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persons were invited to submit comments on the proposal within 60 days. Comments were received from the Pharmaceutical Manufacturers Association, 12 affected manufacturers and several private individuals. These comments concerned almost every part of the proposal and its accompanying preamble. In addition, many other comments were received from physicians and recipients of bacterial vaccines which, although referring to these regulations, did not offer any comments on the proposed procedure, but rather concerned themselves only with the review for safety and effectiveness of bacterial vaccines and antigens whose label bears the statement "No U.S. standard of potency." These comments were considered as being responsive to the call for information on such bacterial vaccines and antigens which was published in the same issue of the FEDERAL REGISTER (37 FR 16690), and have thus been filed with other data received on these products.

GENERAL COMMENTS

1. Comments received from some physicians indicated concern that the Food and Drug Administration will spend public funds on a review which will result in the removal from the market of drugs which physicians are currently using and which patients need. As the advisory review panels will be constituted in such a manner that practicing physicians will be well represented, the needs of the patients for whom they care will be fully considered. Furthermore, any persons, particularly physicians, who have scientific and/or clinical information concerning these products will be given full opportunity to present such data to the advisory panels. It should be noted that the FDA has no desire to reduce the number of biological products available to the practicing physician and his patients. The agency's overriding purpose is to assure everyone who administers or receives a biological product that he is utilizing a product which is safe and effective for its labeled purpose.

2. Many comments were received which indicated that for many biological products there is a positive correlation between potency standards and clinical effectiveness, and that therefore the review should be limited to products for which ability to control disease has not been demonstrated. If not so limited, one comment requested that for products recognized as effective, a group submission should be permitted. Section 273.745 (b) of the proposed regulations indicated that the submission should follow the published format unless changed in the formal FEDERAL REGISTER notice requesting data, thus indicating an awareness by the FDA that such information may not always be requested. This section has been modified to clearly indicate that when the Commissioner of Food and Drugs determines that the available documented data are clear concerning the safety, effectiveness, or proper labeling of such products, the particular request for data and information will indicate that the usual format need not be

followed, and will also specifically indicate what information should be submitted and in what format.

3. Many comments stated that the proposed regulations combined the substance of the requirements of the Federal Food, Drug, and Cosmetic Act with the procedural requirements of the Public Health Service Act, by making the standards of safety and effectiveness set forth in the new drug provisions of section 505 of the Federal Food, Drug, and Cosmetic Act applicable to biological products through the employment of the licensing provisions of the Public Health Service Act. These comments contended that such a combination was not legally permissible. To the contrary, biological products, subject to regulation under section 351 of the Public Health Service Act, are also drugs, within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act, and are therefore also subject to regulation under that act. Furthermore, Congress has clearly indicated its intentions in this regard in that both acts clearly and unequivocally state that nothing in either act shall be construed so as to in any way affect, modify, repeal, or supersede the provisions of the other act. It is therefore clearly permissible for the agency to develop a comprehensive regulatory program which combines the applicable provisions of both acts so as to regulate all biological drugs uniformly and efficiently.

4. Some comments argued that the license of a biological product which is not a new drug within the meaning of section 505 of the Federal Food, Drug, and Cosmetic Act cannot be revoked solely because a product is lacking in substantial evidence of effectiveness. With respect to biological products which are new drugs, these comments argued that the agency can only withdraw approval of the products under the procedures, and subject to the judicial review provided for, in the Federal Food, Drug, and Cosmetic Act. Regardless of whether a particular biological product is a new drug, however, all biological products are subject to the misbranding provisions of both section 502 of the Federal Food, Drug, and Cosmetic Act and section 351(b) of the Public Health Service Act. A biological product whose label purports, represents, or suggests it to be effective and/or safe for certain intended uses, and which is not safe and effective for such uses, is misbranded within the meaning of both acts, and therefore should not and will not be licensed under section 351 of the Public Health Service Act. Congress has clearly stated that a misbranded biologic may not be distributed in interstate commerce.

