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# Food Drug Cosmetic Law JOURNAL

Additional Papers Presented at the 18th Annual Educational Conference of the Food and Drug Law Institute, Inc. and the Food and Drug Administration

A COMMERCE CLEARING HOUSE PUBLICATION
PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis contributions and comments are invited.

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# FOOD DRUG COSMETIC LAW JOURNAL

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# REPORTS

## TO THE READER

**Eighteenth Annual Educational Conference of the FDLI and the FDA.** The following papers were presented at the 18th Annual Conference of the Food and Drug Law Institute and the Food and Drug Administration, which was held in Washington, D. C. on December 3rd and 4th, 1974.

*Taylor M. Quinn* is Director of the Division of Regulatory Guidance of the Bureau of Foods in the Food and Drug Administration. His article, "FDA Plans and Activities in the Food Area," beginning on page 200, is a brief outline of the planning activities of the Bureau of Foods in five specified program areas—Food and Color Additives, Industrial Chemicals and Heavy Metals, Food Sanitation and Quality Control, Nutrition and Special Dietary Activities, and Economic Activities.

*John A. Wenninger,* Deputy Director of the Division of Cosmetics Technology in the Food and Drug Administration, is the author of "Voluntary Cosmetic Product Experience Reporting—The FDA Viewpoint." This article, which begins on page 204, reports on the progress and substance of the cosmetic experience program and presents data collected during its first reporting period.

In his article "Current Problems and Trends in Testing of Human Drugs—Especially in Regard to Institutional Review Committees," *Craig D. Burrell* discusses the need for and the regulations concerning safeguards in human experimentation. Mr. Burrell is Vice-President of Sandoz, Inc. and his article begins on page 213.

"Product Experience Reporting — An Industry View" is the title and subject of an article by *Michael Pietrangelo* on page 219. Mr. Pietrangelo is Secretary and Legal Director of Plough, Inc.

*Robert P. Giovacchini* discusses the determination of safety of ingredients in cosmetic products in "The Significance of the Over-the-Counter Drug Review with Respect to the Safety Considerations of Cosmetic Ingredients." Dr. Giovacchini, whose article begins on page 223, is Vice-President of Corporate Product Integrity in the Gillette Company.

*Eugene I. Lambert,* General Counsel of the Cosmetic, Toiletry and Fragrance Association, is a partner in the law firm of Covington & Burling. Mr. Lambert reviews the development of a regulation concerning labeling of cosmetic ingredients in an article on page 228. The article is titled "Working Out Cosmetic Ingredient Labeling or 'The Little Engine That Could.'"

*Robert M. Schaffner* presents an overview of the Food and Drug Administration's activities in the cosmetic field in his article "What's on the Horizon? FDA's Plans, Priorities and Activities for Cosmetics." Written by the Associate Director for Technology of the Bureau of Foods in the Food and Drug Administration, the article begins on page 233.

*Larry R. Pilot,* Acting Director of the Division of Compliance of the Bureau of Medical Devices and Diagnostic Products in the Food and Drug Administration explains the reasons for and the methods of product recall. His article on page 239 is titled "Regulatory Options and Ramifications of Recall."

"*In Vitro* Diagnostic Regulations—A Regulatory Ordeal" traces the history of the Food and Drug Administration's methods in regulating this industry. Written by *Richard D. Manthei,* Corporate Director of Regulatory Affairs and Quality Assurance in the American Hospital Supply Corporation, the article begins on page 247.

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Food·Drug·Cosmetic Law Journal

# FDA Plans and Activities in the Food Area

By TAYLOR M. QUINN

Mr. Quinn Is Director of the Division of Regulatory Guidance of the Bureau of Foods in the Food and Drug Administration.

AS YOU KNOW, this session is supposed to be about what's on the horizon. I would like to be able to say that we knew with certainty what was going to be on the horizon in the food area for the next year. However, as you know, we can't be sure of this. I don't think any of us foresaw the mushroom crisis and all the problems that it caused us and it may be that some unforeseen crisis will again occur in the immediate future which would cause us to change our plans and activities. However, let's hope that this year we will be able to proceed roughly along the lines that we have set for ourselves. With this hope in mind, I will try to give you some insight into our plans.

## Continuation of Activities

As you are all aware, over the past few years the Food and Drug Administration (FDA) has instituted a number of new initiatives in the food area. I do not believe that you will see any startling new initiatives in the next year in the food area, but rather, a continuation of the activities we have already started. This will involve adding bits and pieces to the new activities to round them out to what we had in mind and also, enforcement of these initiatives.

As most of you know, our planning activities in the Bureau of Foods are set up under a program manager system. This involves

breaking our plans into a number of segments or programs, each of which is under the overall supervision of a separate program manager. In this presentation, I will attempt to use this program system to outline our activities, although in the interest of brevity I am going to combine some of the program areas. The five areas I would like to discuss today are Food and Color Additives, Industrial Chemicals and Heavy Metals, Food Sanitation and Quality Control, Nutrition and Special Dietary Activities and finally, Economic Activities.

In the Food and Color Additives area, we expect to continue our current activities. We have recently published a large package of regulations in the food additives area and expect to publish a few more in the next year. Our GRAS (generally recognized as safe) review program seems to be coming along quite well and we expect to continue and, hopefully, accelerate our activities in this area. In the enforcement area, we expect to continue a program of inspections, sample collections and analysis to determine if the food additives being used in food meet the Food Codex specifications and to determine if there is any misuse of food and color additives in the food supply.

## Market Basket Surveys

The Industrial Chemicals and Heavy Metals category includes such things as pesticides, polychlorinated biphenyls (PCBs) and heavy metals such as lead and cadmium. We expect to continue our market basket surveys to obtain information on the residues of pesticides, PCBs and selected metals in the dietary intake of people in the United States. These surveys will include both adult diets and infant and toddler diets. We use this primarily to determine trends and to help us program follow-up activities in these areas. We have published a regulation concerning permissible PCB levels in foods and food packaging. We are going to spend some time this year looking at both domestic and imported foods and their packaging to make sure that these levels are not exceeded. As some of you are aware, we have had some difficulties in the past with excessive leaching of lead and cadmium from dinnerware. We expect to continue monitoring and taking necessary legal actions to insure that harmful amounts of these heavy metals do not leach into consumers' foods from their dinnerware.

Food Sanitation and Quality Control is an area in which the FDA has always invested a large amount of its resources and we expect to continue that in the next year. We are well into our new

approach involving hazard analysis and critical control point (HACCP) inspections and expect to expand this approach for other areas in the food field. For those of you not familiar with the HACCP approach, it involves placing greater emphasis on inspection of plant quality control systems and the management of these systems by appropriate plant personnel. We also expect to make a large number of sanitary inspections to insure that the industry is taking the proper steps to keep our food supply from being adulterated with filth or poisonous substances. We also expect to put considerable manpower into collection and examination of samples of imported food for the same purpose.

## Microbiological Quality Standards

We are continuing to work on good manufacturing practice regulations and hope to issue several of these in the next year. We also expect to continue our studies on additional foods to obtain base data to allow us to set microbiological quality standards for foods and also to update our defect action levels for filth and extraneous matter in foods.

Things have changed just a bit in the Nutrition and Special Dietary Acvtities areas. We expected that our nutrition-labeling regulations would be fully effective at the end of this year, but, as those of you who read the *Federal Register* know, we published a notice on November 14, 1974 extending the effective dates for compliance to June 30, 1975 and also made provisions for individual extensions to the end of 1975. We are informed, however, that many products bearing nutritional labeling either are already on the market or will be on the market very shortly, and we expect to monitor these products to see if they are meeting the requirements of nutrition-labeling regulations.

On June 14, 1974, we published a proposal entitled "General Principles Governing the Addition of Nutrients to Foods" which set forth a proposed set of principles to govern the addition of vitamins, minerals and protein to foods. At that time, we also published several more proposed nutritional quality guidelines. We have received a large number of comments on these proposals and are currently evaluating them. We hope to finish our evaluation and publish final proposals in these areas in the near future. We are also completing our review of regulation 125.6 covering foods for use in weight control and hope to publish a final order on this subject also in the near future.

## Six-Month Extension

In the Economic Activities area, we also had a number of regulations such as the flavor regulation, several common or usual name regulations and a number of food standards which were expected to be fully effective at the end of the year. These, too, were given a six-month extension on November 14. Therefore, there will be an additional grace period before these regulations will be enforced. This does not mean that we will not be enforcing the economic provisions of the Food, Drug, and Cosmetic Act. We will continue to devote manpower to this area and we will continue to take the necessary regulatory actions to see that misbranded foods are not marketed.

We also expect to continue in the regulation-writing business in this area. In the June 14 issue of the *Federal Register* that I mentioned earlier, we published a number of proposals concerning such things as misleading vignettes, declaration of ingredients, common or usual names and portion sizes. We have received many comments on these proposals and are currently digesting them with the expectation that final regulations will be issued in the near future. We also expect that you will see a number of other proposals for common or usual names within the next year. As I said earlier, we are not proposing any startling new initiatives. What we expect to do instead is to fill in the holes and solidify the initiatives that we have previously started and proceed with our task of insuring a safe, clean and properly labeled food supply for the nation. **[The End]**

# Voluntary Cosmetic Product Experience Reporting— The FDA Viewpoint

By JOHN A. WENNINGER

Mr. Wenninger Is Deputy Director of the Division of Cosmetics Technology in the Food and Drug Administration.

FOR THIS WORKSHOP SESSION, I was asked by the moderator to comment on the voluntary cosmetic product experience reporting program. In preparation for my discussion, I could not help but take note of the fact that today we are meeting for the fourth time at a Food and Drug Law Institute, Inc. (FDLI) Cosmetic Workshop Session to discuss the voluntary programs. We have come a long way in the past four years and it is with great satisfaction that today I can say we have a fully operational voluntary program for cosmetics at the Food and Drug Administration (FDA). We must not, however, lose sight of the fact that voluntary programs cannot be successful unless they receive the backing of a substantial segment of the regulated industry. Today I will try to answer a few of the questions raised during the past year, which hopefully will help to increase participation in our programs.

As most of you are aware, the voluntary cosmetic regulatory program is designed to support the efficient enforcement of the Food, Drug and Cosmetic Act by making available information pertaining to the manufacture and composition of cosmetic products, as well as data regarding consumer adverse reactions. The information will permit the FDA to correlate in a meaningful way the products and ingredients which are associated with allergic reactions or other injury reports that are alleged to be the result of the use of cosmetic products.

The program is divided into three parts:

(1) Voluntary Registration of Cosmetic Product Establishments;

(2) Voluntary Filing of Cosmetic Product Ingredient and Raw Material Composition Statements; and

(3) Voluntary Filing of Cosmetic Product Experiences.

Parts 1 and 2 of this program became effective on May 29, 1972 and September 23, 1972, respectively. Part 3, the experience reporting program, became effective on March 8, 1974 and the initial reporting period for this program was established as January 1 to June 30, 1974.

## Industry Concerns

At last year's cosmetic workshop, Mr. Lambert, representing the Cosmetic, Toiletry and Fragrance Association (CTFA), raised several legal and practical issues regarding the product experience program at the FDA. The issues raised, I believe, can be restated in general terms as follows:

(1) What is the scope of protection from public disclosure for information submitted under the product experience reporting program?

(2) What is the meaning of an "audit" as it relates to the program for product experience reporting?

(3) What constitutes an adequate screening procedure for product experience reports?

## Confidentiality of Information

The first issue raised concerning the confidentiality of voluntarily submitted information will be resolved when the Agency publishes the final regulation on Freedom of Information (FOI). I am advised that this regulation will be published in the *Federal Register* in the near future. We realize that there has been a certain reluctance by some to participate in the voluntary cosmetic program until the Agency clarifies its position on this matter. Procedures being established by regulation will end this concern. Basically, the regulation will retain the provision expressed in the proposal of May 5, 1972, wherein the name of the manufacturer and the name of the product associated with reportable experiences will be held in confidence by the FDA when such information is voluntarily submitted by the firm marketing the product. In contrast, however, cosmetic adverse reactions reported to the Agency by consumers will be available for public disclosure without the deletion of the name of the firm and the brand name of the product. Time will not permit a more complete discussion of the confidential status of voluntarily submitted product experience information. However, we are making available publicly, at this session, the first tabulation of data received for the first reporting period of the volun-

tary product experience reporting program. The first reporting period covered the months of January through June of 1974. This report will give you some insight into the type of information that will be available to all under this program. Later, I will discuss this data in more detail.

