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OTC CONSIDERATIONS FOR EXPANDING ACCESS TO NONPRESCRIPTION MEDICINES: A CRITICAL SYNTHESIS OF QUESTIONS FROM THE FOOD AND DRUG ADMINISTRATION TO ITS ADVISORY COMMITTEES ON Rx-TO-OTC SWITCH

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ABSTRACT

Consumer behavior studies and thorough reviews of Rx drug safety and efficacy are expected components of Rx-to-OTC new drug applications in the U.S. Understanding the expectations of the Food and Drug Administration (FDA) for these studies and other data required for switch is vital for successful OTC drug development programs.

The core research questions were: (a) has the nature of the questions used by FDA to frame advisory committee deliberations of first-in-class switches changed in the period 1992-2011? (b) do FDA's questions to advisory committees for first-in-class switches further inform 1990 and 1998 "switch principles" articulated by FDA representatives such that they can be consolidated into a modern comprehensive list of OTC Considerations?

Data collection derived principally from FDA advisory committee transcripts and background materials, FDA guidance, and the medical literature. Data synthesis resulted in the integration of published "switch principles" into a comprehensive list of Rx-to-OTC Considerations.

From 2002-2011 there has been a downward trend in the number of Rx-to-OTC switches in the U.S. There were 50% fewer first-in-class switches in the U.S. than the prior 10-year period, a comparable number of line extensions and direct-to-OTC new drugs, and about 25% fewer follow-on switches.

A list of OTC Considerations with specific questions to explore for unique first-in-class switches encompasses evidence pertaining to safety, efficacy, OTC labeling, self-selection and effectiveness. This list is reflective of materials given to advisory committees and presented at public committee deliberations of first-in-class switches from the last ten years. Depending on novelty and uniqueness of the proposed OTC indication or Rx active ingredient, the intrinsic and extrinsic toxicity of the switch candidate, the robustness of the published and NDA-derived data and worldwide post-marketing surveillance evaluations, FDA uses its discretion to select areas of concentration for OTC drug development programs and advisory committee discussions on switch.

In conclusion, an updated framework of OTC Considerations for Rx-to-OTC switch has been developed through an in-depth assessment of FDA advisory committee deliberations of first-in-class switches, and may serve not only as a milestone to document the progress that FDA and industry have made in developing the evidence base for switch, but also as a framework for OTC drug development and training of new OTC regulatory personnel.

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Key words: Rx-to-OTC, Switch, Nonprescription, Self Care, OTC Drug Development.

INTRODUCTION

In the U.S., OTCness means "…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"[1]. Today, there are an estimated 300,000 nonprescription drug products on the U.S. market encompassing over 80 therapeutic categories, such as flu-related aches and fever, migraine, heartburn, diarrhea, allergy treatment and prevention, cavity and gingivitis prevention, athlete's foot and vaginal candidiasis, among others[2,3]. OTC availability in the U.S. may include not only over-the-counter (OTC) access but also behind-the-counter pharmacy-only access for selected medicines (i.e., insulin, pseudoephedrine, levonorgestrel)[4,5,6].

Since 1972, U.S. evidence requirements supporting OTCness have their basis in the regulatory definitions of safety, effectiveness, and labeling set forth by the Food and Drug Administration (FDA) pursuant to the 1962 amendments of the Food Drug & Cosmetic Act (FD&C Act; see also Appendix A)[7]. During the 1970's, clinical experience was a core element of the evidence base for safety and effectiveness of already marketed OTC drug products being evaluated under the OTC Review. For example, in the absence of well-designed dose-response studies, dosing directions for children's cough/cold products were based on the clinical axiom of one half the adult dosage for those 6 to under 12 years of age, and one quarter for those 2 to under 6[8].

As reviewed by Soller (2002), beginning in the 1980's a more rigorous clinical pharmacologic approach based on efficacy and post-marketing surveillance was applied to products being introduced under New Drug Application (NDA) provisions of the FD&C Act, including for example: considerations of time and extent of marketing to ensure full characterization of the prescription (Rx) parent molecule; international experience; pharmaco-dynamic data; dose evaluation to identify the minimally-effective dose, and nationally representative data relating to physician prescribing practices of the parent drug[9]. In general, the perspective in this period was largely drug-centric as articulated at a 1990 OTC industry conference by Dr. Carl Peck, Director of FDA's Center for Drug Evaluation and Research (Appendix B)[10]. In this period, consumer studies on label comprehension were rudimentary and uncommon. Only the vaginal contraceptive category incorporated a consideration of in-use effectiveness data[11]. Indeed, the evidence base for the mid-80's switch of ibuprofen had little in the way of behavioral studies relating to consumer understanding, product self-selection and actual use[12].

In the 1990's, FDA received more complex Rx-to-OTC switch applications with new pharmacologic approaches to self care relating to prevention (e.g., H2 receptor antagonists for heartburn, cromolyn sodium for allergies), long-term use before obvious signs of effectiveness (e.g., minoxodil for treatment of alopecia), more complex dosage directions (e.g., levonorgestrel for emergency contraception), among others[13]. During this period, the focus turned from

Accepted for publication 29 September 2011

the intrinsic toxicity of the drug to a consumer-centric approach, as articulated at a 1998 OTC industry conference by Dr. Robert DeLap, Director, FDA Division of OTC Drug Products (Appendix B)[14]. Results from label comprehension studies (LCS), self-selection studies (SSS), and actual use studies (AUS) became what is now an expected triad of evidence for first-in-class switches – i.e., those uniquely pushing the boundary of OTCness.

Since the 2002 review of FDA's 1990 and 1998 switch principles articulated by Drs. Peck and DeLap, there have been no published updates on how FDA frames its advisory committee deliberations on Rx-to-OTC switch, leading us to explore following questions:

- Comparing the decades spanning 1992-2011, have total and first-in-class switch approvals by FDA increased or decreased?
- Has the nature of the questions used by FDA to frame advisory committee deliberations of first-in-class switches changed over the same period?
- Do FDA's questions to advisory committees for first-in-class switches further inform 1990 and 1998 "switch principles" articulated by FDA representatives such that they can be consolidated into a modern comprehensive list of Rx-to-OTC Considerations for the purposes of OTC drug development and regulatory training?

