OTC Squares
February 22, 2005
Questions and Correct Answers

Game 1: "Looking Back, Envisioning the Future" (History and Organization of the Division of OTC Drug Products)

1. What U.S. Presidential candidate had a key role in the establishment of OTC drugs as a separate class of drugs?
Hubert Humphrey, 1968 Presidential Campaign

2. What U.S. President was in the White House when the OTC Drug Review began?
Richard Nixon. The OTC Drug Review was initiated by publication of a final rule in the Federal Register on May 11, 1972.

3. Approximately how many FTEs (Full Time Equivalent employees) work in the Division of OTC Drug Products?
   A. 25
   B. 40
   C. 60

B. 40

4. What are the 4 review disciplines that comprise the division?
project managers, medical officers, interdisciplinary scientists, and a social scientist

5. What review discipline has always been part of the division?
The interdisciplinary scientist ("IDS").

6. When did medical officers initially join the division?
   A. 1970s
   B. 1980s
   C. 1990s

C. 1990s. 1993?

7. Who was the first director of the OTC Drug Review?
Gary Yingling

8. The Office of New Drugs plans to reorganize in 2005. How does OTC fit into the new organization?
Plans are for the OTC Division to become an Office within the Office of New Drugs.

9. About how many drug categories does the OTC Division regulate?
   A. 20
   B. 50
   C. 100

C. 100

10. Of the approximately 3900 drugs reviewed under DESI (the Drug Efficacy Study Implementation program), how many were OTC drugs?

A. 42
B. 420
C. 840

B. 420. These 420 OTC drugs were chosen as broadly representative of the whole range of the OTC market. The National Academy of Science-National Research Council panels' conclusions, were that only approximately 25% of the drugs reviewed had an indication that was classifiable as effective.

11. What was the first OTC drug monograph to be finalized?
The Antacid Monograph, 1974

12. What was the first "direct-to-OTC" NDA to be approved after the inception of the OTC Drug Review?
doxylamine succinate, as a nighttime sleep-aid (Unisom)

13. What celebrity act does Charlie Ganley impersonate at the annual Division holiday party?
Johnny Carson as Carnac the Magnificent

14. When was the "first" Office of OTC Drugs established?
1993

15. When was the "first" Office of OTC Drugs re-organized as a division?
CDER reorganization around 1996.

16. Where was FDA located prior to the Parklawn Bldg?
Crystal City, VA

17. What were the IDS team leaders called during the 1980s?
They were called "branch chiefs".

18. Which of the OTC "celebrities" has had a close encounter with a midwestern tornado?
Deputy Director Curt Rosebraugh.

19. Next year is the centennial of what important piece of legislation affecting the regulation of food and drugs in this country?
Pure Food and Drugs Act of 1906

Game 2: "Rules and Regulations: Antiperspirants to Zinc Oxide" (OTC Monographs)

1. Each OTC drug monograph is intended to cover:
   A. a drug product
   B. an active ingredient
   C. a drug category

C. a drug category

2. How many "steps" are required in OTC drug monograph rulemaking?

Three. ANPR, TFM, FM

3. The initial number of drug categories to be covered by an OTC drug monograph under the OTC Drug Review in 1972 was:
   A. 26
   B. 47
   C. 88

A. 26

4. Approximately how many panels did FDA form to establish the monograph system in 1972?
   A. 6
   B. 16
   C. 26
   D. 36

B. 16.

5. Each Advisory Review Panel contained seven voting members. (T/F)

True.

6. There was at least one toxicologist and one pharmacist on each Advisory Review Panel. (T/F)

True.

7. Approximately what percent of monographs are final?
   A. 25%
   B. 50%
   C. 75%
   D. >90%

C. 75%

8. Is FDA considering the development of any new monographs (not considered by the advisory review panels of the 1970s)?

Yes. The 12/31/03 Call-for-Data Notice requested data/information on nasal moisturizers, vaginal lubricants, urinary analgesics/antiseptics.

9. Which monograph was the first to finalize?

The Antacids Monograph (11/12/73 – 6/4/74).

10. Which monograph has taken the longest to finalize, as of today?
The Antimicrobial/Antiseptic Monograph.

11. What happens to an active ingredient that is still "Category III" at the FM stage?
The active ingredient becomes nonmonograph for that indication.