## The Meaning of the Term "Audit"

I would now like to clarify the FDA viewpoint on the meaning of the term "audit" as it relates to product experience reporting. The regulation provides that firms filing product experience reports may either file all "reportable experiences" or file only those experiences determined to be "reportable experiences" after using an appropriate "screening procedure." It is the Agency's position that the submission of information on product experiences that have been appropriately screened to eliminate any unfounded or spurious complaints would be more meaningful. When a screening procedure is used, the regulation provides that:

> the procedure be on file with the FDA and subject to public inspection;
>
> the procedure be designed to provide a reasonable basis for concluding that the alleged injury *did not* occur in conjunction with the use of the product;
>
> the procedure be subject to an FDA audit to determine that it is consistently being applied and is not disregarding reportable information.

Quite frankly, we thought that the regulation was sufficiently explicit on this point to avoid any misunderstandings. We will be conducting audits in a manner that will involve a methodical examination of records to verify that the screening procedure is consistently being applied and reportable experiences are not being disregarded. Circumstances alone will dictate the extent of any FDA-conducted audit. We can foresee circumstances where it will be necessary for us to carry out a comprehensive review of all reports and correspondence to verify that the screening procedure is being properly followed. We would also like to point out that in adopting the voluntary product experience reporting program, the Commissioner of the FDA reserved the right under 21 CFR 174.5(f) to request as much additional information from persons submitting reports as he deems appropriate, and that records should be retained for a period of three years by those participating in the program. In extreme circumstances, we see no reason why an audit of a screening procedure should not be combined with a request for additional information that the Commissioner deems appropriate to protect the public health and welfare. It

must be remembered that such a request is provided for in the regulation, whether or not a screening procedure is used.

## Screening Procedures

The final issue raised concerned the question of what constitutes an adequate screening procedure for product experience reporting. I have reviewed those submitted so far and they vary from inadequate to very good. The CTFA screening procedure, if conscientiously followed by an individual firm and applied with good judgment, would in my opinion, be a good procedure to follow. I believe that the only way to effectively evaluate the screening procedures on file will be through the auditing process. Once we have had the opportunity to conduct such audits, we will be able to make some general statements regarding the key elements needed for an adequate screening procedure.

## Cosmetic Product Experience Data for First Reporting Period, January—June, 1974

As I had indicated earlier, we are making available publicly the first tabulation of cosmetic product experiences. In Table 1* we have tabulated the data reported on FD Forms 2706 "Summary Report of Cosmetic Product Experience by Product Categories." This data is based on information received for the first reporting period, January through June 1974, as received by the FDA as of November 30, 1974. Product experience reports for the first reporting period were requested to be filed by September 30, 1974. However, we are continuing to accept late filings for the program.

One must keep the results being reported in perspective. The most important fact to remember is that only 85 firms are represented in the tabulation. This is not a significant number when one considers over 800 firms have registered establishments and nearly 600 firms have filed formulations. For the 85 firms reporting, 19 used a screening procedure and 66 did not. The data tabulated does not reflect whether or not the reportable experiences were the result of the use of a screening procedure. The screened and unscreened are grouped together for the first report because of the low number of firms reporting.

It should be pointed out that only 85 of 92 firms submitting product experience reports are included in Table 1. For administrative reasons, the data from seven firms could not be included in the tabulation at this time.

* For Table 1, see pages 208—211.

It is of importance to note, however, that the product experiences being reported today represent nearly one billion cosmetic product units distributed. From this number we can calculate that the overall experience rate for all product categories is 1.87 experiences per million units distributed.

## Statistics for Voluntary Cosmetic Regulatory Programs as of November 30, 1974

The statistics for the voluntary program are shown in Table 2.★ In regard to these figures, we estimate that we have registered about 80 percent of the establishments and that the registered establishments manufacture and pack over 95 percent of the volume of cosmetics on the market. We also estimate that about 60 percent of the cosmetic formulations now marketed in the United States are on file at the FDA.

In conclusion, I trust that participation in the product experience reporting program will dramatically increase for the second reporting period. If it does not, we simply will not have the information we need to make the program meaningful for the consumer in terms of increased protection.

### TABLE 1

Tabulation of Cosmetic Product Experience Reports Submitted to the Food and Drug Administration Under the Voluntary Cosmetic Regulatory Program

Data Tabulated from FD Forms 2706 *"Summary Report of Cosmetic Product Experience by Product Categories"*

(Based on screened and unscreened reports submitted by 85 firms for the first reporting period, January—June 1974 and reported as of November 30, 1974.)**

| Product Category Code | Type | Number of Firms Reporting for Category | Total Number of Experiences | Estimated Units Distributed (Millions) | Number of Experiences Per Million Units Distributed |
|---|---|---|---|---|---|
| 1 | *BABY PRODUCTS* | | | | |
| 1A | Baby Shampoos | 6 | 48 | 35.5 | 1.35 |
| 1B | Lotions, Oils, Powders, and Creams | * | * | * | * |
| 1C | Other Baby Products | 8 | 51 | 42.7 | 1.19 |

[Table 1 is continued on next page.]

★ For Table 2, see page 212.

* When three or less firms reported information for a specific product category (e.g., 2C, Bath Capsules) the data is tabulated under "other" in that category (e.g., 2D: Other Bath Preps).

** Prepared by Division of Cosmetics Technology, Food and Drug Administration, 200 "C" Street, S.W., Washington, D. C. 20204, November 29, 1974.

| Product Category Code | Type | Number of Firms Reporting for Category | Total Number of Experiences | Estimated Units Distributed (Millions) | Number of Experiences Per Million Units Distributed |
|---|---|---|---|---|---|
| 2 | *BATH PREPARATIONS* | | | | |
| 2A | Bath Oils, Tablets and Salts | 28 | 54 | 21.1 | 2.56 |
| 2B | Bubble Baths | 12 | 24 | 9.5 | 2.53 |
| 2C | Bath Capsules | * | * | * | * |
| 2D | Other Bath Preparations | 14 | 17 | 4.6 | 3.70 |
| 3 | *EYE MAKEUP* | | | | |
| 3A | Eyebrow Pencil | 14 | 7 | 9.8 | 0.71 |
| 3B | Eyeliner | 16 | 31 | 6.7 | 4.63 |
| 3C | Eye Shadow | 23 | 113 | 20.5 | 5.51 |
| 3D | Eye Lotion | — | — | — | — |
| 3E | Eye Makeup Remover | 9 | 10 | 0.7 | 14.29 |
| 3F | Mascara | 20 | 90 | 28.5 | 3.16 |
| 3G | Other Eye Makeup Preps. | 11 | 21 | 5.9 | 3.56 |
| 4 | *FRAGRANCE PREPARATIONS* | | | | |
| 4A | Colognes and Toilet Waters | 25 | 27 | 36.9 | 0.73 |
| 4B | Perfumes | 19 | 17 | 10.1 | 1.68 |
| 4C | Powders (dusting & talcum, excluding aftershave talc) | 18 | 23 | 20.3 | 1.13 |
| 4D | Sachets | 6 | 10 | 12.5 | 0.80 |
| 4E | Other Fragrance Preps. | 6 | — | 0.06 | — |
| 5 | *HAIR PREPARATIONS* (NON-COLORING) | | | | |
| 5A | Hair Conditioners | 14 | 16 | 4.8 | 3.33 |
| 5B | Hair Sprays (aerosol fixatives) | 11 | 11 | 7.4 | 1.49 |
| 5C | Hair Straighteners | * | * | * | * |
| 5D | Permanent Waves | 5 | 121 | 4.3 | 28.14 |
| 5E | Rinses (non-coloring) | 15 | 10 | 3.8 | 2.63 |
| 5F | Shampoos (non-coloring) | 27 | 45 | 36.0 | 1.25 |
| 5G | Tonics Dressings, and Other Hair Grooming Aids | 17 | 14 | 22.2 | 0.63 |
| 5H | Wave Sets | 9 | 3 | 7.4 | 0.41 |
| 5I | Other Hair Preparations | 7 | 5 | 0.19 | 26.31 |
| 6 | *HAIR COLORING PREPARATIONS* | | | | |
| 6A | Hair Dyes and Colors (all types requiring caution statements and patch tests) | * | * | * | * |
| 6B | Hair Tints | — | — | — | — |
| 6C | Hair Rinses (coloring) | — | — | — | — |

**[Table 1 is continued on next page.]**

* When three or less firms reported information for a specific product category (e.g., 2C, Bath Capsules) the data is tabulated under "other" in that category (e.g., 2D; Other Bath Preps).

| Product Category Code | Type | Number of Firms Reporting for Category | Total Number of Experiences | Estimated Units Distributed (Millions) | Number of Experiences Per Million Units Distributed |
|---|---|---|---|---|---|
| *HAIR COLORING PREPARATIONS—Continued* | | | | | |
| 6D | Hair Shampoos (coloring) | — | — | — | — |
| 6E | Hair Color Sprays (aerosol) | — | — | — | — |
| 6F | Hair Lighteners w/color | — | — | — | — |
| 6G | Hair Bleaches | * | * | * | * |
| 6H | Other Hair Coloring Preps. | 7 | 95 | 15.5 | 6.13 |
| 7 | *MAKEUP PREPARATIONS* (NOT EYE) | | | | |
| 7A | Blushers (all types) | 17 | 30 | 6.2 | 4.84 |
| 7B | Face Powders | 18 | 14 | 8.3 | 1.69 |
| 7C | Foundations | 16 | 107 | 16.5 | 6.48 |
| 7D | Leg and Body Paints | * | * | * | * |
| 7E | Lipstick | 21 | 24 | 28.5 | 0.84 |
| 7F | Makeup Bases | 7 | 4 | 0.9 | 4.44 |
| 7G | Rouges | 7 | 4 | 1.1 | 3.64 |
| 7H | Makeup Fixatives | — | — | — | — |
| 7I | Other Makeup Preparations | 9 | 3 | 3.7 | 0.81 |
| 8 | *MANICURING PREPARATIONS* | | | | |
| 8A | Basecoats and Undercoats | 5 | 3 | 2.3 | 1.30 |
| 8B | Cuticle Softeners | 4 | 5 | 1.0 | 5.0 |
| 8C | Nail Creams and Lotions | * | * | * | * |
| 8D | Nail Extenders | — | — | — | — |
| 8E | Nail Polish and Enamel | 11 | 35 | 29.6 | 1.18 |
| 8F | Nail Polish and Enamel Removers | 7 | 1 | 22.3 | 0.04 |
| 8G | Other Manicuring Preps. | 3 | — | 0.19 | — |
| 9 | *ORAL HYGIENE PRODUCTS* | | | | |
| 9A | Dentifrices (aerosol, liquid, pastes and powders) | 6 | 11 | 4.1 | 2.68 |
| 9B | Mouthwashes and Breath Fresheners (liquids and sprays) | 5 | 4 | 13.1 | 0.31 |
| 9C | Other Oral Hygiene Products | * | * | 2.8 | * |
| 10 | *PERSONAL CLEANLINESS* | | | | |
| 10A | Bath Soaps and Detergent | 14 | 35 | 202.5 | 0.17 |
| 10B | Deodorants (underarm) | 23 | 261 | 55.1 | 4.74 |
| 10C | Douches | * | * | * | * |
| 10D | Feminine Deodorants | 8 | 27 | 5.7 | 4.74 |
| 10E | Other Personal Cleanliness | 13 | 5 | 73.6 | 0.07 |

**[Table 1 is continued on next page.]**

* When three or less firms reported information for a specific product category (e.g., 2C, Bath Capsules) the data is tabulated under "other" in that category (e.g., 2D; Other Bath Preps).