METHODS

A process of data gathering and data synthesis was undertaken to address the research questions. Data sources included:

- FDA advisory committee meeting information (i.e., transcripts, presentations from industry and FDA pertaining to safety; efficacy; effectiveness; committee recommendations and votes). Advisory committee background materials and transcripts are not available on the FDA website for meetings held prior to 1997, and were not included as source materials[15].
- FDA guidance documents[16];
- External speeches by FDA division and office directors[17,18];
- Medical literature search on topics related to Rx-to-OTC switch [19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43];
- FDA and OTC industry maintained sources of ingredients and dosages transferred from Rx-to-OTC status or new OTC approvals[44,45];

Information from the above data sources was synthesized to enrich a consideration of each research question. For the rate of switches by year and classification by first-in-class, the FDA and industry switch lists were primary sources, with confirmation from FDA advisory committee transcripts. For the evaluation of first-in-class switches, total switches in a given time period were filtered, eliminating line extensions, follow-on switches, and direct-to-OTC introductions. Since more recent first-in-class switches that were approved or denied would raise higher

Accepted for publication 29 September 2011

levels of concern than follow-on switches that are second- or third-in-class switches or brand name line extensions combining a prior switch ingredient with an existing OTC ingredient, the questions posed by FDA for advisory committee deliberations of all first-in-class switches from 1999-2011 were extracted and synthesized into a master list to compare questions by topic, year and advisory committee, then integrated into FDA's 1990 and 1998 "switch principles" to create a comprehensive list of OTC Considerations for switch.

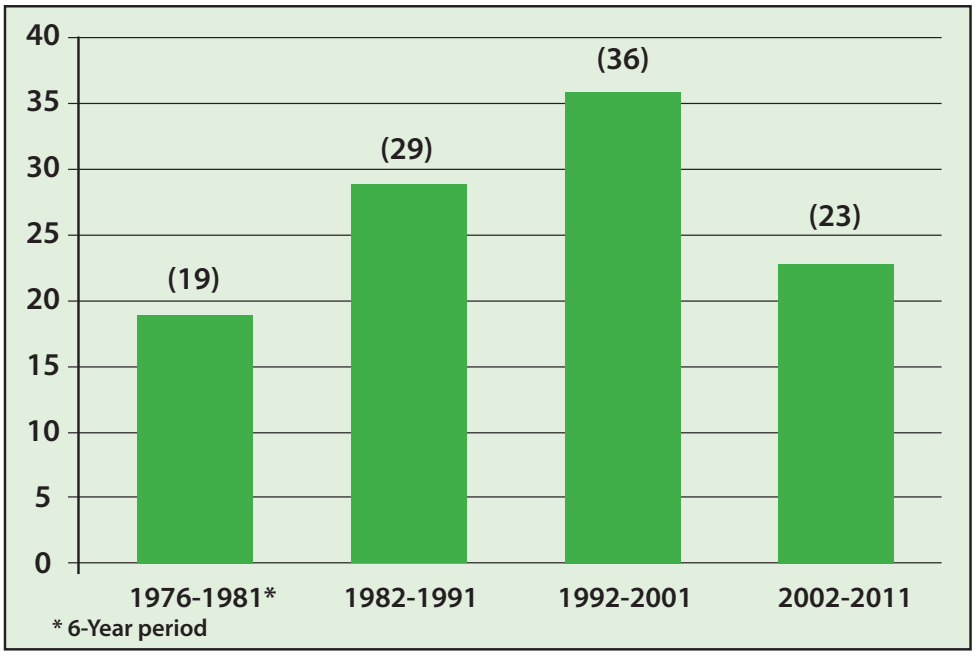
To place a regulatory calibration on outcomes from LCS, SSS and AUS, presentations of agency reviewers to advisory committees considering first-in-class switches were searched to extract agency commentary on the outcome rates of LCS, SSS, and AUS. Appendix C contains FDA definitions of LCS, SSS and AUS[46,47].

RESULTS

U.S. Switch Trend

The last ten years has been associated with a downward trend in the total number of switches compared to the two prior ten-year periods (Figure 1). Overall, from 1974-2011 there have been 106 active ingredients and dosage forms transferred from Rx status or directly introduced to the OTC market. These are represented either by the identical Rx products with new OTC availability (i.e., same active, indication, dose, dosage form, dosing directions), by "modified switches" (i.e., different in one or more ways from the Rx parent product), or by direct OTC introduction. Roughly 30% (n=33) were completed through the OTC Review monograph system, and the remainder by New Drug Application (NDA). Since the 1992 appointment of the Nonprescription Drug Advisory Committee (NDAC), all switches (n=56) have been approved for marketing by NDA. (i.e., the last OTC Review monograph switch was published in December, 1992 circa the date of the first NDAC meeting).