5. One comment argued that the proposed procedure would illegally shift the burden of proof upon the licensee to show that his product is not misbranded. This is not the situation. No license has been issued in the past for a product that the agency believes to be misbranded. The burden is on the prospective licensee, as it is upon a new drug applicant, to show a lack of misbranding to obtain a license or an approved new drug application, and

SUBCHAPTER F—REGULATIONS UNDER SPECIFIC ACTS OF CONGRESS OTHER THAN THE FOOD, DRUG, AND COSMETIC ACT

PART 273—BIOLOGICAL PRODUCTS

Procedures for Review of Safety, Effectiveness and Labeling

A proposal regarding procedures for the review of safety, effectiveness and labeling of biological products was published in the FEDERAL REGISTER of August 18, 1972 (37 FR 16679). Interested

this burden remains on the licensee or new drug applicant after the license or new drug application is issued and approved.

COMMENTS RELATING TO SPECIFIC PROVISIONS OF PROPOSED § 273.245 (21 CFR 273.245)

I. PARAGRAPH (a)—ADVISORY REVIEW PANELS

1. Numerous comments were received requesting that the final order indicate the categories of products to be reviewed and their anticipated order of review, and further, that in the call for data and information for a particular category, the proper name of all products included in the category be stated. It is anticipated that nine designated categories of biological products shall be reviewed, the reviews to commence in the following order:

- (a) Bacterial vaccines and bacterial antigens bearing labeling stating "No U.S. standard of potency."
- (b) Bacterial vaccines and toxoids with standards of potency, single or in combination.
- (c) Viral vaccines, single or in combination, and Rickettsial vaccines.
- (d) Allergenic extracts.
- (e) Skin test antigens.
- (f) Immune serums, antitoxins and antivenins.
- (g) Blood and blood derivatives.
- (h) In Vitro diagnostic reagents.
- (i) Miscellaneous (all other biological products not falling within one of the above therapeutic categories).

2. Several comments suggested that the regulations require that the advisory panels include persons from lists submitted by interested organizations, rather than allowing the inclusion of such persons to be discretionary. Further, they stressed that qualified persons of divergent views be mandatorily included. The Commissioner intends that the advisory review panels be both highly qualified and broadly representative of responsible medical and scientific opinion. Therefore, these comments are accepted and the regulations have been revised accordingly.

II. PARAGRAPH (b)—REQUEST FOR DATA AND VIEWS

1. Many comments were received questioning the FDA's authority summarily to revoke a license for a biological product on the ground that the requested data and information were not submitted. The FDA has sufficient authority under section 351 of the Public Health Service Act to revoke a license for a willful failure to submit required safety and effectiveness data. Nevertheless, the Commissioner has determined to revise the procedures governing the treatment accorded licensees failing to submit safety and effectiveness data for their products. Licenses for such products will not be revoked until such time as the Commissioner has published the final order establishing standards for the safety, effectiveness, and labeling of the particular category of biological prod-

ucts, and the products for which no data have been submitted fail to meet those standards. This approach has been adopted so as to ensure that no person currently receiving a licensed biological product in a medical context will be deprived of any of the possible benefits of the product until an expert, advisory panel has made a thorough evaluation of all available safety and effectiveness data concerning the product. As the majority of currently licensed biologics have been in use for a substantial period of time, and were evaluated for safety prior to initial licensure, the Commissioner finds that no substantial safety risk will be presented by allowing such products to remain on the market pending a thorough review. The Commissioner expects that all responsible licensees will actively participate in the review by submitting all relevant safety and effectiveness data at their disposal. A consideration of the public interest in assuring that only safe, effective, and properly labeled biologics are available to the American public demands nothing less than full participation by all concerned manufacturers. Should such participation not be forthcoming, the Commissioner reserves the right to reconsider this decision to permit interim marketing of products for which no submission has been made.