| Product Category Code | Type | Number of Firms Reporting for Category | Total Number of Experiences | Estimated Units Distributed (Millions) | Number of Experiences Per Million Units Distributed |
|---|---|---|---|---|---|
| 11 | *SHAVING PREPARATIONS* | | | | |
| 11A | Aftershave Lotion | 21 | 6 | 15.2 | 0.39 |
| 11B | Beard Softeners | — | — | — | — |
| 11C | Men's Talcum | * | * | * | * |
| 11D | Preshave Lotions (all types) | 4 | 3 | 5.3 | 0.57 |
| 11E | Shaving Cream (aerosol, brushless and lather) | 11 | 13 | 16.0 | 0.81 |
| 11F | Shaving Soap (cakes, sticks, etc.) | * | * | * | * |
| 11G | Other Shaving Preparation Products | 6 | 2 | 4.302 | 0.46 |
| 12 | *SKIN CARE PREPARATIONS* (Creams, lotions, powder and sprays) | | | | |
| 12A | Cleansing (cold creams, cleansing lotions, liquids, and pads | 27 | 56 | 13.1 | 4.27 |
| 12B | Depilatories | * | * | * | * |
| 12C | Face, Body, and Hand (Excluding shaving preparations) | 31 | 75 | 58.0 | 1.29 |
| 12D | Foot Powders and Sprays | 6 | 5 | 4.8 | 1.04 |
| 12E | Hormone | 5 | 4 | 0.1 | 40.00 |
| 12F | Moisturizing | 24 | 103 | 10.3 | 10.00 |
| 12G | Night | 12 | 37 | 3.4 | 10.88 |
| 12H | Paste Masks (mud packs) | 9 | 16 | 2.4 | 6.67 |
| 12I | Skin Lighteners | 6 | 46 | 3.5 | 13.14 |
| 12J | Skin Fresheners | 14 | 8 | 3.3 | 2.42 |
| 12K | Wrinkle Smoothing (removers) | 6 | 1 | 0.09 | 11.11 |
| 12L | Other Skin Care Preparations | 16 | 14 | 3.0 | 4.66 |
| 13 | *SUNTAN AND SUNSCREEN PREPARATIONS* | | | | |
| 13A | Suntan Gels, Creams and Liquids | 12 | 25 | 2.6 | 9.62 |
| 13B | Indoor Tanning Preparations | — | — | — | — |
| 13C | Other Suntan Preparations | 6 | 2 | 0.09 | 22.22 |
| | TOTALS | | 1852 | 989.922 | 1.87 |

* When three or less firms reported information for a specific product category (e.g., 2C, Bath Capsules) the data is tabulated under "other" in that category (e.g., 2D: Other Bath Preps).

## TABLE 2

Statistics for the Voluntary Cosmetic Regulatory Program at the Food and Drug Administration as of November 30, 1974

| | |
|---|---|
| **1. Voluntary Registration of Cosmetic Product Establishments (FD Form 2511)** | |
| Total Number Establishments Registered | 816 |
| **2. Voluntary Filing of Cosmetic Product Ingredient Statements (FD Form 2512)** | |
| Total Number Forms Received | 16,063 |
| Firms Represented | 605 |
| *Status of Requests for Confidentiality for Information Submitted on FD Form 2512* | |
| Total Number Forms Involved | 658 |
| % of Total Number of Forms Received | 4% |
| Total Number of Requests Granted | 260 |
| Total Number of Requests Pending | 139 |
| **3. Voluntary Filing of Cosmetic Raw Material Composition Statements (FD Form 2513)** | |
| Total Number of Forms Received | 2,109 |
| Firms Represented | 127 |
| *Status of Requests for Confidentiality for Information Submitted on FD Form 2513* | |
| Total Number Forms Involved | 192 |
| % of Total Number Forms Received | 9% |
| Total Number of Requests Granted | 91 |
| Total Number of Requests Pending | 6 |
| **4. Voluntary Filing of Cosmetic Product Experience Reports Cosmetic Product Experience Report (FD Form 2704)** | |
| Total Number Received | 536 |
| Firms Represented | 92 |
| Firms Using Screening Procedures | 23 |
| *Summary Report of Cosmetic Product Experience by Product Categories (FD Form 2706)* | |
| Total Number Received | 92 |
| Firms Represented | 92 |

**[The End]**

# Current Problems and Trends in Testing of Human Drugs — Especially in Regard to Institutional Review Committees

By CRAIG D. BURRELL

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IT IS GOOD THAT THE TERM "institutional review committee" was used for this program, rather than the previously-used term "peer review committee." This was confusing as there already existed National Institutes of Health (NIH) grant committees referred to as Peer Review Committees. Moreover, peer review was also a misnomer, for the best review group would be composed neither exclusively of peers of the subject nor of the investigator.

However, even the term "institutional review committee" is a poor one; it suggests to many that it is either the institution which is under review or that the review is conducted mainly by the institution. I gather that the Food and Drug Administration (FDA) and the Department of Health, Education and Welfare (HEW) are searching for a term comparable to institutional review committee to apply to groups set up to cope with research conducted outside an institution. Surely the term used at the National Council on Crime and Delinquency (NCCD)[1] conference last year is applicable (and very simple)—research review committee. Research review committee is an apt description, whether the research is conducted inside or outside an institution.

The fact that the FDA, the HEW and the NCCD, among others, are looking for appropriate terminology in this field suggests that there are matters of concern about research.

[1] Proceedings of the Conference on Drug Research in Prisons, Research Center of NCCD, Davis, California, 1974.

## Research Protocols

How did we get to the present state of concern over review of research protocols and the conduct of research? I have gone into this matter at some length elsewhere[2] but will briefly review the situation here.

There is no doubt that by the middle of the 1960's, medical technology had outstripped our ethical practices and our laws. As researchers developed renal dialysis and organ transplants, we even had to face up to the need for a better definition of death. Prior to the middle 60's, most people would have said that death was a relatively cut-and-dried matter. It was rather like being pregnant. Either you were or you weren't. Of course, since then we have become involved with problems about pregnancy insofar as the date of viability of the fetus is concerned. And there is debate on how dead is dead.

With technological advances in communication, the scientific world, though almost hypnotized by heart transplants, began to realize that this might be an idea whose time had not yet come.

## Tuskegee Research

In psychology, by the middle 60's, there was a strong trend toward clever experimentation on exotic topics with zany manipulation of the subjects.[3] And then much later the impact of the Public Health Service-sponsored Tuskegee research added fuel to the fire. And, of course, there were other horror stories about situations where government review committees had passed on the protocols and/or research in the light of then-current customs.

Whatever the causes, and they were many, scientific opinion plus public concern fueled by professional consumer advocates increased the pressure on scientists to look to their ethics. And there was need for them to do so.

Much has been made of the need to set up review committees because of the extreme hazards to which investigational subjects are exposed. Nowhere are these pressures greater than in regard to Phase I studies. Yet nowhere does the evidence suggest that the risks are lower than with Phase I studies.

Last year, informal discussion with responsible scientific or legal representatives of the 20 largest pharmaceutical companies in the United States

[2] Burrell, Craig D.: Some Ethical and Legal Considerations of Drug Testing in Humans, First World Congress of Environmental Medicine and Biology, Paris, France, July 1-5, 1974.

[3] Jacobson, Sharol F.: Nursing Forum 12:59 (No. 1) 1973.

led me to believe that, at least since 1967 (and perhaps for some time before), there have been no serious side effects or deaths in Phase I studies.

## Phase I Studies

Dr. Frances Kelsey has told me that in August 1973, in reference to Phase I studies, she said, "No one, prisoner or not, has died or been seriously injured by an experimental drug in recent memory." Despite the fact that it is only in the very recent past that Phase I studies have been conducted under obligatory research review committees, responsible pharmaceutical companies had become increasingly careful about where and how such studies were conducted. In fact, a number of research review committees were set up voluntarily.

Now, I see review of a research protocol and of the research itself by a committee as only one part of an interlocking network of safeguards that are desirable and necessary in human experimentation. At least four aspects must be considered.

First is the level of ethics of the investigator. I will not discuss this in depth, but I must say that Henry K. Beecher, the eminent Harvard academician, feels that, in general, the physician is the greatest safeguard in experimentation.[4] Pointing out that nearly all therapy—not research, but "routine" therapy—involves trial-and-error experimentation, he goes on to say, "I think with tongue in cheek, that legal writers and jurists evidently feel that nothing should be done for the first time!"

Is there a real danger of this philosophy surfacing with a lawyer on a review committee?

## Physicians' Ethics

As an aside, let me say that I find it fascinating that in the United States, the loudest cries about physicians' ethics come from lawyers, politicians (who are largely lawyers) and professional consumerists (who are largely lawyers). They seem to feel that, as Mark Twain said, "Nothing so needs reforming as other peoples habits."

Second, and related, is some sort of classification by the investigator of the level of hazard of the experiment, the benefit-to-risk ratio evaluation.

Third is the matter of government regulation and control of human research. How much can you legislate ethics or integrity?

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[4] Beecher, Henry K.: Editorial: Consent in Clinical Experimentation: Myth & Reality, JAMA 195:124, 1966.

We need controls, but we must avoid the danger of throwing out the baby with the bath water.

And a real problem that I face when I raise this is that sincere and thoughtful criticism is often latched upon, quite unfairly and falsely, as advocating "open slather" in research, without controls. It is as hard to be against any aspects of controls on research as it is to be against apple pie or Mom. But there are apple pies and apple pies, Moms and Moms, controls and controls.

## Protection of Human Subjects

And that leads me to the latest series of HEW rules and regulations on the protection of human subjects. As one academic critic commented in an official response to the HEW proposals, they are "a bureaucratic procedural cure for a disease."[5] He went on to say, "None of the major and effective biological treatments now used in psychiatry would ever have been developed under the proposed guidelines. Chlorpromazine would never have been approved for use in acutely disturbed psychotics, and electroconvulsive therapy would never have been given to anybody. The whole document is massively weighted to attempt to make all human research very, very difficult to do in the hope that this will also make it safe. Such an approach may or may not enhance safety, but it will surely discourage discovery of new treatments and new facts about mental illness."

There is a real danger of building layer upon layer of bureaucracy in the form of review committees that review the review committees' findings, etc.

Finally, I come to the fourth force at work, the institutional or rather let us say, the research review committee.

Although these committees were formed primarily to defend the rights of the subjects, there is a real danger that some institutions may want to have research review committees mainly to defend their institutional rights against legal action. And how about the investigator? What about his rights? Surely the committee must consider all three aspects.

## Composition of the Committee

How about the composition of the committee? I believe the best review committee would be composed neither exclusively of the peers of patients nor investigators, but would be a mix of both the peers of the investigator and the subjects, with a leavening of other concerned

[5] Cole, Jonathan O., Letter dated December 28, 1973, to Dr. Robert S. Stone, Director, NIH.

persons, such as nurses. You might have realized earlier that I do not consider lawyers or professional consumerists to be necessarily or automatically competent to bring ethical concerns into discussions of clinical research. While many of my best friends are ministers of religion, I feel they can be classified with lawyers in this regard.

There can be no question but that the move to establish committees for reviewing protocols and overseeing clinical research is a healthy and long overdue one—as a protection for the rights of both subjects and investigators.[6, 7]

The real difficulty surely must be finding appropriate people whose vested interests do not preclude a fair consideration of specific research projects. We all have vested interests, if only as members of the general public desperately wanting new and effective remedies for major or minor disorders. Just as lawyers are used in screening prospective jurors, there is a great need to screen potential committee members for conflict of ideology. And I do not mean seeking out only the blindly acquiescent, but also considering the "dedicated anti-research concepts" person. It is apparent that the FDA has some concern about the balance or composition of review committees, because one group of "Kelsey's Raiders" looks into review committees.

## Professional Consumer Organizations

How do you find somebody who can truly represent the research subject? Certainly none of the spokesmen or spokeswomen of the professional consumer organizations truly represent the great mass of the public, or even the informed public (whatever that is), let alone the research subject.

How do you represent patient interests?