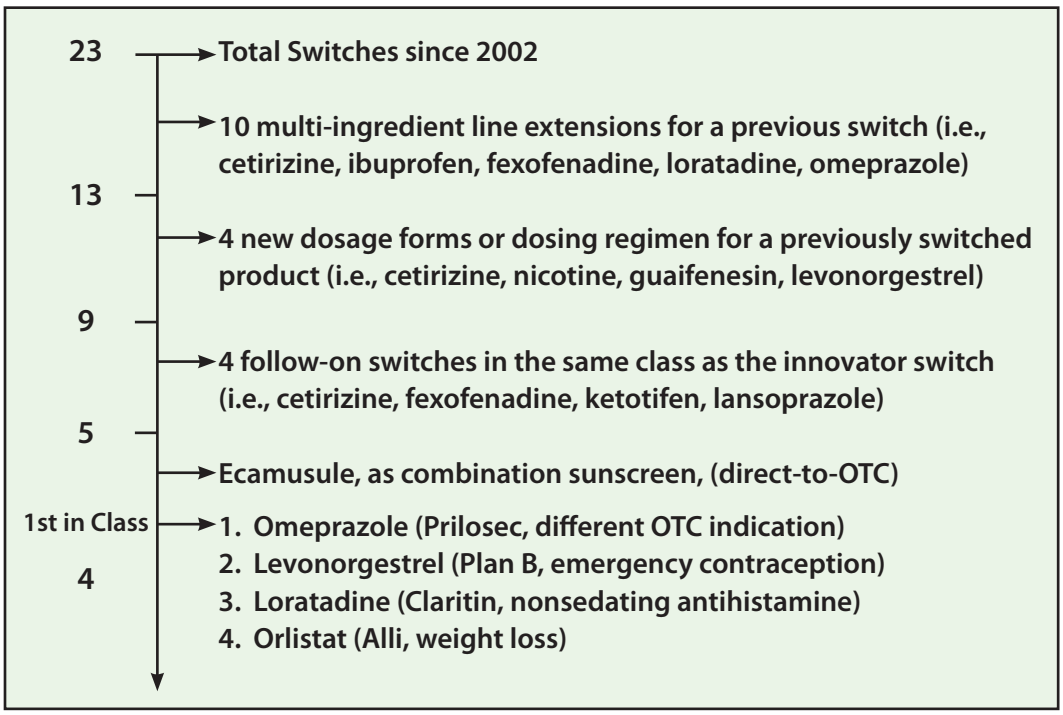
Figure 1 - Ten Year Cohorts of Ingredients, Dosage Forms and Direct OTC Introductions from 1976-2011 in the U.S.



Accepted for publication 29 September 2011

Assuming that more complex switches will be first-in-class and have higher interest regarding OTC considerations for NDAC, the 23 OTC approvals in the period 2002-2011 were filtered by progressively eliminating the following: 14 line extensions (i.e., multi-ingredient combos, new dosage forms or dosing regimens), 4 follow-on switches in the same class, and one direct-to-OTC new drug (Figure 2). The remaining 4 first-in-class switches were: (a) omeprazole: a proton pump inhibitor for frequent heartburn; (b) levonorgestrel: hormonal emergency contraceptive; (c) non sedating antihistamine (i.e., loratadine): allergies; and (c) orlistat: weight loss. A similar filter for the prior 10-year period (1992-2001) yielded eight first-in-class switches (i.e., nicotine replacement therapy, smoking cessation; famotidine: H2 blocker, heartburn; cromolyn sodium: allergy prevention; docosanol: cold sores; ketoconazole: antidandruff shampoo; OTC combination analgesic: migraine indication; minoxidil: hair regrowth; triclosan: antigingivitis agent), one direct switch (bentoquatam: poison ivy prevention), 12 line extensions (i.e., multi-ingredient combos, dosage, dosage form), and 15 follow-on switches (not shown in Figure 1).

Figure 2 - Derivation of First in Class Exact U.S. Switches in the U.S. Since 2002.



Thus from 2002-2011, there were 50% fewer first-in-class switches in the U.S. than the prior 10-year period, a comparable number of line extensions and direct-to-OTC new drugs, and about 25% fewer follow-on switches. Over the past two decades, 61% of first-in-class switch applications (n=11 of 18) were approved by FDA after one NDAC meeting each, and 17% (n=3) after two meetings each (Table 1). Of the 22% (n=4) first-in-class switches with negative NDAC recommendations, one was reviewed at one meeting, two at two meetings, and one at three meetings. It is noteworthy that, while this review covers the period through 2011, NDAC has not met on a switch proposal since 2007.

Accepted for publication 29 September 2011

Table 1: Switch Submissions Reviewed by NDAC*: 1993-2011

Switch Ingredient	Indication	Brand	AC M/Yr**	Comment
Approvals Requiring One NDAC Meeting				
Naproxen	Pain	Aleve	06/93	2nd in class^^
Ketoconazole	Dandruff	Nizoral	02/94	1st in class
Famotidine	Heartburn	PepcidAC	07/94	1st in class
Ibuprofen	Pediatric fever, pain	Advil	03/95	Product line extension
Ranitidine	Heartburn	Zantac	07/95	3rd in class^^
Ketoprofen	Pain	Orudis	07/95	3rd in class
Nicotine	Nicotine Replacement Therapy	Nicorette	09/95	1st in class
Nizatidine	Heartburn	Axid	09/95	3rd in class
Triclosan	Gingivitis	Total	02/96	1st in class
Nicotine (dermal)	Smoking cessation	Nicotrol, Nicoderm	09/96	2nd and 3rd in class (n=2)
Cromolyn sodium	Allergy prevention	Nasalcrom	10/96	1st in class
Minoxidil	Hair regrowth	Rogaine ES	07/97	Product line extension
Loratadine Loratadine/PSE Cetirizine Fexofenadine Fexofenadine/PSE	Allergies	Claritin Claritin D Zyrtec Allegra Allegra D	05/01	1st in class: non-sedating antihistamines (n=3)^^^
Loratadine	Hives	Claritin	04/02	New indication for prior switch
Levonorgestrel	Emergency Contraception	Plan B	12/03	1st in class
Orlistat	Weight loss	Alli	1/06	1st in class
Approvals Requiring More than One NDAC Meeting				
Cimetidine	Heartburn	Tagamet	09/93 07/94 03/95	2nd in class***
Minoxidil	Hair regrowth	Rogaine	07/94 11/95	1st in class
Omeprazole	Frequent heartburn	Prilosec	10/00 01/06	1st in class
Not Approved				
Acyclovir	Cold sores (herpes)	Zovirax	05/94 01/95	1st in class
Cholestyramine	Lipid lowering	Questran	09/95 05/97	1st in class (bile acid sequestrant)
Dex-ibuprofen	Pain, fever	(no name)	10/96	4th in class^^
Cyclobenzaprine	Muscle relaxant	Flexeril	07/99	1st in class
Lovastatin Pravastatin	Lipid lowering	Mevacor Pravachol	07/00 01/05 12/07	1st in class (statin)

* "Switch" broadly defined, see Results; NDAC, FDA's Nonprescription Drug Advisory Committee; list derived from NDAC meeting list provided by Consumer Healthcare Products Association

** AC Mo/Yr: month and year of the NDAC meeting

*** Although cimetidine was the ground breaker for H2 antagonists, it technically is a 2nd in class switch due its 1995 approval date being 2 months after that of famotidine.