2. Several comments were received requesting that the data submitted pursuant to these review procedures be considered confidential, even after the evaluation of the particular advisory review panel has been completed. The FDA position in this matter is that while data submitted in confidence is being reviewed by the panel, FDA will protect the data's confidentiality if it is entitled to such treatment under the provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). However, the data would be made available to the public 30 days after publication of the proposed order unless the person submitting the data can demonstrate that it is in fact still entitled to such confidentiality. Such action protects both the confidentiality of true trade secrets as well as the public's right to understand the basis for governmental decisions that vitally affect it. In keeping with the congressional intent of the Freedom of Information Act (5 U.S.C. 552), the FDA is making available to the public as much of the biologics effectiveness review data and information as is permissible under the law.

3. Several comments were received indicating that the time of 60 days which was allotted for submission of data was insufficient, especially in those cases in which a manufacturer is licensed for several products within the same category. The Commissioner recognizes that in certain instances 60 days may be an inadequate period of time in which to gather and submit the requisite data. On the other hand, in certain instances submission of data may be in an abbreviated form, and the time should be set accordingly. Therefore, this section has been amended to indicate that the submission

shall be within 60 days, unless otherwise indicated in the notice for a particular category.

III. PARAGRAPH (b) (3), ITEM I

A. Label or labels and all other labeling. 1. Comments were received requesting that the requirement for submission of labels be limited to the final container label, package label, and package enclosures. In addition, several comments indicated that they assumed that the requirement for labeling pertained only to domestic labeling. While the only labeling that need be submitted by a manufacturer is the container and package label, as well as the package insert, the Commissioner intends that export as well as domestic labeling be submitted, since section 351 of the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act regulate the export of biological products as well as interstate commerce in such products. The regulations have been revised to clarify this point.

PARAGRAPH (b) (3), ITEM III

B. Complete quantitative composition of the biological product. 1. Comments were received stating that the Food and Drug Administration's request for the complete quantitative composition of the biological product was not necessary because the review covered only the safety and efficacy of active ingredients. Since inactive ingredients may markedly affect the stability, and therefore the potency and effectiveness of a product, the composition of all ingredients must be known. These comments have therefore been rejected.

PARAGRAPH (b) (3), ITEM VII

C. Summary. 1. Several comments suggested that the last sentence in this section should be revised to indicate that the explanation of the absence of controlled studies in the materials submitted be permitted to include not only why such studies are not considered necessary, but also why they are not considered to be feasible. As it is not the Commissioner's intention to require controlled studies where they are clearly not feasible, the suggestion has been accepted and the regulations have been revised accordingly.

PARAGRAPH (b) (3), ITEM VIII

D. Signed statement. 1. There was a request that this section be revised to indicate clearly that the designated statement be permitted to be filed either as a corporate submission, a submission signed by the responsible head, or a submission signed by the individual responsible for the submission. In order to clarify the meaning of this section, it has been revised to state that the statement must be signed by the person who is the "responsible head" as designated in 21 CFR 273.500. The request that corporate submissions be permitted is rejected, for the Commissioner is convinced that requiring the responsible head of an establishment to sign the statement will promote the submission

comprehensive and balanced

PARAGRAPH (c)—DELIBERATIONS OF AN ADVISORY REVIEW PANEL

1. Several comments concerned the provision that any interested person may request an opportunity to present his views orally to the panel. They stated that oral presentations made to the panel should not be based on whether or not the panel wished to hear such presentations, but that such presentations should be a matter of right. The panel, however, must reserve the right to grant or deny a request to make an oral presentation on the basis of the merits of the request as well as on the amount of time available. The Commissioner has therefore rejected these requests, preferring to leave the panel with discretion to grant or deny a request for an oral presentation, since they alone know whether the presentation requested may present data, information, or views in which they are interested. The Commissioner believes that no reasonable request will be denied.

