and the advertising of those products in all media.”

(Soller, R.W.: OTCness. *DIA Journal* 32: 555-560, 1997)

## Topics of Discussion

### The R&D Puzzle Called Switch (or OTCness)



## Statutory Foundation

- By law in the U.S.:
  - any drug which cannot safely be used without medical supervision must be labeled for sale and be dispensed only by prescription of a licensed practitioner, otherwise it is OTC
- Meaning:
  - Rx by exception: If it can be OTC, it must be OTC
  - Any Rx category is potentially switchable.

## Scientific/Regulatory Paradigm

- Case-by-case
- Weight-of-the-evidence
- Data-driven
- Dialogue-driven

(Soller, R.W.: The move toward new self-care paradigms. RA Focus, March, 1999)

### OTCness Criteria

- **Safety:**
    - Carcinogenic & repro-tox potential
    - Side effects, when used as recommended
    - Potential therapeutic hazards
      - Potential misdiagnosis
      - Potential OTC treatment failure
      - Potential incorrect use (overdose and abuse potential)
    - Drug interactions
  - **Effectiveness:**
    - Definition of target population(s)
    - Dosing regimen(s)
  - **Labeling**
    - Specific components
    - Specific formatting requirements
  - **Benefit/Risk**
- (Soller, R.W.: OTCness. DIA Journal, 32: 555-560, 1997)

## Testing Tools

- **Post-Marketing Surveillance**
- **Clinical Studies**
  - **Special Clinical Testing**
  - **Actual Use Studies**
- **Label Comprehension Studies**

### Benefit/Risk Assessment

#### Starts with a Question(s)

Is a modest (x%) improvement in one or more specific clinical endpoints related to self-care of the condition or disease under study ... worth the unlikely (but perhaps uncertain) risk of a particular adverse event (e.g., GI side effects, drug-drug interaction, etc.) or consequence (e.g., unacceptable level of undiagnosed cases, or increased viral resistance, etc.)?

#### Answered by data:

- Post-marketing surveillance
- Special clinical studies
- Actual use studies
- Label comprehension studies

## Nicotine Replacement Therapy (NRT)

- What is the NRT-induced quit rate in the OTC where there is limited behavioral support compared to that in the typical Rx setting?
- Will increased OTC access allow more to try to quit, leading to more quitting, than in an Rx setting?

## Nicotine Replacement Therapy (NRT)

- 17 MM/year attempt to quit smoking
- Response rate to quitting smoking varies:
  - ~ 3% continuous quit rate (cold turkey)
  - 49% with intense behavioral support
  - 16% - 19%: OTC vs. Rx
    - Three times as many in the Rx arm failed to initiate therapy than in the OTC arm, in part due to the inability to get the prescription filled
- OTCness means easier & expanded access at lower cost
  - ~ 1 million more people would successfully quit smoking with OTC NRT than would be achieved from continued restricted Rx usage

### Pediatric Ibuprofen

- Are the known dose-related pediatric fever reducing benefits of ibuprofen worth the potential for rare, unproven, but potentially significant side effects of GI, kidney, and liver toxicity or of Reye syndrome?

### Pediatric Ibuprofen

- 80,000 children with febrile illnesses
- Assess potential increased risk of acute GI bleed, renal failure, anaphylaxis or RS following ibuprofen use
- Power to detect small differences in these conditions, down to 10 cases per 100,000 treated children
- Separate risk assessments were made for safety-specific endpoints for acetaminophen to demonstrate comparable safety profiles for OTC pediatric ibuprofen and acetaminophen

## Ketoconazole Shampoo

- Is the long term safety of ketoconazole used per OTC directions comparable to placebo?
- Does the dermal absorption profile for ketoconazole change after prolonged use per OTC directions?

## Ketoconazole Shampoo

- Anti-dandruff remedy
- Safety Questions
  - Extent of absorption and long term safety
  - 14 month actual use study
    - Lack of absorption at 9 months (4 and 8 hours post application)
    - A safety profile comparable to vehicle at 1, 2, 4, 6, 8, 10, 12, 13, 14, months.

## Cholestyramine for OTC Cholesterol-lowering

- Is the management of surrogate endpoints of a chronic life-threatening disease comparable in OTC and Rx settings?

## Cholestyramine for OTC Cholesterol-lowering

- Actual Use Study
  - > 3,500 subjects, already following Step I or II American Heart Association diets, responded in <6 weeks of full recruitment
  - Simulated OTC and Rx settings showed comparable compliance
    - 80-120%, target compliance endpoint: 77% in both OTC and Rx groups
    - Health-related benefits: 16% and 17% reduction in total and LDL cholesterol in the OTC and Rx groups
    - Adverse events: 49% in the OTC arm, 60% in the Rx arm
- FDA Negative Guidance
  - Issued with no explanation

## Cholestyramine for OTC Cholesterol-lowering

- Is the Rx management of the surrogate endpoints optimal?
- If the Rx management is not optimal, then even if the simulated Rx management is comparable to simulated OTC management, have we fulfilled the statutory mandate that “if it can be OTC, it must be OTC?”

## What This Means

- Unless industry strongly advocates switch as a testable hypothesis, potential novel OTC categories will be blocked by regulatory authorities.
- Remember:
  - If it can be OTC, it must be OTC.
  - OTC criteria are generally well established.
  - Tools to test the hypothesis exist.
  - OTC scientific/regulatory paradigm.
    - The most important part of the puzzle to develop the benefit/risk question

## Next Steps

- 1 Develop country (or region)-specific OTCness.
- 2 Seek to orient stakeholders to OTCness and the concept that switch is a testable hypothesis.
- 3 Develop the regulatory dialogue pre-R&D to define the testable switch question (hypothesis).
- 4 Consider available research tools to develop the data needed to test the hypothesis.
- 5 Agree that negative regulatory responses should provide reasons why the data do not answer the switch question (i.e., hypothesis).
- 6 Reassess OTCness criteria in the context of OTC use for chronic conditions.

## OTCness