^^ Naproxen, 2nd in class post 1984 ibuprofen switch; ketoprofen, 3rd in class; Dex-ibuprofen 4th in class

^^^ Switch submission by Blue Cross of California by Citizen Petition

Accepted for publication 29 September 2011

OTC Considerations for Switch

Based upon FDA's 1990 and 1998 switch principles and FDA's questions to advisory committees evaluating first-in-class post-2002 switches, an inclusive set of "OTC Considerations" was derived (Table 2)[48,49,50]. This list encompasses all topics that FDA posed to jointly-convened NDAC and Rx advisory committees for each of these first-in-class switches. However, depending on novelty and uniqueness of the proposed OTC indication or Rx active ingredient, the intrinsic and extrinsic toxicity of the switch candidate, the robustness of the published and NDA-derived data and worldwide post-marketing surveillance evaluations (not shown), FDA uses its discretion to select areas of concentration for advisory committee discussions on switch.

For example, while most OTC Considerations in Table 2 were addressed in safety, efficacy, LCS, SSS and AUS presentations for every first-in-class switch, discussions for levonorgestrel were focused principally on: patterns of consumer actual use in the context of recommended labeling; generalizability of studies to the expected population of potential non-Rx users; potential for misuse (i.e., substitution of Emergency Contraception (EC) for the regular use of other contraceptive methods); and access to safe use by the intended target population. To some degree, these questions derived from potential questions in the supportive studies themselves as opposed to concerns relating to intrinsic toxicity or efficacy of the agent *per se*. Thus, the strategy of broadly covering OTC Considerations in Table 2, but trimming focus to pivotal areas of uncertainty is observed in FDA's approach to managing its advisory committee deliberations on switch.

Of note is the switch of non sedating antihistamines, which are also identified in Figure 2 as first-in-class switches. The issue was prompted by a Citizen Petition (CP) from California Blue Shield – a health plan, not a drug industry sponsor[51]. The CP and supplemental material provided a literature review of available efficacy and safety information, economic and safety arguments supporting switch, but nothing from LCS, SSS and AUS.* A pharma company opposed the CP, stating that non sedating antihistamines should retain prescription status[52], and opining: "allergies may not be appropriately treated without physician supervision;" "the safety profile for OTC use of second-generation antihistamines has not yet been established;" and "taking second generation antihistamines OTC may result in decreased access and will not necessarily decrease the use and issues associated with first-generation antihistamines."[53]

In response to the petitioner's unique request for the OTC switch of six Rx products (i.e., Claritin, Claritin-D, Allegra, Allegra-D and Zyrtec), FDA provided the committee with summary reports of all available data in the Rx NDAs and postmarketing surveillance data by agency medical reviewers, which concluded for loratadine and fexofenadine that their "thorough

*Note, economic information in support of switch bears no weight in FDA's decisions on OTCness.

†An extensive review of adverse event reports associated with use of cetirizine "revealed possible associations between cetirizine and sedation, neuropsychiatric events, including seizures, cardiac arrhythmias, and thrombocytopenia potential." The medical review concluded: "The data are inconclusive with regard to a causal relationship between cetirizine and arrhythmias and thrombocytopenia." In his oral presentation to the committee, Dr. Robert Meyer (Director, Division of Pulmonary and Allergy Drug Products) concluded for cetirizine, "no significant safety signal from original NDA." (Ref 56)

Accepted for publication 29 September 2011

Table 2: OTC Considerations

Derived from Selected Post-2002 First-in-Class Switches and FDA 1990 and 1998 Switch Principles

Rx Fundamentals

SAFETY

1. Has the Rx product been on the market for a sufficient time and extent to enable full characterization of the drug's safety profile? Including:
   - a) Margin of safety;
   - b) Safety across the drug's therapeutic range and at high doses;
   - c) Potential masking of serious disease by short or long term use;
   - d) Potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity;
   - e) Any known special toxicity with discontinuation of therapy;
   - f) Drug-drug interactions;
   - g) Safety in special populations (e.g., women of child-bearing age, children, elderly);
   - h) Other special conditions or toxicity in its class that may be associated with acute, chronic or chronic intermittent use.
2. Can the condition be adequately self-diagnosed, or is there a need for physician diagnosis?
   - a) To what extent is misdiagnosis associated with current Rx practices relating to the intended OTC use of the product?

EFFICACY

3. Is the minimally effective dose known?
4. Are there efficacy studies needed to support the intended OTC use of the switch candidate?

RX USE PATTERN

5. What are the patterns of diagnosing, prescribing and patient use in the Rx setting related to OTC intended use?

OTCness

GENERAL

6. Are the studies supporting OTCness generalizable to the intended OTC target population?

LABEL COMPREHENSION: ***Can safety be handled entirely by the label?***

7. Do consumers understand key communication objectives of the label, relating to directions for use, contraindications, in-use warnings and precautions?
8. Do consumers show they would be likely to be able to assess and take action on the treatment effect (e.g., take appropriate action if the drug is not working, serious side effects emerge, or self-monitoring is needed)?

ACTUAL USE:

9. Do consumers demonstrate successful self-selection and de-selection of the product under conditions (or simulated conditions) of actual use?
10. Does the pattern of actual use support that the label can be successfully used in practice? That is, does the pattern of use show that consumers will likely:
    - a) Know when they should see a physician before using the product and once they have begun using the product;
    - b) Not use the drug on an acute or chronic basis for conditions other than that intended by labeling;
    - c) Use the correct dosage for the period of time specified in the label;
    - d) Evaluate response(s) to treatment and successfully monitor progress with therapy, including identifying serious adverse events symptomatically or, for example, with periodic lab tests;
    - e) Take other actions, as specific to the switch candidate.