Strangely enough it may be easier when the subject is a prisoner-volunteer. One of our conclusions at that NCCD Conference on research in prisons that I mentioned earlier[8] was that it was desirable to have an inmate or an ex-inmate on the committee. They are often more easily identified than a true representative of patients or the public.

So we need fair, reputable people without blinding vested interests (or, at least, those who openly acknowledge their vested interests) who believe

[6] Blomquist, Clarence: The Ethics of Medicine and Its Position in Sweden, Medical Tribune, p. 16, April 24, 1974.

[7] Report of the Conference on Human Rights in Medicine, Council of International Organizations of the Medical Sciences, Geneva, Switzerland, November 21, 1973.

[8] See footnote (1).

in the desirability of some form of research review system, who are not rigid and who, to quote Dr. Curtis Morris (who was himself paraphrasing the late Fuller Albright) are "strong enough and confident enough to act on their convictions, steadfast enough to take the heat of the aggrieved and frustrated petitioner, humble enough to consider it possible that a reviewer might be wrong in his original judgment and magnanimous enough to change position when warranted."[9] As I was preparing this talk and writing down the last couple of sentences, somebody who had been reading over my shoulder said, "Yeah. In a world where people's concerns should be Arab terrorism, IRA bombers, Ugandan racial discrimination, Ethiopian revolutionary justice, etc., I'm sure it should be an easy task to find the people you want all around the world." There's the cynicism showing again.

Which brings me back, in conclusion, to the positive point that despite all the regulations and guidelines, in the final analysis we come down to people, to ethics, to integrity and to a sense of fairness.

Nobody has been able to legislate those attributes effectively. But they exist. We must pursue people who have them and get such people involved in all aspects of the problems I have discussed. **[The End]**

## BLUE RIBBON REVIEW OF CYCLAMATES BY NATIONAL CANCER INSTITUTE

The National Cancer Institute (NCI) has been asked by the Food and Drug Administration (FDA) to review the scientific data on cyclamates and their possible carcinogenic effects. The NCI's Blue Ribbon Committee will try to settle the controversy that has continued over cyclamates since 1969 when NCI decided that cyclamates were carcinogenic. Some reports, including one from the World Health Organization's Food and Agriculture Agency, have concluded that the 1969 decision regarding cyclamates was erroneous. The FDA has indicated that other possible adverse health effects of cyclamates in the reproductive and cardiovascular systems must be studied by it before cyclamates could be marketed again.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,350

[9] Morris, R. Curtis, Jr., Clin. Pharm. & Therapeut. 13:782 (No. 5, Part 2), 1972.

# Product Experience Reporting— An Industry View

By MICHAEL PIETRANGELO

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LAST YEAR GENE LAMBERT, distinguished General Counsel for the Cosmetic, Toiletry and Fragrance Association (CTFA), entitled his address to this very same group, "Carrot and Stick: Product Experience Reporting and Cosmetic Ingredient Labeling." Presumably, the carrot referred to product experience reporting and the stick to ingredient labeling. I thought an appropriate title for my brief remarks might be: "The Carrot Revisited." It has been slightly more than one year since the Food and Drug Administration (FDA) published two notices in the *Federal Register* (38 *FR* 28913)—one dealt with voluntary filing of cosmetic experiences (21 CFR Part 174), and the other with mandatory cosmetic ingredient labeling (21 CFR 1205).

It is interesting to note the effective date provisions of each. In the former the provision reads as follows:

"Although it is anticipated that Form FD-2704, Form FD-2705 and Form FD-2706 will not be available until a date to be announced in the *Federal Register* in November, 1973, the Commissioner considers it reasonable that the initial reporting period for this program be established as beginning July 1, 1973, and ending December 31, 1973, so that first reports will be received no later than March 1, 1974."

In the later notice, it reads: "Effective dates. All cosmetic labeling ordered after March 31, 1974, and all cosmetic products labeled after March 31, 1975, shall comply with this regulation."

## A Year Away

Pursuant to proper administrative procedures, various cosmetic firms, trade associations, and others filed objections to both of these notices. As far as cosmetic ingredient labeling is concerned, after months of give and take by members of the industry and the FDA, we are at least another year

away from the beginning of the implementation of the regulation. And there is still the possibility of a hearing which could delay the effective dates even further.

With regard to product experience reporting, even though the FDA was unable to provide reporting forms until early this summer, over 80 manufacturers, packagers, and distributors have already voluntarily submitted information on cosmetic product experiences for the first six months of 1974. It is anticipated that this number will be significantly increased when the current reporting period ends on December 31, 1974.

It would be an oversimplification to suggest that the mere voluntary aspect of one regulation, as compared to the mandatory aspect of the other, is the reason for the differences in implementation. The differences are much more. For example, there still exists the question of whether or not cosmetic ingredient labeling will perform a useful purpose—will it really aid the consumer in making a true comparison between different brands of cosmetic products? Assuming, for the sake of argument, that this is true, is the listing of colors necessary and meaningful to this comparison?

## Better Grasp

With cosmetic product experience reporting, however, there is a different, perhaps more substantive, question which will be answered by implementation of this program. In 1974, when Commissioner Schmidt testified before Senator Kennedy's Health Subcommittee, he stated, "FDA does not have as good a grasp as it would like on the incidence of injuries from cosmetics." Many critics of the cosmetic industry have grossly misstated the number of injuries resulting from the use of cosmetic products. Industry has not only maintained that the number of injuries is low, but has boasted of its exellent safety record. Now, under the reporting program, industry will have an opportunity to substantiate its position, and the Commissioner will have a better grasp on the number of reported injuries.

I would like now to briefly highlight just two of the main issues in the product experience reporting regulation. These are the concept of "audit" by the FDA, and the use of a screening procedure. I am sure Mr. Wenninger's comments* and the subsequent question and answer period will elaborate on these and other issues. As you know, voluntary cosmetic product experience reporting is the third step in a massive voluntary program undertaken by CTFA and many members of the cosmetic industry. The other two are registration of cosmetic manufacturing establishments, and filing of cosmetic ingredient and raw material information.

* See page 204.

Under the program, manufacturers, packagers, and distributors of cosmetic products have a choice of filing all reportable experiences, as that term is defined in 21 CFR 174.1(d), or using a screening procedure. The procedure must be filed with the FDA and designed to determine that there is a reasonable basis for concluding that an alleged injury did not occur in conjunction with the use of the product [21 CFR 174.1(d)].

If a firm elects to use a screening procedure, the procedure and the implementation thereof are subject to "audit" by the FDA. The purpose of the audit is to insure that the procedure is being consistently applied and that it is not disregarding reportable information. It has been the CTFA position that the "audit" does not require that a person maintain any particular records, but only that information be maintained, and made available to the FDA so that it can evaluate the application of the procedure with complaints received. It is also the CTFA position that representative samples of reportable and nonreportable experiences can establish this. I believe the FDA does not agree with this position. It must be remembered, however, that the audit concept is distinct from the potential need on the part of the Commissioner to request additional information for a particular product category [21 CFR 174.5(f)].

## Screening Procedure

Presumably, the potential need for additional information will only arise when the Commissioner, as a result of analysis of information received and evaluated, believes there may be a problem. The need does not arise, however, when the FDA wants to audit a firm to determine if the screening procedure is being properly applied. As a practical matter, if a company agrees to participate in the program, it demonstrates an inclination toward cooperation rather than confrontation, and a mutually agreeable settlement of this issue would seem likely.

A decision to use a screening procedure, therefore, does not throw all of a firm's records regarding product experiences open to an FDA "audit."

The type of screening procedure selected is entirely up to the individual firm. The main factor to keep in mind in developing a screening procedure is that all complaints of injury are reportable unless they are determined to be unfounded or spurious. The purpose of a screening procedure is to eliminate unfounded or spurious complaints, and if a reasonable basis cannot be found for excluding the complaint, the complaint is reportable.

CTFA has developed a screening procedure, and it can be modified to meet the particular situations of individual companies. Obviously, it would

be wrong to assume the one procedure can apply to all companies, regardless of size. Each firm must decide whether or not to screen, and what type of screening procedure is best for it.

I will conclude by stating that the voluntary filing of product experiences is now operational, and it imposes upon both the industry and the FDA obligations which are perhaps more onerous than one would otherwise suspect. On the part of the FDA there is an obligation to make sure that the information received is properly tabulated, and judiciously used. If the FDA uncovers a problem with a particular product or category of products, the matter should be immediately brought to the attention of the firm or firms involved. Further, individual company statistics must be received by the FDA as confidential information. Hopefully, the new Freedom of Information regulations will recognize this. The continued confidential status of information submitted by manufacturers, packagers or distributors is essential for industry participation in the program.

Industry, too, has obligations under this program. While it is true that each firm must make its own decision whether or not to participate in the program, once the decision to participate is made, participation can only be in the true spirit of the law; the mere "letter of the law" will not suffice. Our industry will be judged not only by what the results and composite figures reveal (and hopefully these results will establish the relative safety of cosmetics), but by how well we participate in the program.

Both the industry and the FDA are exploring new and meaningful areas of exchange. Hopefully, each will have respect and understanding of the other's problems—remembering we are both working toward the same end result, which is to insure that the American public receives only safe cosmetic products. **[The End]**

# The Significance of the Over-the-Counter Drug Review with Respect to the Safety Considerations of Cosmetic Ingredients

By ROBERT P. GIOVACCHINI

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ON JANUARY 4, 1972, when the then Commissioner of Food and Drugs, Dr. Charles C. Edwards, announced a massive and unprecedented program that would review the many thousands of over-the-counter (OTC) drugs to insure that the ingredients in these products were safe, effective and accurately labeled,[1] the announcement was of general interest to the cosmetics and toiletries industry. The full significance of this review and the subsequent import it would have on the cosmetics and toiletries industry were not fully appreciated by many. Only a few concluded that these review panels could have a direct effect on the ingredients used by the industry, on the type of safety evaluation considered adequate, and also on the type of label and labeling requirements that might be imposed on the cosmetics and toiletries industry. While it is true that many of these panels' recommendations bear no relationship to the formulation, safety evaluation and manufacturing of toiletries and cosmetic products, they are, in my judgment, directly related to the future safety evaluation considerations of cosmetic-toiletries ingredients as well as the final cosmetic-toiletries product. Why? Because an ingredient found unsafe by an OTC panel for use in a topically-applied product could cer-

[1] 37 *F. R.* 85 (Jan. 5, 1972).

tainly not be used indiscriminately in a topically-applied cosmetics and/or toiletries product. Thus, safety and benefit-to-risk are the issues.

Safe is defined, in the *Federal Register*[2] to mean:

"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 from 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 collaborated by unpublished studies and other data."

"Benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness." No other definition is given. However, in the Preamble[3] it states:

"any drug which claims to be effective must have some pharmacological action whether it is beneficial, aggravates an already existing condition, or results in an adverse reaction or side effect. In every instance, the Panel must evaluate whether, balancing the benefits against the risk, the target population would experience a beneficial rather than a detrimental effect. Where little or no benefit is obtainable, of course, little or no risk is acceptable."

## Antimicrobial I Panel

Each OTC panel, therefore, must wrestle with the definition of adequate data to substantiate safety and with the benefit-risk ratio issues. The Antimicrobial I Panel, for example, after due deliberation, developed its own proposed guidelines for the safety testing of OTC topical antimicrobial agents which are, to say the least, quite comprehensive. Interestingly enough, the current Antiperspirant Panel is again wrestling with the same concepts of what should be adequate data to substantiate safety. The problem, of course, is that rarely is there scientific agreement on the meaning of adequate. Webster defines adequate as "equal to or sufficient for some (specific) requirement; proportionate or correspondent. Such as is lawfully and reasonably sufficient." How can we meet this definition when each year, more sophisticated toxicological testing procedures are being developed; where regardless of the amount of data submitted there is rarely scientific agreement on the meaning of the results; where one can rarely discard a poor animal study with positive (adverse) findings, but only test and retest to attempt to dilute the original test result which will always carry weight regardless of the scientific adequacy of the study or its interpretation vis-à-vis human exposure. Thus, safety issues are decided in the dust of differing scientific opinion based on poorly understood animal or human toxicological and/or safety studies. From this, risks v. benefit

[2] 37 *F. R.* 9474 (May 11, 1972). [3] 37 *F. R.* 9469 (May 11, 1972).

must be assessed How can this be done reasonably and with technical credence? Thus, a fundamental philosophical change is occurring in what is considered adequate with respect to safety evaluation.