V. PARAGRAPH (d)—STANDARDS FOR SAFETY, EFFECTIVENESS, AND LABELING

A. Paragraph (d), subparagraph (1)

safety. 1. Several comments were made requesting that the definition of safety be broadened so as to include a consideration of the benefit to risk ratio of the particular product under review. As subparagraph (3) of this paragraph indicates that the benefit to risk ratio of a biological product shall be considered in determining both safety and effectiveness, the proposed revision of the definition of safety is unnecessary.

B. Paragraph (d), subparagraph (2) *effectiveness.* 1. Several comments requested that the definition of effectiveness be extended to allow in certain situations for alternative methods, such as serological response evaluation in clinical studies, and appropriate animal and laboratory assays, to serve as adequate substantiation of effectiveness. Although this subparagraph as originally proposed indicated that in certain circumstances alternative methods of investigation will be adequate to substantiate effectiveness, this subparagraph has been amended to indicate with greater specificity that alternative procedures may be considered satisfactory.

VI. PARAGRAPH (e)—ADVISORY REVIEW PANEL REPORT TO THE COMMISSIONER

1. Comment was received requesting that the report of the advisory review panel be submitted to the concerned manufacturers at the same time that it is submitted to the Commissioner. This request has been rejected, since the report of each panel is advisory to the Commissioner, who has the final authority either to accept or to reject the conclusions and recommendations of the panel. It should be noted in this connection that the regulations provide that at such time as the Commissioner publishes the proposed order in the FEDERAL REGISTER, he shall also publish the full report

or reports of the panel. It should further be noted that interested parties, including consumers and manufacturers, will be kept fully informed of the deliberations of the panel through liaison representatives. It is therefore anticipated that concerned members of industry and the general public will have ample opportunity to express their views to the panel. The Freedom of Information Act would also prohibit any special submission of the panel report to industry before its general release.

2. Comments were also received asserting that the advisory panels cannot state the type of studies that should be done for biological products deemed to be neither safe and effective nor unsafe and ineffective, since the design of study protocols are the prerogative of the licensee and not of the advisory panel. The Commissioner has no intention whatever of infringing on the right of a manufacturer to conduct whatever studies it wishes. The Commissioner will, however, give careful consideration to the recommendations of the advisory panels regarding appropriate studies during his evaluation of the adequacy of a licensee's or applicant's proposed studies.

VII. PARAGRAPHS (f) AND (g)—PROPOSED AND FINAL ORDERS

1. Comment was received requesting that the proposed and final orders be made available to concerned licensees prior to their publication in the FEDERAL REGISTER. Inasmuch as industry, along with consumers, will have a liaison member on the panel to keep it informed, and because the Commissioner has an obligation to all members of the public to keep them informed as promptly as possible, no change will be made in either of the two paragraphs concerning the procedures to be followed with respect to the availability of the proposed and final orders.

VIII. PARAGRAPH (h)—ADDITIONAL STUDIES

1. Some comments indicated that 30 days is an inadequate period of time in which to undertake any further studies which may be needed. These comments stressed that, except in rare instances, studies which may be required could probably not begin within that time period due to necessary planning. Although the Commissioner has indicated that this 30-day period may be extended if necessary, the regulations have been amended to more specifically provide for an additional period of time from the publication of the final order, providing certain prescribed conditions are met.

IX. PARAGRAPH (i)—CATEGORIES OF BIOLOGICAL PRODUCTS TO BE REVIEWED

1. Some comments were received concerning the need for a different type of review for those biological products which are also in vitro diagnostic reagents. It is anticipated that the format for submissions may in fact need to be revised for in vitro diagnostic reagents, but it is believed that the format is

sufficiently flexible to cover these products. It should further be noted that such products are also the subject of the impending in vitro diagnostic product review (37 FR 16513), and that the two reviews will be coordinated.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042, as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371), the Public Health Service Act (sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243, as amended; 5 U.S.C. 553, 702, 703, 704), and under authority delegated to the Commissioner, Part 273 is amended by adding a new section, as follows:

§ 273.245 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of reviewing biological products that have been licensed prior to July 1, 1972, to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products.