12. What court decision ended Category III status after an FM?
Cutler v. Kennedy

13. An active ingredient in an OTC drug product that was not on the U.S. market as of May 11, 1972 is still eligible for inclusion in an OTC drug monograph. (T/F)
True. (Limit your answer to something like: "True, I believe there are mechanisms by which these active ingredients can still be added to existing monographs." The following question will address the mechanisms by which an active ingredient can be added to an existing monograph.)

14. By what mechanisms can an active ingredient be added to an existing monograph?
Citizen petition or TEA

15. To submit a TEA, a product must have prior marketing history in at least 3 countries. (T/F)
False. A marketing history in one country may be sufficient depending on the time and extent of marketing in that country.

16. The review of a TEA is confidential. (T/F)
True. Submission of a TEA will be handled as confidential until such time as a decision is made on the eligibility of the condition for consideration in the OTC drug monograph system (Ref. 21 CFR 330.14(d).)

17. How long is the comment period typically after a proposed rule, or TFM?
90 days.

18. Where can all documents used in an OTC drug review rulemaking be found?
Division of Dockets Management

19. What primary regulation(s) covers the monograph process?
21 CFR 330 ("Part 330 – OTC Human Drugs which are Generally Recognized as Safe and Effective and Not Misbranded"). The individual drug monographs follow ("Part 331 – Antacid Products for OTC Human Use…")

20. 21 CFR 310.545 contains a list of ingredients for many of the drug categories. What's the purpose of this list.
Identifies ingredients that are nonmonograph for specified use(s).

21. An OTC active ingredient can fall under more than one monograph. (T/F) Name an example.
True. (e.g., zinc oxide – Sunscreen and Anorectal Monographs)

22. Which of the following monographs does not provide information for professional labeling?

A. Antimicrobial
B. Cough and cold
C. Internal analgesics
D. Ophthalmic

Antimicrobial.

23. Any active ingredient included in an OTC drug monograph must also be recognized in an official compendium (e.g., the U.S. Pharmacopeia). (T/F)

True.

24. Products covered by a published tentative final monograph (proposed rule) may continue to be marketed even though a final rule has not been issued. (T/F)

True.

25. An OTC drug product that conforms to all the conditions in an applicable OTC drug monograph still needs to be manufactured in compliance with cGMPs (current good manufacturing practices). (T/F)

True.

26. Drug manufacturers must submit data to FDA demonstrating that all *inactive* ingredients in a monograph drug product are safe and do not decrease the effectiveness of the product. (T/F)

False.

GAME 3: "Just the (Drug) Facts" (OTC Labeling)

1. Must ***Drug Facts*** information always be included in a "box" or similar enclosure set off by barlines?
No. § 201.66(d)(10)(v). If the required information takes up >60% of surface area, boxes or other enclosures may be omitted if the ***Drug Facts*** labeling is set off from the rest of the labeling by use of color contrast.

2. What is the minimal font size for text in the ***Drug Facts*** box?
6-point type. § 201.66(d)(2)

3. Do ***Inactive ingredients*** for drug products (that are not also cosmetic products) have to be listed in alphabetical order?
Yes. § 201.66(c)(8)

4. What type of study measures consumer *behavior*? Actual use or label comprehension?
An actual use study. Merely understanding what a label says doesn't mean consumers will behave appropriately.

5. Homeopathic OTC drug products are subject to ***Drug Facts*** labeling requirements. (T/F)
False. Drug products labeled as homeopathic AND listed in the Homeopathic Pharmacopeia of the United States are outside the scope of § 210.66. Labeling for these products is covered in the Compliance Policy Guide 7132.15 on "Conditions Under Which a Homeopathic Drug Product May be Marketed."