The cosmetic industry states categorically that its products are safe, citing the long history of safe use. This position usually has been countered with the rebuttal that this is a claim and a request for the types of proof for the claim. Years of experience? Low incidence of dermal reactions? These may have been sufficient prior to the OTC review but the panels are developing internal safety evaluation guidelines which require considerably more than experience in the field as the sole criteria for safety. Utilizing these guidelines, what data do you have in your files that provides scientific evidence on the safety of your ingredient and/or your marketed product? Do you have sufficient information? Would a third party scrutinizing your product's safety profile today conclude that the ingredients and the product are generally recognized as safe for its labeled use? What does safe mean? Does it mean what the notice in the *Federal Register* says or does it mean "free from unreasonable risk of injury under reasonable foreseeable conditions of use"?

## OTC Review

How can one begin to respond to what appears to be a new criteria for insuring safety of ingredients in products? If Company A uses an antimicrobial ingredient in an antimicrobial (drug) product and subjects the ingredient/product to the proposed studies recommended by the Antimicrobial I Panel to determine adequacy of safety, can Company B run less than those studies if Company B uses the same antimicrobial ingredient in a deodorant (cosmetic) product? The fact that it would be a cosmetic in the latter case would have little effect upon the Food and Drug Administration review of the product for adequacy of safety. I believe that many of the other panels reviewing products that may be drugs by law but are considered by the consumer as cosmetic and toiletries products would impact in a similar manner as some of the panels already have upon the question of adequacy of safety testing. The OTC review of a limited number of physiologically-active ingredients is not the best approach to a review of the safety of thousands of cosmetic ingredients.

The industry must establish and define what it means when it says a cosmetic is safe. Does this mean that there is a reasonable certainty in the minds of competent scientists that the ingredients are not harmful? We know it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any substance. Wheth-

er safety is determined by accepted scientific procedures or by peer acceptance of safety; in my view, a toxicologist should consider:

(1) the probable concentration of the ingredient in the product;

(2) the cumulative effect of the ingredient, taking into account any chemically or pharmacologically-related substance or substances;

(3) safety factors which, in the opinion of experts, are generally accepted as appropriate;

(4) the type of scientific procedures; including human, animal, chemical, and other scientific studies whether published or unpublished, that are appropriate to establish the safety of the ingredients in the product;

(5) the proposed amount and extent of human exposure;

(6) the mode of application; and

(7) any documented history of safe use.

From such a review a competent toxicologist could conclude that a cosmetic ingredient can reasonably be expected to be safe. Where new scientific questions arise, the need for testing should be examined and instituted if required; but, where no demonstrable hazard exists, a battery of tests to constantly re-establish the safety of the product should not be required.

As I see it, this would be an appropriate area for the industry to develop guidelines and procedures. Then, when an ingredient can reasonably be expected to be safe, it can reliably be used in cosmetics and toiletries, under specific conditions of use, formula levels and product categories.

There are a variety of procedures for the development of dynamic lists of reasonably accepted as safe cosmetic and toiletries ingredients. I urge that we as an industry institute this type of review to insure that the products these ingredients are used in and for the purposes for which they are used in our industry do indeed reflect the safety of these ingredients.

## First Step

Therefore, from my viewpoint, it is imperative that the cosmetic and toiletries industry take the first step and review the literature for scientific information on the safety of cosmetic ingredients. We should then develop scientific programs where data is lacking. Each company would want to use the information garnered from these programs to develop a proper prognostic safety evaluation for its particular products.

The cosmetic and toiletries industry's ultimate goal must continue to be to insure that each proposed new product will be safe for a significant majority of its users under the proposed conditions of use. We must review

and keep abreast of what the OTC panels are doing with respect to ingredients that are used by the cosmetic and toiletries industry. However, in those cases where the cosmetic and toiletries industry feels that the type of safety evaluation required for the ingredient as a drug differs from the needs for it as a cosmetic, we should be in a position to outline clearly the scientific programs necessary to evaluate the safety of the ingredient as a cosmetic. Otherwise, we are faced with the potential of having to evaluate thousands of cosmetic and toiletries ingredients under the general guidelines that will be instituted by the expert Panels reviewing several hundred OTC drug-active ingredients. Such a situation would be scientifically disastrous as it would be scientifically unjustified. **[The End]**

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## PRESCRIPTION DRUG LABELING AND ADVERTISING REVISION PROPOSED

Requirements for the use of comparative statements and effectiveness claims in prescription drug advertising have been proposed by the Food and Drug Administration (FDA). Although the FDA recognizes that physicians need data on the differences in action, methods of administration, therapeutic efficacy, and the type of adverse effects among drugs, such comparisons are often based on inadequate or inconclusive information. Under the proposed requirements, which revise a proposal published in the *Federal Register* August 22, 1972, comparative safety and effectiveness claims would be allowed when such a representation had been approved as part of the labeling in a new drug or antibiotic application or biologic license. For all other prescription drugs, the claims must be supported by substantial evidence derived from adequate and well-controlled studies. The advertisement requirements do not establish a pre-clearance procedure for the content of comparative claims, but instead establish a means of determining whether there is adequate evidence to support the claims.

The proposal would also establish a standard format for stating information on indications and usage, contraindications, warnings, precautions, and adverse reactions in prescription drug labels. The FDA stated that the purpose of the labeling guidelines is not to establish new regulatory requirements, but to provide standards so that all package inserts would be written to reflect the highest industry standards. Comments on the proposal must be filed by June 6, 1975.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,261

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# Working Out Cosmetic Ingredient Labeling or "The Little Engine That Could"

By EUGENE I. LAMBERT

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NOW THAT COSMETIC INGREDIENT LABELING appears about to become a reality, it is perhaps worthwhile to review the development of the requirements that are expected to be issued in final form very shortly. It makes not only an intriguing case study of the interplay of varying pressures on a government agency, but also an example of how, in accommodating the varying pressures, a proposal goes from the relatively simple to the highly complex.

In May 1972, Professor Joseph Page, one of his then students, who is now engaged in the practice of law here in Washington, and the Consumer Federation of America petitioned the Food and Drug Administration (FDA) for the issuance of a regulation under the Fair Packaging and Labeling Act (FPLA) to provide for the ingredient labeling of cosmetics, including the common or usual name of each color, fragrance and flavor. The petitioners almost immediately agreed to hold the petition in abeyance while ingredient labeling was considered by Congress as part of pending legislation to establish a Consumer Product Safety Commission.

## No Congressional Action

In early August, the Commissioner published a "guideline" on the voluntary disclosure of cosmetic ingredients that permitted the collective designation of color, fragrance and flavor. When no Congressional action was taken on legislative proposals, the Page petition was reactivated and

published as a formal proposal on February 7, 1973, together with the Commissioner's counterproposal that simply turned the August guideline into a mandatory system. In addition to the basic issue of authority under the FPLA, the two proposals posed to industry the new issue of the disclosure of all ingredients as against the use of certain collective designations. Although not evident at the time, it was this conflict that was to provide the basic thread of disagreement between industry and the FDA and was to form the basis for the highly complex resolution of the conflict a year and a half later.

The Cosmetic, Toiletry and Fragrance Association (CTFA) comments on the proposal basically covered three issues. First is the legal basis for the proposal. Second are practical problems with the proposal, and third, the necessary transition time that would be required if the proposal were adopted in whole or in part.

On the legal side, the CTFA comments pointed out the failure of the Commissioner to make the necessary finding that the proposed regulation was necessary to prevent the deception of consumers or to facilitate value comparisons by consumers.

## Product-Line Basis

The comments emphasized that the burden of establishing this finding was on the Commissioner and Professor Page as the proponents of the regulation, and that the legislative history of the FPLA made it clear that the determination had to be made essentially on a product-line basis and could not be made on as broad a category as "cosmetics." The CTFA pointed out that it was unaware of evidence that would support a finding that the statutory criteria were met either for cosmetics generally or for any particular class of cosmetics.

On the practical side, the CTFA urged that the Commissioner's version form the basis for any final regulation, including its use of collective designations for color, fragrance and flavor. The CTFA urged modifications that would permit the protection of trade secrets, the adoption of off-package disclosure of ingredients in labeling accompanying the cosmetic, and the permission to use smaller type sizes than the 1/16 inch proposed by the Commissioner. In terms of effective date, the CTFA urged that any final regulation be issued simultaneously with proposed aerosol-warning regulations so as to eliminate the need for multiple label changes. An 18-month period to put new labeling into production was also requested.

In a subsequent filing, the CTFA urged that the CTFA Cosmetic Ingredient Dictionary, first published in 1973, be recognized as the preferred

compendium for ingredient names. The CTFA also responded to a late filing by the Federal Trade Commission urging the specific identification of colors and some fragrances.

The final FDA order was issued October 17, 1973. It followed basically the format of the Commissioner's proposal while incorporating the CTFA recommendation for the protection of trade secrets. It also recognized the CTFA Cosmetic Ingredient Dictionary as the preferred compendium for nomenclature.

## Off-Package Labeling

The final order also carried with it a number of elements that CTFA members found highly objectionable. First, the order required the specific identification of all colors in descending order of predominance by weight along with other ingredients. Second, no provision was made for small package sizes or for off-package accompanying labeling disclosure of ingredients. The Commissioner also made the FPLA finding and rejected the CTFA position that the term "commodity" in the FPLA is to be interpreted on a product basis rather than on a class as broad as cosmetics.

As provided for in the FPLA and Section 701 of the Federal Food, Drug and Cosmetic Act, the CTFA filed objections and a formal request for hearing on the color labeling and small package/off-package labeling issues in the final order. Three member companies also filed objections and requests for hearing. The CTFA separately pointed out the need for a uniform effective date for all regulations affecting cosmetics in light of the proposal by the FDA on feminine deodorant sprays.

In December, the CTFA petitioned the FDA to establish exemptions from the labeling regulation comparable to those that had been established for foods with respect to incidental ingredients and to permit scarce ingredients to be designated by class names. The CTFA also urged that the FDA acknowledge that the initial trigger date of March 1974 contained in the October 1973 order was deferred even for those parts of the final order to which no objection had been filed.

## Legislative Resolution

As a practical matter, consideration of the FPLA regulation became a secondary issue to Congressional consideration of overall cosmetic legislation—S. B. 863 proposed by Senator Eagleton. That bill included its own provision on cosmetic ingredient labeling on which the CTFA commented in a formal statement filed with the Committee. The FDA similarly was diverted from the pending order to the possibility

of a legislative resolution, and the Commissioner acknowledged at the CTFA 1974 Annual Meeting that all labeling dates were deferred. The indefinite deferral was confirmed by Associate Commissioner Fine later in 1974.

After the prospects for prompt legislation diminished, interest again turned to the pending order. After informal meetings with FDA representatives, the CTFA Board of Directors considered whether any form of compromise would be acceptable to the Association. The maximum compromise was encompassed in a letter to Associate Commissioner Fine on May 15, 1974. That letter proposed as a central point that individual color ingredients, if they were to be identified specifically, should be permitted to be listed without regard to predominance at the end of the entire ingredient list, and that lists of color ingredients should be permitted to include all of the colors that might be used in a single line of products in order to simplify the labeling of shaded items as well as protect trade secrets involved in formulating complex colors.

The CTFA again urged the adoption of the exemption for incidental ingredients, the use of off-package labeling to identify temporary ingredient changes in the case of shortages, the use of off-package labeling for small cosmetics, and a reduced type size for cosmetics having a PDP area not exceeding five square inches.

## Formal Meeting

The next move was the FDA's. In July, it made public a tentative revised final order and granted additional time for commenting on the revision. A formal meeting was held between CTFA representatives and FDA representatives on August 20, 1974, to go over the elements of the proposed final order. Following review by the CTFA Board of Directors, formal CTFA comments on the tentative revised final order were submitted September 24, 1974. These comments reiterated the basic CTFA position from the May 1974 CTFA letter and November 1973 CTFA objections.