(a) *Advisory review panels.* The Commissioner of Food and Drugs shall appoint advisory review panels (1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act, (2) to review the labeling of such biological products, and (3) to advise him on which of the biological products under review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) *Request for data and views.* (1) The Commissioner of Food and Drugs will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products.

(2) Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the

advisory review panel and the Food and Drug Administration as confidential until publication of a proposed evaluation of the biologics under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Office of the Hearing Clerk of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of these statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8½ x 11 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating "none" or "not applicable" where appropriate, unless changed in the FEDERAL REGISTER notice:

BIOLOGICAL PRODUCTS REVIEW INFORMATION

I. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export.

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

V. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.

5. Pertinent medical and scientific literature.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.

5. Pertinent medical and scientific literature.

VII. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

VIII. If the submission is by a licensee, a statement signed by the responsible head (as defined in 21 CFR 273.500) of the licensee shall be included, stating that to the best of his knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensee, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

(c) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner of Food and Drugs with respect to the safety, effectiveness, and labeling of the biological products in the designated category under review.

(1) A panel may also consult any individual or group.

(2) Any interested person may request in writing an opportunity to present oral views to the panel. Such written requests for oral presentations should include a summarization of the data to be presented to the panel. Such request may be granted or denied by the panel.

(3) Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (b) (3) of this section and within the time period established for the biological product category in the notice for review by a panel.

(d) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is safe and effective and not misbranded.

(1) Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.

(2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 130.12(a) (5) (ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluation may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case report, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components: (i) When each active component makes a contribution to the claimed effect or effects; (ii) when combination of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and (iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicable requirements of §§ 273.600 through 273.605 and 1.106 of this chapter.

(c) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

(1) A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

(2) A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.

(3) A statement which designates those biological products determined by the panel not to fall within either subparagraph (1) or (2) of this paragraph on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded. The report shall also recommend whether the product license should or should not be revoked, thus permitting or denying continued manufacturing and marketing of the biological product pending completion of the testing. This recommendation will be based on an assessment of the present evidence of the safety and effectiveness

of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.

(f) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a proposed order containing:

(1) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness, and may propose corresponding amendments in other regulations under this Part 273.

(2) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefor. All licenses for such products shall be proposed to be revoked.

(3) A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are insufficient to classify such biological products under either subparagraphs (1) or (2) of this paragraph. Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis. Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the product license for any biological product, falling within this paragraph will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The tests necessary to resolve whatever safety or effectiveness questions exist shall be described.

(4) The full report or reports of the panel to the Commissioner of Food and Drugs.

The summary minutes of the panel meeting or meetings shall be made available to interested persons upon request. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Hearing Clerk during regular working hours, Monday through Friday.

(g) *Final order.* After reviewing the comments, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

(h) *Additional studies.* (1) Within 30 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to paragraph (f) (3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal Government may undertake the studies. The Commissioner may extend this 30-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product license or licenses shall be revoked.

(2) A progress report shall be filed on the studies every January 1 and July 1 until completion. If the progress report is inadequate or if the Commissioner of Food and Drugs concludes that the studies are not being pursued promptly and diligently, or if interim results indicate the potential benefits do not outweigh the potential risks, the product license or licenses shall be revoked.

(3) Promptly upon completion of the studies undertaken on the product, the Commissioner of Food and Drugs will review all available data and will either retain or revoke the product license or licenses involved. In making this review and evaluation the Commissioner may again consult the advisory review panel which prepared the report on the product, or other advisory committees, professional organizations, or experts. The Commissioner shall take such action by notice published in the FEDERAL REGISTER.

(i) *Court Appeal.* The final order(s) published pursuant to paragraph (g) of this section, and any notice published pursuant to paragraph (h) of this section, constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at his discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

Effective date. This order shall become effective on February 13, 1973.

Dated: February 6, 1973.

SHERWIN GARDNER,
Deputy Commissioner
of Food and Drugs.

[FR Doc. 73-2826 Filed 2-12-73; 8:45 am]