Overall

11. Do the benefits of OTC availability outweigh the risks?

Accepted for publication 29 September 2011

review... failed to identify conclusive evidence of a causal relationship between use of loratadine [or, fexofenadine] and serious adverse events."[54] † In directions to the advisory committee, FDA framed the discussion on whether "these agents, given their marketing history, safety profiles, and the fact that they are in a class of drugs already accepted for OTC availability, could be used appropriately and safely by consumers without the intervention of a learned intermediary."[55] Dr. Robert Meyer (Director of FDA's Office of Pulmonary and Allergy Drug Products) stated to the committee that: "neither an actual-use study or a label comprehension study is necessary of the OTC switch proposed;" 'FDA is not seeking advice on: allergic rhinitis as an OTC condition, or on the effectiveness of Claritin, Zyrtec of Allegra in the OTC setting;" and "FDA has established appropriate OTC labeling for antihistamine products."[56] ‡ Hence, one general question was presented by FDA for each Rx ingredient (e.g., "Does loratadine have a safety profile acceptable for OTC marketing without a learned intermediary?). By skirting consumer behavioral issues through an affirmative preemptive decision on the matter, the agency effectively directed discussion on evidence consistent with the 1990 "switch principles," which the agency noted to the committee "remain useful in deciding which drugs may be suitable candidates for OTC switch."[57] In effect, then, a concerted effort was made by FDA to either directly or indirectly address virtually all the elements in Table 2 in responding to the Citizen Petition§. At best, however, the curious case of non sedating antihistamines remains an anomaly among U.S. switches.

Of the five first-in-class switches that received negative recommendations from NDAC (Table 1), cyclobenzaprine (muscle relaxant) and lovastatin (lipid lowering agent) were used as examples to evaluate the comprehensiveness of OTC Considerations listed in Table 2 in addressing issues associated with denied switch submissions. Lovastatin was reviewed at three joint meetings of NDAC and the Endocrinologic and Metabolic Drugs Advisory Committee. FDA minutes of the final meeting summarize the difficulties of predicting consumer behavior relating to OTCness, and specifically developing an adequate OTC label to ensure safe and effective use. Unresolved ambiguities are encompassed in the OTC Considerations (Table 2) and related to: self-diagnosis, self-selection and self-monitoring in the OTC self care setting that potentially could lead to overuse/underuse for low/high cardio-risk individuals; uncertain findings of an actual use study that did not study the proposed label; lack of large scale studies to support generalizability; uncertainty about the role of the physician in lifetime self-care and long-term consumer self-monitoring[58].

In the case of the muscle relaxant, cyclobenzaprine, questions to NDAC also fell within the framework shown in Table 2. Nuances in the questions held some hold-over from the drug-centric questions posed in the 1990 "switch principles" (e.g., questions about full characterization of metabolism and excretion in order to adequately characterize potential

‡Note: prior to the 2001 meeting, no OTC antihistamines had been supported in their OTC market approvals with evidence from ingredient- or class-specific label comprehension or actual use studies.

§Claritin (loratadine) and Claritin-D (loratadine plus pseudoephedrine) were switched on November 27, 2002. Zyrtec (cetirizine) was switched on November 16, 2007. Allegra (fexofenadine) and Allegra-D (fexofenadine plus pseudoephedrine) were switched on January 24, 2011. None were considered by a second FDA advisory committee.

Accepted for publication 29 September 2011

drug-drug interactions), yet as with each of the other examples FDA narrowed considerations to pivotal issues – in this case, whether the intended use of a muscle relaxant was a consumer self-diagnosable condition and one that could be appropriately self-treated in light of the drug's inherent toxicity. Specifically, the FDA medical reviewer concluded that cyclobenzaprine has: a "small" therapeutic margin and potential delayed onset after dosing leading to concerns about "dose creep" by consumers as well as morning drowsiness during driving to work; inadequate assessment of cardiovascular effects and other safety concerns particularly relating to concomitant use with alcohol and recreational drugs; inadequate data on actual use longer than seven days to know if repeat use leads to reduced efficacy; and uncertainty as to whether the patient population in the pivotal efficacy studies are the same population in the AUS[59]. Of critical note is that the AUS showed that only 73% of consumers took cyclobenzaprine per label directions. In sum, the questions to NDAC on cyclobenzaprine encompassed the types of questions routinely placed before the committee in terms of self-diagnosis, overuse, and ingredient-specific side effects, as driven by the inherent toxicity of the medicine and defined by the profile of projected consumer behavior patterns.

Briefing materials and FDA presentations at the advisory committee meetings shed light on what constitutes acceptable LCS, SSS and AUS outcomes. Typically in presentations to advisory committees, FDA reviewers of LCS cite regulations that OTC medicine labels "shall be written in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use" (Appendix A)[60]. On this foundation, LCS reviewers characterize primary communication objectives (PCOs) with percentage correct answers below the 70th percentile as "not impressive" or "troubling results" indicating "low comprehension."[61]. A descriptor of "excellent results" indicating "very high comprehension" has been applied by LCS reviewers to describe for PCOs with correct consumer responses in the 90th percentile, and "well understood" for correct answers of directions for use in the 80th percentile or higher[62]. Results on more than a few PCOs in the 80-85% range may be viewed as concerning or ambiguous. Generally speaking, LCS results for consumers with lower literacy (i.e., less than the U.S. 8th grade reading level) run 10-20% lower in correct responses for approved first-in-class switches.

FDA accepts a hierarchical approach to interpreting results from LCS, as shown in the favorable review of levonorgestrel (emergency contraception), which had the following results by PCOs: >90% for: not for pregnant women, does not prevent sexually transmitted diseases, to prevent pregnancy after sex, and not for women allergic; 85-90% for side effects including nausea and vomiting, second pill 12 hours after first, and first pill within 72 hours; 80-84% for: first pill as soon as possible after sex, for severe abdominal pain seek immediate medical care; and <80% for: do not use if unexplained vaginal bleeding, for backup, not regular contraception[63].