At that point it appeared that industry and Government had moved no closer to a resolution of their basic disagreements; they seemed as far apart as they had been when the order had initially been issued in October 1973. Although adjustments had been made with respect to incidental ingredients and ostensible accommodating changes had been made concerning the issues of color and small packages, in fact the basic areas of disagreement loomed as large as ever.

The next meeting between the CTFA and the FDA representatives was on October 10, 1974. At that point, a viable compromise appeared to

be reached on the color-labeling issue. Although individual colors would be identified, the FDA would accept their identification at the end of the ingredient listing without regard to predominance by weight. The FDA also agreed with the CTFA interpretation of the tentative revised final order that permitted lines of cosmetics to list all of the colors used in the line without identifying the particular composition of each shade.

## Mandatory Information

The FDA requested further information with respect to small package sizes and with respect to off-package labeling. CTFA member companies reviewed the product lines to which the off-package labeling might be critical and provided examples both of products and of display situations. A meeting was held with the FDA counsel on November 1 to review these materials. Out of that meeting came a suggestion that perhaps the off-package labeling situation could be resolved if it were limited to shaded items and the mandatory information was displayed as part of a color identification chart for such shaded items. Subject to the actual language involved, CTFA members accepted this approach and, on November 7, we were informed that this approach would be acceptable to the FDA. The CTFA's formal proposal on this compromise is embodied in a November 13 letter to Associate Commissioner Fine.

As you can see from the course of these negotiations, it was the FDA determination that there had to be identification of individual color ingredients that, in large measure, resulted in the complexity both of the negotiations and, in all likelihood, of the final order that will be issued with respect to cosmetic ingredient labeling. The small size of shaded items and the manner in which they are displayed or held for sale, and the normal variety of shades within a given line all necessitated practical accommodations if the goal of ingredient labeling was not to become so economically onerous as to be counter-productive in terms of cost versus potential consumer benefit. Agreement was also reached with the FDA on realistic time periods for working in cosmetic ingredient labeling and to prevent economic loss in decorative containers that are also "packages" within the meaning of the FPLA. **[The End]**

# What's on the Horizon? FDA's Plans, Priorities and Activities for Cosmetics

By ROBERT M. SCHAFFNER

Dr. Schaffner Is Associate Director for Technology of the Bureau of Foods in the Food and Drug Administration.

VARIOUS KEY PEOPLE in the Food and Drug Administration (FDA) are being asked to outline the Agency's plans, priorities, and activities for the next 12 months.

My colleagues and I frequently are asked to predict when specific research programs, investigations and regulations are going to be issued for foods, drugs and cosmetics. I am afraid that our batting averages as fortune tellers, seers, and Delphic Oracles are not too good. Nevertheless, I will try to predict the cosmetic regulation activities of the Agency for 1975.

## Unfinished Business

First, let us look at unfinished business—the proposed regulations that are not yet final orders with confirmed effective dates.

The ingredient labeling regulation is the most important one. It has been discussed from both the FDA and the industry viewpoint by other speakers. Based on their remarks and many other discussions and after studying the gospel of the "pink sheet," I think it is safe to predict that the final order on ingredient labeling will be issued shortly. We can also expect to see large numbers of cosmetic products with ingredient labeling on the retail shelves toward the end of 1975.

A regulation on warning statements on aerosols was proposed by the Agency on March 7, 1973, and a regulation regarding labeling of feminine deodorant sprays was proposed on June 21, 1973. I believe that if we had

been asked some time ago, we would have predicted that the final orders would be in effect by now. However, concerning the aerosols regulation, the Agency had to consider not only the cosmetic implications but the food and drug implications, and this has delayed the issuance of the final orders. I believe that the final orders will be issued early in 1975.

## "See-Through" Labels

A proposal for both drugs and cosmetics on "see-through" labels was published by the Agency on July 20, 1974. During 1975, we will also see the finalization of this proposal.

Perhaps the most controversial cosmetic labeling proposal of the Agency was the hypoallergenic definition proposal which appeared in the *Federal Register* on February 25, 1974. Many of you will recall that I and others in the Agency had been urging the cosmetic industry to come forward with a definition for these products. Apparently, there were widespread differences of opinion, not only among the cosmetic manufacturers but among dermatologists, and nothing was proposed until the Agency publication in the *Federal Register* in February of 1974. The philosophy of the proposal was based on the concept that "hypo" means "less than normal." The FDA proposed that the term "hypoallergenic" only he used after a product had been tested to demonstrate in meaningful studies with groups of people that the hypoallergenic cosmetic resulted in fewer adverse reactions of statistical significance than the leading cosmetic products in the same general category. The FDA received 33 comments on this proposal; they are on file with the Hearing Clerk. Industry's comments were mainly to the effect that comparison testing was not the correct way to go about it. They suggested that certain standard tests should be set up and, if products met these tests, they could be labeled "hypoallergenic." One of the questions that we in the Agency are asking is how extensive should these tests be to differentiate them from normal tests that are made or should be made to establish the safety of general-use cosmetics before they are introduced to the public? The vision in my crystal ball on this proposal and its final order is rather cloudy. The FDA certainly hopes that a final order can be written which will meet the consumer's needs. During the past four years, the FDA and the cosmetic industry have been able to reach compromises that have benefited consumers. Cannot the consumers, the industry and the FDA work out a solution to this problem that will also be in the public's interest?

Now let's look at possible "new business" regulations. One of the first proposed regulations that we see in the future is one pertaining to the use of polyvinyl chloride containers for cosmetics. The FDA has drafted and is studying a proposal that will cover all of the interests of the Agency for containers for foods, drugs, cosmetics, veterinary drugs, animal feeds, biologics and medical devices. The problem with vinyl chloride was highlighted, as you recall, in February of 1974 when Professor Maltoni disclosed that, when inhaled by animals, vinyl chloride gas produced angiosarcoma of the liver. The FDA immediately sent out over 4,000 letters to known cosmetic manufacturers and distributors and requested the recall of any cosmetic products that contained vinyl chloride as a propellent in aerosols. Only a very small number of manufacturers of hair sprays and of other preparations were on the market; nine companies were involved and 91 products were recalled—the ingredient is now banned.

## Economic Implications

The Agency then turned its attention to the packaging materials used in foods, drugs and cosmetics. Discussions and meetings were held with the plastic industry manufacturers and food, drug and cosmetic manufacturers to first establish methodology that would determine precisely how much of the monomer was present in a plastic container. After the methodology on this matter had been settled, we then worked on analytical methods that could detect parts-per-billion quantities of the monomer in simulated food, drug and cosmetic products. We, of course, are not unaware of some of the economic implications of the proposal but safety must take precedence over economics. We will be soliciting data from the affected industries, and all of this information will be carefully weighed and considered before the final regulation is issued.

There are at least two other proposed regulations that I think we will see in the *Federal Register* during the next 12 months. As a general rule, we find that an effective means of increasing consumer safety is to promulgate appropriate regulations for certain classes of products. The type of regulation frequently limits the use of individual ingredients or calls for the use of specific warning and use statements on the label. Each month we summarize the consumer complaints coming to the Agency. Complaints on two types of products occur from month-to-month. Bubble bath products and shampoos are always on our list. Some of you will recall that in 1971 we had a rather extensive investigation of bubble baths. At that time, we suggested to manufacturers that they limit the quantity of the surfactant in these bubble baths to reduce skin and mucous membrane irritations. This

was done but the problem apparently has not been solved by using only this approach.

## Bubble Bath Product

A bubble bath product, for example, may be promoted as a fun product by implying through statements, design or other means that it is mild and safe and by recommending that it be used frequently and without concern for exposure time. Furthermore, if the consumer is not cautioned through an appropriate statement that it may, under certain circumstances, cause a rash, irritation or urinary tract infection, this product is more likely to cause adverse reactions than one offering proper directions, cautioning the consumer against possible adverse reactions. If this bubble bath product causes an irritation or infection under conditions of what has become the customary use, it is considered both adulterated and misbranded.

We feel that warning statements should be shown conspicuously with uniform wording on bubble bath products, particularly those for use by children. Unfortunately, too often these bubble bath products seem to play the role of a "baby sitter" and the children are either exposed to too much of the product or exposed for too long a time in the bath. Some of the manufacturers have placed warning statements on their labels but more must be done by all manufacturers. We feel that the equitable treatment of all products of this category calls for a uniform statement, and we are considering preparing a proposed regulation along those lines.

## Shampoos

We in the Agency also receive many complaints about shampoos, reporting eye irritations and, in some cases, damage. We are studying this matter carefully and perhaps a regulation calling for the reduction in concentration of certain ingredients as well as label warning statements would be in order.

In 1975 we will see the further implementation of the three voluntary cosmetic regulations that we have talked about so much at Food and Drug Law Institute Workshops and at other cosmetic meetings during the past three years. This coming year we plan to use the information collected as a result of these regulations to start a more comprehensive and orderly review of cosmetics. We will be comparing approximately 600 annual consumer complaints with those reported by the companies through the product experience reporting system. Many of the cosmetic firms that are reporting adverse reactions use screening procedures. During the next six months, we will be starting to audit the screened product experience reports by having our Cosmetic Technology Division personnel and

field inspectors visit the companies to monitor the reports to see how well the system is working.

## Preliminary Report

Mr. Wenninger* has shown the preliminary report on the results of the first period of product experience reporting. The tabulated results, as the regulation pointed out, are public information and the summary will be made available to the general public. We trust that more companies will be reporting their July 1974 through December 1974 product experiences so that the next summary will be more inclusive. We plan to issue the second report probably in April or May of 1975. The Agency has a "contract study" now under way that will give an indication of the number of adverse reactions that consumers are experiencing from cosmetic products. This report will also be issued in the spring of 1975; then I think we can stop all debate on that magic figure of 60,000 incidents that has been quoted and requoted for so many years.

Comments have been made about ingredient reviews which have been called "REAS," reasonably expected as safe. During 1975, the FDA probably will not be fully engaged in the review of the ingredients. By the end of the year, however, we certainly should have a system set up so that an orderly review of cosmetic ingredients can be off to a good start during our country's two hundredth anniversary. There are many forms that this review can have, and we would like to take this opportunity to urge the industry and the consumers to suggest various methods by which meaningful reviews of cosmetic ingredients can be made.

## Middle Ground

During these days of increased prices, we hope this can be done with a minimum impact on the consumer's pocketbook. The citizens will have to pay for these safety reviews through the cost of cosmetic products if the industry does most of this work, or by tax dollars if the Government carries out most of the investigations. We must find some "middle ground" that can provide optimal safety information on cosmetic ingredients and not overburden both the industry and the government in costly reviews on products that may have had long years of experience of safe use throughout the cosmetic field.

I guess a "What's on the Horizon?" discussion would not be complete without some mention of possible legislation. I have studied the leading seers on this subject, including such authorities as James Merritt, Peter

* See article on page 204.

Hutt, Wallace Werble and Senator Thomas Eagleton. At this moment, I have concluded that no one can predict with certainty that new legislation will be passed in 1975. But the position of the FDA on the need for new legislation was clearly put forth by Dr. Schmidt at the Kennedy hearings last winter. I would like to highlight and paraphrase some of the Commissioner's and the Agency's opinions:

(1) Cosmetics are deemed to be important but not absolutely essential to human progress.

(2) Because cosmetics are not essential, they must be as safe as they can be made.

(3) No one has a monopoly on good intentions, and industry, Government and the consumer public all share a common wish for safe cosmetics, fairly labeled and honestly promoted.

(4) The sum of all known reported and suspected problems of the cosmetic industry do not add to anyone's first priority when compared with many other safety issues before society. Therefore, cosmetic safety probably ranks lower on the Agency's priorities than do foods, drugs or medical devices.