6. An ingredient claimed to be a pharmacological adjuvant should be listed in the label as an:
   A. active ingredient
   B. inactive ingredient

A. active ingredient

7. On its own initiative or in response to a written request from a manufacturer, FDA can exempt or defer one or more of specific labeling requirements specified in § 201.66. (T/F)
True. If strict adherence would make the labeling inapplicable, impractical, or contrary to public health and safety. (§ 201.66(e))

8. Labeling on drug products marketed in the United States in predominately Hispanic areas, may be labeled in Spanish only. (T/F)
False. Labeling must be in English and may include Spanish if the manufacturer wishes. Products distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is Spanish may be labeled solely in Spanish. (§ 201.15(c)(1))

9. In the fall of 2005, labeling for all prescription drugs will have to be written in a machine-readable format (replacing electronic labeling prepared in Microsoft Word or Adobe Acrobat). All FDA-regulated products (including OTC drug products and medical devices) will have to use this new format by the end of 2007. What is the new format?

Structured Product Labeling (SPL) based on XML (a relative of HTML used on the Internet)

10. ***Drug Facts*** headings, such as ***Uses, Warnings, and Directions***, must appear in bold, underlined typeface. (T/F)
False. Bold, italics

11. What must be included in the ***Drug Facts*** box to print it on multiple carton panels?
A visual graphic (arrow) signaling continuation to adjacent panel [to] retain the required order and flow of headings and info. § 201.66(d)(5)

12. Do ***Active ingredients*** for drug products have to be listed in alphabetical order?
Yes. § 201.66(d)(6)

13. Is a ***Questions?*** or ***Questions or comments?*** section required in ***Drug Facts*** labeling?
No. Draft Guidance. § 201.66(c) Content Requirements.

14. Can a bulleted statement appear on the same line as a heading or subheading?
Yes - but not in the ***Warnings*** section. § 201.66(d)(6)

15. Given that there IS an outside container, if an immediate container is too small to bear label information required by the Act, it does not need to be labeled with which of the following:
    A. the established name of the drug
    B. Warning: KEEP OUT OF REACH OF CHILDREN
    C. an identifying lot or control number
    D. manufacturer, packer, or distributor name

B. Warning: KEEP OUT OF REACH OF CHILDREN

16. In a study to determine consumer preference regarding the format of OTC drug product labels, the most important factor was:
    A. the presence of a title (i.e., "***Drug Facts***")
    B. the appearance of "***Warnings***" before "***Directions***"
    C. the presence of barlines and hairlines
    D. the placement of "***Active ingredients***" at the top of the label

A. the presence of a title (i.e., "***Drug Facts***")

17. Labeling regulations allow flexible labeling of indications (***Uses***) as long as the language is truthful and not misleading. (T/F)
True.

18. ***Drug Facts*** labeling must be included on the immediate container of an OTC drug product whether or not it is contained within an outer carton or package. (T/F)
False. Drug Facts must appear on the outside container of the retail package or on the immediate container if there is no outer carton. § 201.66(c)

19. Manufacturers must specify, if using the term “infant” on labeling of an OTC drug product, whether this refers to a child not more than one year of age or a child not more than two years of age. (T/F)
True. § 201.19. Apart from regulations affecting special dietary foods (§ 105.3(e)) in which an infant is defined as not more than 12 months old, FDA has not established a definition for infant.

20. There is no exception to the regulation that expiration dates, where required by § 211.137, shall appear on BOTH the immediate and outside containers of a drug product. (T/F)
False. The expiration date doesn’t need to be included on both the immediate and outside containers of drug products if such information on the immediate container can be seen through the outer packaging. (§ 201.17)

21. An identifying lot or control number must be included on the immediate container of a drug product. (T/F)
True. This is specified in § 201.10(i)(1)(iii)

22. How many subjects are recommended in the ICH (International Committee on Harmonization) Guidelines for an actual use study?
There is no such recommendation in the ICH Guidelines.

GAME 4: "From Script to (Open) Shelf" (Rx-to-OTC Switches)

1. Where is the procedure for making a switch described?
In a MaPP (Manual of Policies and Procedures)
6020.5, "NDA General Procedures: OTC Marketing and Rx-to-OTC Switch"

2. An NDA sponsor seeking to convert its prescription product to OTC status should submit a supplement to its existing NDA to the Division of Over-the-Counter Drug Products. (T/F)
False. Submit to SSMRD (Specific Subject Matter Review Division) that reviewed the prescription product

3. An applicant for an Rx-to-OTC switch must conduct a label comprehension and actual-use studies. (T/F)
False. These studies are only required if label communication of safety/effectiveness is in question.