For benchmarking SSS and AUS, a 5% incorrect self-selection rate was acceptable for levonorgestrel[64]. On the other hand, a 24% rate of incorrect self-selection of omeprazole for all "correct" criteria (i.e., heartburn > 2 days/week, > 18 years of age, not pregnant/lactating, not allergic to omeprazole, no contraindicated symptoms not reported to a health care professional,

no contraindicated medicines) led a FDA reviewer to conclude: "omeprazole is likely to be used by consumers with contraindicated symptoms"[65]. In the case of the December 2007 NDAC meeting on lovastatin, the appropriateness of correcting self-selection results (e.g., by including "mitigations" such as: an intention to talk to their doctor before use; giving a "reasonable rationale for treatment; or giving evidence of not understanding the self-assessment question") received close scrutiny. None of the mitigations had been defined *a priori* in the study design. About half of incorrect subjects in the lovastatin SSS at the 2007 NDAC meeting were mitigated, according to the FDA reviewer to NDAC, with the commentary that it cannot be verified that the subjects would actually talk to their doctor, and that reviewers and the company did not agree on a number of the mitigations[66]. Yet, even after the mitigations, only about 50% of subjects had correct self-selection on key communication objectives relating to cholesterol numbers (e.g., only 22% of participants knew their LDL level, and 43% had LDL too high for correct self-selection). While subsequent discussions between FDA and the company may have modified this perspective presented to NDAC, the point is that at the meeting a complex proposed label for deciding lovastatin's potential OTCness did not have ninety percentile self-selection scores similar, for example, to Plan B. For AUS, consumers in the orlistat study showed compliance with label directions in the 90th percentile and were described as "dos[ing] orlistat according to direction throughout the study."[67]. Because the adverse event profile of the parent Rx drug is usually well known and because of the limited size of AUS (e.g., n< 1,000), it is not atypical for AUS to have no new safety signals.

Finally, FDA has regularly used advisory committees to explore general concepts of OTCness. This process is helpful to air concerns and provides companies with guidance on the evidence base required for switch. From May 2004-October 2008, NDAC met eleven times either alone or jointly with other Rx committees to address scientific, medical and public health implications of switch (Table 3). Study design and analytical approaches were often emphasized at these meetings, and unique ideas on OTCness shared. For example, in the meeting on potential OTC availability for certain Rx dermatologic corticosteroids, FDA created a regulatory algorithm for addressing Hypothalamic Pituitary Adrenal (HPA) axis suppression (Figure 3)[68]. The decision tree represents a hierarchal systematic approach for considering when switch candidates in this category may, or may not, be eligible for OTCness with or without additional labeling.

DISCUSSION

Since the initiation of formal review of OTC medicine safety, efficacy and labeling in 1972, FDA has transferred over 106 ingredients and dosages to OTC availability. A significant outcome of this process has been a formalized framework for applying scientific and medical evidence to OTC Considerations of Rx-to-OTC switch (Table 2). The value of this type of experientially-derived evolving framework is that the latest information and scientific perspective is applied to decisions of OTCness. Further, from a regulatory standpoint for both government and industry, the framework allows a predictable and consistent approach to OTC Considerations of switch, creating fairness for a competitive drug development system. This framework also facilitates orientation of new advisory committee members to the scientific nuances of self-care with

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Table 3: FDA Advisory Committee Meetings on Product Category Issues Related to Switch

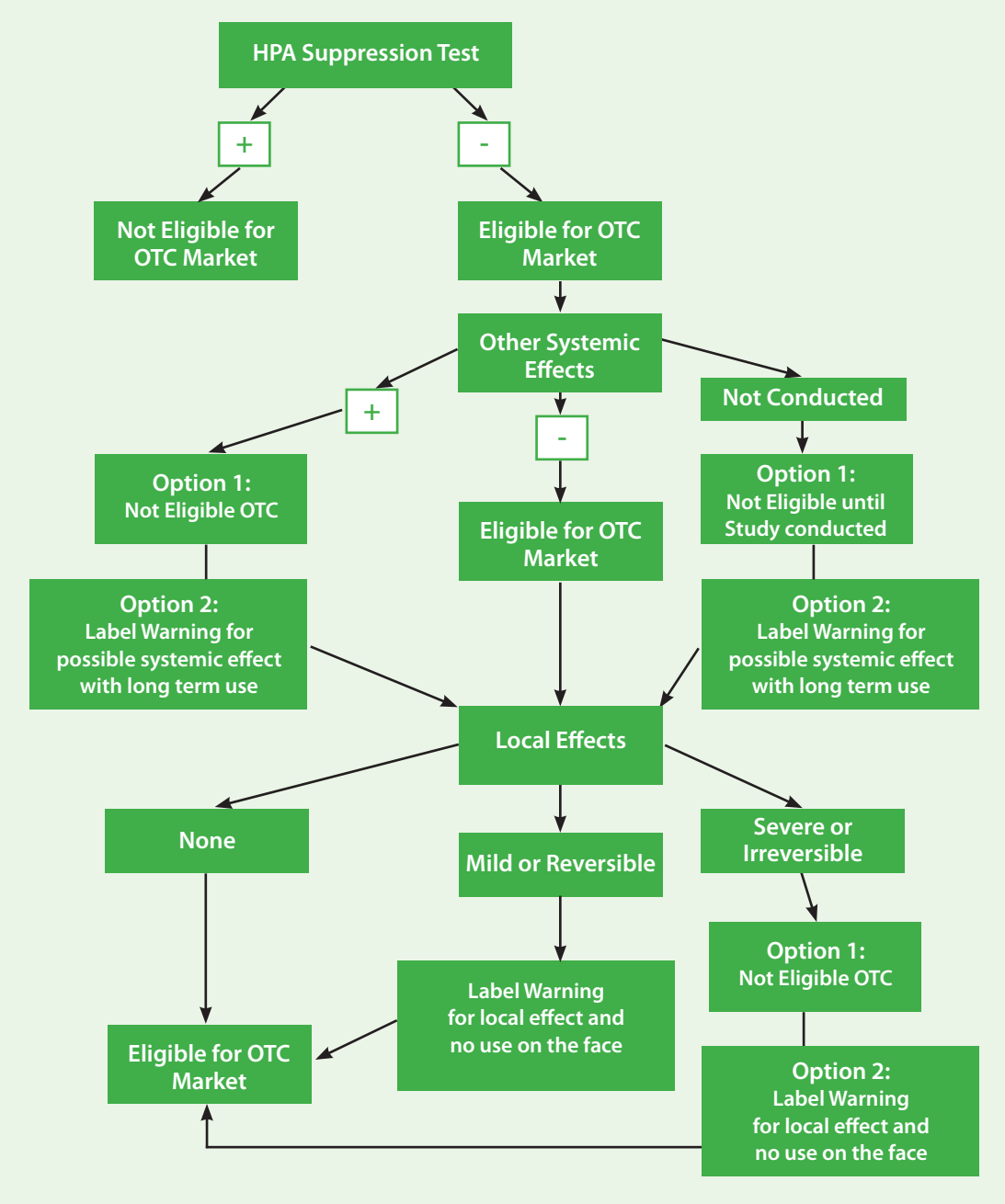
Topic	Advisory Committees	Date
Acyclovir for acute and suppressive management of recurrent genital herpes	Joint NDAC-Antiviral Drugs Advisory Committee	May19, 1994
Are there Rx asthma products suitable for switch?	Joint NDAC-Pulmonary Allergy Drug Advisory Committee	Nov 14, 1994
Potential for development of antibiotic resistance with OTC use of topical erythromycin in treatment of acne	Joint Dermatologic Drugs and Anti-Infective Drugs Advisory Committees (NDAC invited)	Nov 16, 1994
OTC Drug Facts Label (broadly related in terms of label comprehension considerations for switch)	Nonprescription Drugs Advisory Committee	Jul 14, 1997
Performance Expectations and Testing Requirements Antimicrobial Wash Products	Nonprescription Drugs Advisory Committee	July 29, 1998
Safety considerations related to the switch of dermatologic corticosteroid	Joint NDAC and Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)	March 24, 2004
Efficacy and labeling issues for the over-the-counter drug products used in treatment of tinea pedis in patients 12 years of age and over	Joint NDAC and Dermatologic and Ophthalmic Drugs Advisory Committee	May 6, 2004
(1) Microbiologic surrogate endpoints used to demonstrate the effectiveness of antiseptic products used in health care settings; (2) related public health issues; (3) trial design issues; and (4) statistical issues	Nonprescription Drugs Advisory Committee	Mar 23, 2005
Benefits and hazards of antiseptic products marketed for consumer use (e.g., antibacterial hand-washes and body-washes)	Nonprescription Drugs Advisory Committee	Oct, 2005
Analysis and interpretation of consumer behavior studies	Nonprescription Drugs Advisory Committee	Sept 25, 2006
Potential risks and benefits of 1) nonprescription, "over-the-counter" (OTC), availability of Tamiflu or Relenza MedKits	Antiviral Drugs and Nonprescription Drugs Advisory Committees	Oct 29, 2008