Further on the subject of cosmetic safety, the Commissioner stated at the hearings:

"We are all in basic agreement with the principles that manufacturers of cosmetics are responsible for the safety of their products and have the duty to perform adequate testing to assure safety. The only question is the extent to which government should get involved in assuring that the manufacturer's duty to substantiate its safety is not neglected. Our basic concern is that manufacturers actually perform this testing. We believe that as long as there is a system which accomplishes this result there is no need for affirmative FDA clearance prior to marketing or premarket reporting, as required in one of the Bills. We do believe, however, that it is proper that the safety substantiation reports be submitted to FDA upon specific requests, and the Administration's Bill (that was proposed at that time) would enable the Agency to require manufacturers to submit to FDA data that they have, substantiating the safety of their products."

## Voluntary Basis

Another specific, you will recall, was that the Commissioner felt that it was desirable that the three voluntary programs be made mandatory. In light of the present economic situation we do not see that this would be an unreasonable burden to be placed on cosmetic manufacturers because most of them are participating in this program on a voluntary basis.

Looking over this list of activities, priorities and plans, I think we can all agree that the one cent per capita that is being spent by the Agency on cosmetics to protect the health and pocketbook will be a good investment if these programs are carried out in an orderly, meaningful and effective manner. **[The End]**

# Regulatory Options and Ramifications of Recall

By LARRY R. PILOT

Mr. Pilot Is Acting Director of the Division of Compliance of the Bureau of Medical Devices and Diagnostic Products in the Food and Drug Administration.

SEVERAL MONTHS AGO, when M. Joseph Radzius asked me to participate in the Medical Devices Workshop, we agreed that a discussion of regulatory options and ramifications of recall would be useful and, hopefully, informative. Needless to say, we were both optimistic that new device legislation would be in effect so that we could discuss the impact of such legislation and weave this into our equally optimistic projections of last year as to the types of topics we would be discussing at this workshop. As you are aware, the legislation has not yet passed the House and the possibility of enactment in 1974 is uncertain. Nonetheless, the subject I am going to discuss fortunately does not require new legislation to be of practical benefit to you.

The Food, Drug and Cosmetic Act and regulations promulgated thereunder provide us with a very effective framework within which to operate. If a device, including a diagnostic product, is adulterated or misbranded, then a violation exists and the regulatory options available to the Food and Drug Administration (FDA) are quite simple. Assuming that we are able to document interstate shipment of a violative device, then we can attempt to seize the device, enjoin interstate shipment of the device, detain shipments of devices imported into this country, or criminally prosecute responsible individuals. While these are extremely effective regulatory tools which have been used successfully by the FDA for almost four decades, they may not represent the most efficient method for securing compliance with the Act. Because of this reason, and others, the FDA has been and is using other procedures to a greater extent. These

include issuance of regulatory letters or commencement and completion of a recall.

## Regulatory Letter

First, let me describe the regulatory letter, which represents a rather recent approach toward the eventual disposition of violations under the Act. A regulatory letter is intended to secure compliance with the law without the necessity of bringing a seizure or injunction action. The letter, directed to the top management of a firm, explains the nature of the violation detected by the FDA and requires that a response be made to FDA headquarters or the appropriate field unit within ten days of receipt of the letter. These letters are clearly marked as regulatory letters and are used:

"a.) as a formal legal notice to firms and individuals of violative situations;

b.) to give the industry an opportunity to bring about correction of the violation;

c.) to implement the law."

Hopefully, the letter will result in the addressee taking corrective action. If no satisfactory corrective action is taken, then the FDA will proceed to seize the device or secure an injunction restraining shipment of the device in interstate commerce. It should be clearly understood that a regulatory letter will not be issued if a criminal prosecution is involved or if the violative device poses a hazard to health. In these cases, citation or other measures which would correct a device to the users' benefit are more appropriate. Often this latter kind of violation requires a recall, although the nature of a violation stipulated in a regulatory letter may also necessitate that a recall be undertaken.

## Importance of the Recall

Generally, recall of a device provides the most efficient and effective method for securing compliance with the Act. Because of this, the remainder of my article will be devoted to discussing the importance of the recall. Those of you who are familiar with the FDA are probably aware of the fact that our "Recall Procedures" are clearly stated in the Regulatory Procedures Manual and that this manual is available to you on request. Nonetheless, in light of the many comments and criticisms we have received about our recall procedures, I believe the definition of what constitutes a recall bears repeating so that there is no misunderstanding about the term. In part, "recall" means:

"A manufacturer's correction of products in the field (field correction) or removal of products from the market which present a threat or potential threat to consumer safety and well-being, involve product adulteration, cause gross fraud or deception of consumers, or are materially misleading causing consumer injury or damage, and which are subject to legal action under FDA's existing compliance policy . . ."

## Violative Devices

The term "recall" is not to be defined or interpreted literally since, in many cases, no physical recall is necessary because the misbranding or adulteration of the device can be corrected in the field. However, it is vital to recognize and accept the fact that any device which is the object of a recall is a violative device because it is adulterated and/or misbranded. Obviously the sanctions within the Act could be applied, but we believe compliance can be achieved without pursuing these extremes.

Over the last several years, the number and variety of device recalls have risen at an unusual rate.* Part of this is due to the fact that we have more resources available to us in order to detect violations and seek correction. Also, manufacturers or distributors have been more willing to notify the FDA when they encounter a problem with their devices. We believe that manufacturers should continue to communicate with us since we believe we can provide them with the assistance that is necessary to best serve the consumer. While the recall represents a voluntary effort on the part of the responsible firm, it is my belief that it would be unwise to undertake such an action without notifying the FDA. In many cases where firms undertook a recall of a device without informing the FDA, further action on the part of the firm was necessary to correct a problem which could have been identified and corrected during the initial phase of the recall. Obviously, this is not the best approach for the manufacturer, the FDA or the consumer.

## Proper Perspective

We have the knowledge, background and experience which is necessary to help you undertake a recall, whether it involves a few devices or a few million devices. We are careful to place the nature of a recall in proper perspective so that it is properly categorized and handled by the Agency. Regardless of whether a recall is categorized as Class I, II or III, we are prepared to respond quickly to help you undertake whatever further action is necessary. Remember, our main objective is to seek the voluntary correction of a violation of the Act without commencing the application of

* See Appendices A & B, beginning on page 244.

other sanctions under the law. We believe that if a firm is willing to recognize that a problem exists and cooperates in the recall of a device, the consumer ultimately will be served better by us.

Lest I leave you with the impression that our major interest is in accumulating large numbers of recalls, I must point out that we would be much happier if there were no recalls and if all devices were in complete compliance with the law. Unfortunately, this ideal condition is beyond our grasp since the manufacturer or distributor clearly has the responsibility to assure that his device is in compliance. All we can do is offer "after the fact" assistance. However, we are optimistic that recognition of problem areas and prompt action by the firm and the FDA will ultimately result in a reduction of the number of recalls. Over the years, we have learned a great deal about why certain types of recalls are necessary and, in our judgment, many of these recalls should not have occurred. Without belaboring the point, I would like to emphasize that significant numbers and types of recalls could have been avoided if the firm had established and followed basic good manufacturing practices. This may sound overly simplistic but a review of the case histories will demonstrate that this observation is correct.

## Obvious Symptom

From our standpoint, the recall becomes an obvious symptom of an underlying condition which must be identified and treated accordingly. Although the recall serves as an effective means for removing a violative device from the market, our work does not end with completion of a recall. We spend a great deal of time investigating and analyzing each recall so that the firm (and, in some cases, an entire industry) will not repeat an unacceptable practice.

On the basis of this experience, I would like to give you some advice which I hope will aid in reducing the number of recalls. In the first place, assuming that a device is safe and effective, take a good and thorough look at its labeling to make sure that it complies with the Act and regulations. Make sure that what is said in the labeling is accurate and supportable and does not overstate or understate the qualities of a device. You must undertake every possible effort to assure yourself that the labeling is perfect and reflects conditions compatible with the prevailing state of the art. If you have any doubts about labeling, please contact us for an advisory opinion.

If you are confident that the labeling for the device is accurate and complies with the law, you must be equally confident that the device is safe and effective for its intended use. You must be certain that the device has been adequately tested and manufactured under conditions which will insure its integrity in the environment for which it is intended to operate throughout its anticipated lifetime. In this regard, you must be absolutely sure that your physical facilities and personnel are adequate, that all necessary testing of raw materials is undertaken, that suppliers of components have complied with your specifications, that appropriate records are kept, and that the quality control procedures applied to the device will withstand challenge.

## Achievable Goals

Hopefully, if you are sensitive to this advice, a great number of conditions which ultimately may lead to a recall can be avoided. This certainly is a goal which we and you must strive toward. It is realistic to assume that this goal is achievable but only you, the manufacturer, can make it happen.

Finally, if for some reason a recall becomes necessary, do not hesitate to contact us. Recognize that our responsibility and yours to the patient is the same and that we can cooperate to achieve our mutual objective. If you are unhappy about the way we handle recalls or believe the present procedures are inadequate, tell us. But be prepared to give us constructive suggestions and advice at the same time, because we are receptive to your views. To quote Dr. Edwards, as I did last year, "if we proceed in the role of regulator vs. regulated or antagonist vs. protagonist, we will all suffer and the ultimate beneficiary, the patient, will be robbed of the best possible health care—the goal we all seek."

[Appendix A begins on page 244.]

## APPENDIX A

### Medical Devices and Diagnostic Products Recalled in FY 69—FY 74

I. Electronics and Electrical Area
   A. Electronic Malfunction
      1. Pacemakers
      2. Defibrillators
      3. Electrocardiographs
   B. Electrical Shock Hazard
      1. Sterilizers
      2. Heating Pads
      3. Electrical Accessories
      4. Blood Pressure Transducers

II. Mechanical Area
   A. Fire and Explosion Hazard
      1. Nebulizers
      2. Oxygen Equipment
         (A) Flow Meters
         (B) Timers
         (C) Cylinders
         (D) Valves
      3. Autoclaves
   B. Inoperative and Inaccurate
      1. Manometers
      2. Respirators and Resuscitators
   C. Broken and Leaking Equipment
      1. Catheters of all Types
      2. Drainage Sets
      3. Blood and Water Filters
      4. Syringes

III. Microbiological Area
   A. Mold and Bacterial Contamination
      1. Catheters of all Types
      2. Feeding Trays
      3. Suture Removal Kits
      4. Tracheotomy Kits
      5. Spinal Manometers

6. Pre-Gelled Electrodes
7. Irrigation Syringes
8. Blood Culture Media

IV. Material Sciences Area
   A. Breakage, Corrosion and Crazing
      1. Mitral Heart Valves
      2. Hip Joint Prosthesis
      3. Plastic Tubes
      4. Stainless Steel Staples

V. Clinical Biochemistry Area
   A. Inaccuracy
      1. Thyroglobulin Test Kit
      2. Standard Sera
      3. Pregnancy Test Kit
      4. Clotting Time Test Kit
   B. Unstable Test Adjuncts
      1. Laboratory Reagents
      2. Glycine-Saline Diluent

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## APPENDIX B

### Medical Devices and Diagnostic Products Recalled in FY 75

I. Electronics and Electrical Areas
   A. Electronic Malfunction
      1. Blood Pump
      2. Pacemakers—9
      3. Treadmill
      4. EKG Preamplifier
   B. Electrical Shock Hazard
      1. Nebulizer
      2. Defibrillator
   C. Electrical Injury
      1. Peripheral Nerve Stimulator

II. Mechanical Area
   A. Inoperative and Inaccurate
      1. Oral Dispenser
      2. Respirators and Resuscitators—2

3. Tracheal Suction Machine
4. Dialyzer

B. Broken or Leaking Equipment

1. Catheters of all Types—2
2. Anesthesia Machine
3. Blood Oxygenators—2
4. Blood Processing Unit

III. Microbiological Area

A. Mold and Bacterial Contamination

1. Connecting Tubing—7
2. Prosthesis Implants—2
3. Tracheal Suction Tray
4. Electrode Lubricant
5. Microbiological Culture Media—91 Products
6. Catheters of all Types—2

IV. Material Sciences Area

A. Breakage, Corrosion and Crazing

1. Ceiling Support Crane

V. Clinical Biochemistry Area

A. Inaccuracy

1. Typing Bacteriological Tests—4
2. Analytical Instruments—2
3. Clotting Time Test Kits—2

B. Unstable Test Adjuncts

1. Laboratory Reagents—8

NOTE: Recalls are primarily a procedure to retrieve or make corrections of products on the market which present a threat or potential threat to consumer safety. Often the result achieved does not constitute a final correction to the existing problem, and should not be considered as such.