4. Following an approved Rx-to-OTC switch, the product can no longer be marketed as a prescription product. (T/F)
False. In the case of a modified switch, the product may continue to be marketed Rx. Usually this involves marketing the product at a lower OTC dose (e.g. naproxyn) or for different uses.

5. The initial Rx-to-OTC switch in a product class requires sign-off at:
   A. Division level or higher
   B. Office level or higher
   C. Center level or higher

B. Office level or higher. Note: the Division of Over-the-Counter Drug Products becomes an Office (probably the Office of Nonprescription Drug Products) after reorganization of the Office of New Drugs (OND).

6. True or False - Pharmaceutical companies ALWAYS need endorsement from FDA to initiate a switch request.
False. The company that developed the drug for prescription use (and therefore knows the most about the drug) can initiate a switch request of an Rx product with or without FDA's endorsement.

7. Does FDA regulate launch advertising for switch products?
No. FTC (Federal Trade Commission)

8. Are user fees associated with switch applications?
Yes.

9. Advisory Review Panels recommended that 27 Rx drugs be switched to OTC status. FDA allowed 18 switches. Name one.
Hydrocortisone, hydrocortisone acetate - antipruritic (anti-itch)
Diphenhydramine hydrochloride - antitussive
Oxymetazoline - nasal decongestant

Stannous fluoride (dental) rinse - dental rinse
Sodium fluoride rinse - dental rinse
Pseudoephedrine hydrochloride, pseudoephedrine sulfate - nasal decongestant

10. The "switch regulation" allows *any interested party* (not just the manufacturer of an Rx product) to petition the FDA to switch any prescription medication to OTC. Dextromethorphan, an antitussive, was switched by this route. (T/F)
True.

11. An advisory committee is always convened for an Rx-to-OTC switch. (T/F)
False. In cases where the switch product is in a line of similar products already switched, where there are no new or outstanding issues, and where the decision to switch the first in the line of these similar products was presented to the advisory committees and the ACs recommended approval, it is not necessary to convene a joint advisory committee meeeting. (MAPP 6020.5)

12. The number of ingredients or dosage strengths that have made an Rx-to-OTC switch (or been newly approved as OTC drug products) since 1976 is nearest:
A. 30
B. 100
C. 200
B. 100. Actually the number is very close to 90. This translates to over 700 OTC products.

13. The switch process can actually work in reverse (i.e., OTC-to-Rx) (T/F)
True. If FDA obtains evidence of a significant safety problem with an OTC product or ingredient it can transfer the product or ingredient back to Rx status (or remove it from the market altogether). Examples are the antimicrobial hexachlorophene in 1977 and the laxative danthron in 1987.

14. The switch process in the United Kingdom is very similar to the process in the United States. (T/F)
True. The Medicines and Healthcare Regulatory Agency (MHRA) in the UK acts very much like the FDA in considering the reclassification of medicines from "prescription only" to "pharmacy" or from "pharmacy" to "general sales list." Complex reclassifications are considered by the Committee on the Safety of Medicines which is analogous to an Advisory Committee in this country.

15. Can FDA initiate a switch on its own?
Yes (theoretically). FDA has only done this once. In 1982 FDA published a TFM which included metaproterenol for asthma. This was rescinded a short time later.

16. More than 10 Rx products have been switched to OTC since February 2000. Name one.
Loratidine (in Claritin)
Butenafine hydrochloride (in Lotrimin Ultra)
Omeprazole magnesium (in Prilosec OTC)

17. (OTC) actual use studies should be conducted under an IND but label comprehension studies do NOT have to be conducted under an IND.
True. Because the results of actual use studies could lead to significant changes in product labeling. (MAPP 6020.5).

18. The review of primary effectiveness data and safety results from controlled clinical trials is ordinarily the responsibility of review team members from the SSMRD (Specific Subject Matter Review Division) and not DOTCDP. (T/F)
True. (MAPP 6020.5)

19. Labeling of switched products must conform to the wording/labeling in OTC drug monographs for similar products. (T/F)
False. Not if the products were marketed under an approved NDA (but every effort should be made to keep labeling for NDA products as similar as possible to similar monographed OTC products. (MAPP 6020.5)