SOURCES: Derived from References 15 and 45.

nonprescription medicines. Overtly, it seems that the system has worked reasonably well, with only four first-in-class and one third-in-class switch application denied by FDA compared with at least 106 ingredients and dosages made available OTC since 1974. However, a number of switch proposals may have been brought before FDA in closed industry-agency meetings that have not been publicly disclosed. As a result, it is unclear the extent to which, for example, switch proposals have been discouraged by the agency (e.g., certain UK pharmacy-only switched products).

Accepted for publication 29 September 2011

Figure 3 - Regulatory Decision Tree Defining a Hierarchy of Clinical Importance of Side Effects: Adrenal Suppression for Topical Glucocorticoids



Source: Food and Drug Administration Executive Summary. Joint NDAC/DODAC Advisory Committee Meeting. Page, March 24, 2005. Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4099B1_01_FDA-Backgrounder.pdf

In the course of the evolution of OTC Considerations relating to switch, there has also been a concurrent growing emphasis on safety, evidenced by high profile drug safety issues affecting millions of patients and consumers worldwide (e.g., Vioxx, Bextra, Serevent, Rosiglitazone, Meridia, Baychol, Propulsid, organ-specific warnings for OTC NSAIDs and acetaminophen, among others)[69,70,71,72,73,74,75]. At the same time, priority emphasis has been placed on consumer-centric labeling of all products regulated by FDA, including foods (e.g., Nutrition Facts Label),

dietary supplements (e.g., Supplement Facts Label), prescription medicines (e.g., Medication Guides), non-prescription medicines (OTC Drug Facts Label), and user-friendly instructions for devices. Only labels of first-in-class Rx-to-OTC switches and devices are likely to be required to have premarket consumer behavioral and human factors testing, respectively. While other government agencies such as the Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom) do not require evidence from LCS, SSS and AUS prior to approval, the UK default system for nonprescription status is "P" (pharmacy only), in which a learned intermediary is available at the time of purchase. Of particular interest in this regard is that there are no published studies on comparative post-marketing outcomes of the U.S. and U.K. switches to determine what if any value is derived from a U.S. premarket requirement for LCS, SSS and AUS, or from a U.K. requirement of pharmacy (P) availability as a required condition of use. In the end, however, it is quite clear that FDA operates in a "fish bowl" and the U.S. requirements for consumer behavioral studies for first-in-class switches will likely continue, so as to provide some publically-visible projection of safety for decisions on switch.

Finally, for OTC drug development teams and new OTC regulatory personnel, the OTC Considerations in Table 2 provide a comprehensive framework to consider the evidence-base needed by FDA for evaluating switch. Further, as a practical matter, it is likely that emergent safety issues for currently marketed OTCs will be framed by the list of OTC Considerations as well. The references in this article provide a jumping off point for further in-depth assessment of study designs, analytical approaches and detailed outcome measures for LCS, SSS and AUS, including an example of a regulatory decision tree (Figure 3) for determining OTCness in the face of rare but serious adverse events potentially associated with a switch product.