**[The End]**

# In Vitro Diagnostic Regulations—A Regulatory Ordeal

By RICHARD D. MANTHEI

Mr. Manthei Is Corporate Director of Regulatory Affairs and Quality Assurance in the American Hospital Supply Corporation.

THE DEVELOPMENT AND USE of *in vitro* diagnostic products has become an important part of health care. Early tests conducted on the blood, urine or tissues of patients were crude and the reagents employed were prepared by the clinician or laboratory worker. Typically, new products were developed by individual clinicians or laboratories in response to a particular need. As the need for more and better products increased, it was necessary to turn to outside sources for preparation of these products. These outside sources were generally small chemical manufacturers who could be equated to prescription pharmacies, preparing small quantities of products as ordered. As the demand for products increased, the number of manufacturers increased, until there are now virtually hundreds of manufacturers offering thousands of products.

Today, *in vitro* diagnostic products range from prepackaged and diluted solutions to automated test systems involving complicated instrumentation. Complete systems are now marketed, including not only reagent materials, but also electronic, optical, nuclear and other measurement devices. The trend toward the marketing of complete systems is a result of the rapidly growing volume of testing and the resultant need for a higher degree of automation.

During the growth of the industry, the regulation of *in vitro* diagnostic products has varied. Some clinical reagents were licensed by the former Division of Biological Standards (DBS). The DBS licensing activity, however, was principally limited to biologicals, such as blood typing and grouping sera, with relatively few clinical reagents outside

this field brought under this licensing activity.[1] The Food and Drug Administration (FDA) activity was more on the basis of reacting to a particular problem than on a systematic approach to regulation. When action was taken against a product, it was generally on the basis that it was a drug. Despite a Supreme Court decision which indicated that a "drug was not limited to products used directly on the body," the FDA appeared hesitant to call all *in vitro* diagnostic products "drugs."[2]

## *Federal Register* Notice

Finally, however, because of concern over the growing number of manufacturers and products, the Commissioner of the FDA published in the *Federal Register* for January 19, 1972, a "Notice to Manufacturers, Packers and Distributors of *In Vitro* Diagnostic Products" which indicated the Agency's intention to propose regulations governing these products.[3] The notice instructed manufacturers to begin assembling evidence to substantiate the accuracy and reliability of their products. The notice also requested manufacturers to develop information which could be used as a basis for providing appropriate instructions for use. This notice was probably of little value to anyone except the FDA, because it apparently only reached a small segment of the industry. Even to most members of the industry who were aware of the notice, it provided little information or assistance.

Thus began what can be described as a "regulatory ordeal." It is, perhaps, a classic example of a regulatory agency attempting to regulate an industry which it did not fully understand, and of an industry which did not understand the regulatory agency which was about to regulate its activities.

In August 1972, the Commissioner of the FDA published a proposal for the regulation of *in vitro* diagnostic products.[4] Shortly after the proposal was published, the FDA conducted several briefing sessions in

[1] The statutory basis for this licensing activity is the Virus Serum and Antitoxin Act of 1902. 42 U. S. C. 262 (1970). The statute covers "any virus; therapeutic serum, toxin, antitoxin vaccine, blood, blood component or derivative, allergenic products, or analogous product" which is "applicable to the prevention, treatment or cure of diseases or injuries."

[2] In *United States v. An Article of Drug . . . Bacto Unidisk*, 394 U. S. 789 (1969), the Supreme Court held that an antibiotic disc which was impregnated with an antibiotic drug was within the purview of the Federal Food, Drug and Cosmetic Act, notwithstanding that it was not administered to the patient.

[3] 37 *F. R.* 819 (1972). In this notice, the Commissioner indicated that authority for regulatory control over *in vitro* diagnostic products was provided in the Federal Food, Drug and Cosmetic Act.

[4] 37 *F. R.* 16613-16617 (1973).

different regions of the country. At these sessions, they attempted to explain the Agency's proposal.[5] Anyone listening to the questions from the audiences and the answers from the Agency panels had to come away with the realization that neither the Agency nor the industry was prepared for the implementation of the proposed regulations.

## Desire to Regulate

The FDA's initial approach seemed to indicate a desire to regulate the *in vitro* diagnostic product industry in a manner similar to the drug industry. The differences between the two did not appear to have been recognized or considered.

The most important difference is, of course, that the end use of the products are substantially different. Drugs by themselves are therapeutic and thus alter the condition of the patient. Once administered, further involvement by the physician is not needed to achieve the intended result. As opposed to drugs, *in vitro* diagnostic products are not taken internally, nor are they otherwise applied to the body. In some instances, *in vitro* diagnostic tests may be performed in close proximity to the body. But in most instances, they are performed away from the patient in a different location, such as the clinical laboratory. *In vitro* diagnostic products do not alter body functions and relate only to the measurement of a specimen removed from the body. The results of this measurement must be interpreted by a physician. While this information is valuable to the physician, it does not constitute a diagnosis. In reaching a diagnosis, the physician must assess the significance of the results along with other information available to him, such as symptoms, patient history and the results of other tests. The potential effect on the patient with drugs is, therefore, significantly greater than with *in vitro* diagnostic products.

## Small Sales Volume

Other differences which should have been carefully reviewed by the FDA is the predominance of small manufacturers in the industry, as well as the relatively small sales volume of most individual *in vitro* diagnostic products.[6] Because of this predominance of small manufacturers and the small sales volume of most products, the expense involved with immediate compliance with drug-like regulations had the potential to

[5] Briefing Sessions were conducted by the FDA in Chicago, New York and San Francisco.

[6] Statement of Adrien L. Ringuette on behalf of Scientific Apparatus Makers Association before the Health Subcommittee on Labor and Public Welfare, September 17, 1973.

force a number of manufacturers out of the *in vitro* diagnostic product business and to remove many products from the market. Also, products classified as *in vitro* diagnostic products include a broad spectrum of products which range from single chemical entities to sophisticated electronic instruments. While almost all drugs can be regulated in a similar manner, the broad spectrum of *in vitro* diagnostic products demands greater flexibility.

Despite these differences, the FDA continued to charge ahead. On March 15, 1973, the Commissioner of the FDA published final regulations noting that 47 comments had been received in response to the FDA's initial proposal of August 17, 1972.[7] The FDA chose not to classify *in vitro* diagnostic products as either drugs or devices. The FDA made it clear, however, that they would be regarded and classified as drugs if such a step were necessary to bring products into compliance.

## Labeling Requirements

A brief look at the final regulations will give you a better understanding of the "ordeal" faced by the industry. The regulations purported to cover virtually all products included or promoted for use in a clinical laboratory for the examination of specimens taken from the human body. The first section contained comprehensive and detailed requirements for labeling. Then acting-Commissioner Sherwin Gardner, in a statement delivered before a Congressional committee on May 30, 1973, characterized the new regulations as the most comprehensive labeling requirements ever issued by the FDA.[8] As Mr. Gardner stated, the regulations required full directions for use, including warnings, precautions, statements regarding history of the tests, procedures for obtaining results, possible interfering agents, normal and abnormal values, cautionary procedures and quality controls, expected results and their meaning, and bibliographies of pertinent references.

The sheer magnitude of gathering this information was formidable. Product lines, labels and labeling had to be reviewed. In many instances it was necessary for research and development, quality control, manufacturing and regulatory personnel to stop all other projects in an attempt to meet the labeling requirements before the effective date, one year later. Many products were eliminated from product lines because of the cost involved in keeping them on the market. Other companies reportedly dropped out of the business for similar reasons. Prior to the deadline,

[7] 37 *F. R.* 7096-7102 (1972).

[8] Testimony of Sherwin Gardner before the Subcommittee on Intergovernmental Relations, House Committee on Government Operations, May 30, 1973.

the FDA found it necessary to issue a six-month extension. Even with this extension, I am aware of a number of firms who were unable to ship products because they could not meet the new deadline.

In addition to the product-labeling requirements, the regulations also established a procedure for the issuance of product class standards.[9] The standard setting program began immediately. A request for data and information to establish a product class standard for the detection or measurement of glucose on total sugars was published by the FDA on May 23, 1973.[10] A notice was published by the FDA on November 2, 1973, containing a request for data and information relative to the establishment of a product class standard for calibrators.[11] On March 8, 1974, the FDA requested information and data for products used for the measurement of hemoglobin taken from the human body.[12] Thus, a manufacturer of a product or products falling within one of these product classes was given the added "ordeal" of gathering or obtaining the necessary data or information to submit on his product if he hoped to influence a product standard. A total of 39 submissions covering 51 marketed products were received by the FDA as a result of their request for information on the proposed glucose standard.

## Slight Attention

On June 28, 1974, the FDA published its proposed product class standard for the detection or measurement of glucose.[13] The proposed standard is extremely comprehensive and, as a result, required extensive analysis by industry. It is my understanding that most of the products currently on the market would not be in compliance with the proposed standard. If this is, in fact, the case, one must believe that the FDA gave slight attention to the 31 previously mentioned industry submissions. It had been hoped, by industry, that standards would pertain to the performance of the product: namely, its ability to reliably and accurately detect or measure a particular constituent taken from the human body. To the extent a standard departs from requirements relating to performance, it becomes increasingly burdensome, thus adding to the "ordeal."

[9] 21 CFR 328.30 (1974). Under the regulations, the FDA can propose a product class standard if it determines that a standard is necessary to reduce or eliminate unreasonable risk of illness or injury associated with the use of an *in vitro* diagnostic product. Product class standards are defined to include performance requirements necessary to assure reliability, specific labeling requirements necessary for the proper use of a particular class, and procedures for testing products to assure satisfactory performance.

[10] 38 *F. R.* 13573 (1973).

[11] 39 *F. R.* 30290 (1974).

[12] 39 *F. R.* 9217 (1974).

[13] 39 *F. R.* 24136 (1974).

In addition to the labeling and standard setting requirements, many manufacturers were now faced for the first time with a written set of "current good manufacturing practices requirements." The new regulations required that the principles established in the Drug Current Good Manufacturing Practice Regulations should be followed as a guideline in the manufacturing of *in vitro* diagnostic products.[14] Because of the thousands of products involving many different kinds of manufacturing processes and control procedures, the interpretation and application of these "guidelines" further increased the "ordeal."

## Better Understanding

My comments have been critical. I firmly believe, however, that if the FDA would have had a better understanding of the *in vitro* diagnostic product industry before implementing a regulatory program, a "regulatory ordeal" could have been avoided. I am unaware of any significant health hazard which could not have been handled adequately by the Agency during the interim. If a more carefully planned, phased approach would have been used, costly haste could have been avoided and both the regulator and the regulated industry would have been in a better position to serve the *in vitro* diagnostic product user, who, after all, should be the ultimate beneficiary of any regulatory program. **[The End]**

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## MEDICAL DEVICES BILLS PENDING IN CONGRESS

Three bills for the regulation of medical devices are presently being considered by Congress, two in the House of Representatives and one in the Senate. H. R. 5545 and S. 510, introduced by Representative Paul Rogers and Senator Edward Kennedy, respectively, would provide a system for classifying medical devices according to type of regulation needed—general controls, performance standards, or individual approval. H. R. 974, introduced by Representative Fred Rooney, would establish a National Medical Devices Commission to study and recommend methods of regulating medical devices. Until the Commission issued its report, the general prohibitions and enforcements procedures in the Federal Food, Drug and Cosmetic Act would be applicable to medical devices.

The Senate bill has been reported out by the Committee on Labor and Public Welfare with a "do-pass" recommendation. This bill is substantially the same as the bill adopted by the Senate in 1974. The Rogers bill and the Rooney bill are currently before the House Committee on Interstate and Foreign Commerce.

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[14] 21 CFR 328.20 (1974).

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