A limitation of this review is that certain advisory committee background materials and transcripts are not available on the FDA website for meetings held prior to 1997, and thus were not included as source materials. While regulatory roots for safety, efficacy and labeling of OTC medicines extend deeply into the fabric of U.S. OTCness, as a practical matter it is latter era switches as included in this paper that are likely to be most relevant to modern day OTC Considerations. In addition, companies have meetings with FDA to discuss switch proposals, and useful feedback by the agency is often given in sufficient detail or implication to allow decisions as to whether to pursue the switch concept. A public listing of such meetings is not readily available, and as a result it is not possible to use "all public and non-public meetings" as a denominator for a first in class approval rate. Nonetheless, for the primary purpose of this paper, which is to derive an integrated perspective of that past 30 years of OTC switch approvals (i.e., Table 2), the concentration on FDA questions to NDAC on switch concepts that have risen to receive the public "light of day" is appropriate to the objective. Finally, study designs and data sources that might be used for drug safety evaluations were considered outside the scope of this paper.

CONCLUSIONS

A consolidated and updated framework of OTC Considerations for Rx-to-OTC switch has been

Accepted for publication 29 September 2011

developed through an in-depth assessment of FDA advisory committee deliberations of first-in-class switches. These OTC Considerations serve as a useful milestone to document the progress that FDA and industry have made in developing the evidence base for regulatory assessments of drug safety and effectiveness prior to OTC approval. OTC Considerations for Rx-to-OTC switch may also serve as a framework for OTC drug development and training of new OTC regulatory personnel.

Conflict of Interests: None

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Accepted for publication 29 September 2011

Appendix A

21 CFR §330.1
Available at: http://frwebgate2.access.gpo.gov/cgi-bin/TEXTgate.cgi?WAISdocID=9mZdJy/18/1/0&WAISaction=retrieve
U.S. Code of Federal Regulations Title 21—Food and Drugs
CHAPTER I—Food and Drug Administration, Department of Health and Human Services
PART 330_Over-the-Counter (OTC) Human Drug Which Are Generally Recognized as Safe and Effective and Not Misbranded.
Subpart A General Provisions
Sec. 330.1 General conditions for general recognition as safe, effective and not misbranded.

(4) Standards for safety, effectiveness, and labeling. The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and the final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in Sec. 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.

Accepted for publication 29 September 2011

Appendix B - Soller RW. Prescription-to-over-the-counter switch criteria. Drug Inf J. 2002;36:309-17.

Pre 1990 Switch Principles	**Pre 1998 Switch Principles**
Elaborated by CDER Director Carl Peck, MD, at the 1990 Annual Consumer Healthcare Products Association Research and Scientific Development Conference. Note the emphasis on the pharmacologic attributes of the drug. • Has a vigorous risk analysis been performed? • Has the drug been used for a sufficiently long time on the prescription market to enable a full characterization of its safety profile? • Does the drug have a large margin of safety? • Does the drug have special toxicity in its class? • Has the drug safety profile been defined at high dose? • Does the drug frequency of dosing affect its safe use? • Have possible drug interactions for drug been characterized? • What is the worldwide marketing experience of the drug? • What foreign countries market the candidate OTC? What is its experience in those countries? • What do the "use data" (from National Prescription Audit, the National Drug/Disease Audit, and/or other sources) show? • Has the efficacy literature been reviewed in a way to support the expected usage and labeling of the drug? • Is there a full understanding of the pharmacy-dynamics of the drug? • Is the minimally effective dose for the proposed OTC indication known?	Elaborated by Office of Drug Evaluation V Director Robert DeLap, MD, at the 1998 Consumer Healthcare Products Association Research and Scientific Development Conference. Note the emphasis on the consumer use and label comprehension. **Fundamentals** • Can the condition be adequately self-diagnosed? • Can the condition be successfully self-treated? • Is the self-treatment product safe and effective for consumer use, under conditions of actual use? **Points to Consider** • Is there a need for physician evaluation of the condition? • What is the nature and severity of adverse effects of consumer misdiagnosis and delay in correct diagnosis? • Regarding effective drug use, what is the nature of consumer understanding of drug use? • What is the consumer's understanding of the expected benefit? • Do consumers have the ability to assess treatment effect? **Safe Product Use** • What is the consumer expectation of safety? • What is the consumer understanding of drug directions for safe use? • What is the consumer's understanding of what to do if the drug is not working? • What is the consumer's ability to identify adverse effects, and the consumer ability to determine when adverse events may require professional care?

Accepted for publication 29 September 2011

Appendix C - FDA Definitions of Label Comprehension, Self-Selection and Actual Use Studies

SOURCE: Food and Drug Administration. FDA advisory committee briefing document. Background materials for the Joint session of the Nonprescription Drugs Advisory Committee and the Endocrinology and Metabolic Drugs Advisory Committee. Pages. 2-4. December 13, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4331b1-01-FDA.pdf

See also: Food and Drug Administration. Guidance for Industry Label Comprehension Studies for Nonprescription Drug Products. August 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf

"A label comprehension study determines whether a general population of potential users and non-users of the study drug can understand the information on a product label. No drug is administered. The study population is enriched with a low literacy cohort (whose literacy level has been determined by a validated literacy testing instrument) and sometimes with other cohorts of special interest. The study is a critical element to the label development process for an OTC drug and, if it succeeds, it demonstrates that respondents understand the tested label intended to accompany a product to market or that will be used in a self-selection study or an actual use study (see below). Label comprehension studies only test comprehension and may not accurately predict consumer behaviors (self-selection, purchase decisions, adherence, etc.)."

"A self-selection study determines if potential OTC users of a drug (some of whom could use the product and some of whom should not use the product), after reading the product label, correctly decide whether or not the product is appropriate for their personal use based upon the indications and warnings. A low literacy cohort and other subpopulations of interest are enrolled. No drug is administered."
Note that based on a September 2006 advisory committee meeting, FDA recommends use of a hierarchy approach to self-selection studies, in which "analysis of self-selection data [is] based upon a pre-determined hierarchy of labeling information that would dictate success in self-selection." In other words, "a ranking of importance (hierarchy) of certain labeling messages [is thought to be] useful in determining self-selection success."

"The purpose of an actual use study is to simulate the OTC use of a product so we can attempt to predict if a drug would be used properly, safety, and effectively in the OTC setting. Study participants receive the product labeling and take the study drug home and use it. Often there is a study diary, but the concept behind a well-designed actual use study is that the data collection methods should intrude as little as possible so as not to bias the study results."

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