Washington, DC 20204–0002, 202–418–3098.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5)(21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 6B4491) has been filed by Ciba-Geigy Corp., 540 White Plains Road, P.O. Box 2005, Tarrytown, N.Y. 10591–4311. The petition proposes to amend the food additive regulations in § 178.2010 *Antioxidants and/or stabilizers* (21 CFR 178.2010) to expand the safe use of oxidized bis(hydrogenated tallow alkyl)amines as a process stabilizer for polypropylene homo- and copolymers and high-density polyethylene homo- and copolymers intended for use in contact with food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before March 25, 1996, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the Federal Register. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the Federal Register in accordance with 21 CFR 25.40(c).

Dated: February 8, 1996.

Alan M. Rulis,

Director, Office of Premarket Approval, Center For Food Safety and Applied Nutrition.

[FR Doc. 96–4063 Filed 2–22–96; 8:45 am]

BILLING CODE 4160–01–P

[Docket No. 91F–0264]

Stockhausen, Inc.; Withdrawal of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal, without prejudice to a future filing, of a food additive petition (FAP 9B4149), proposing that the food additive regulations be amended to provide for the safe use of N-((3-dimethylamino)propyl)-2-propenamide, polymer with 2-propenoic acid, sodium salt as a dispersing aid in paper and paper coatings intended for use in contact with food.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS–216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3081.

SUPPLEMENTARY INFORMATION: In a notice published in the Federal Register of August 1, 1991 (56 FR 36185), FDA announced that a food additive petition (FAP 9B4149) had been filed on behalf of Stockhausen, Inc., 2401 Doyle St. (formerly 2408 Doyle St.), Greensboro, NC 27406. The petition proposed to amend the food additive regulations in § 176.170 *Components of paper and paperboard in contact with aqueous and fatty foods* (21 CFR 176.170) to provide for the safe use of N-((3-dimethylamino)propyl)-2-propenamide, polymer with 2-propenoic acid, sodium salt as a dispersing aid in paper and paper coatings intended for use in contact with food.

Stockhausen, Inc., has now withdrawn the petition without prejudice to a future filing (21 CFR 171.7).

Dated: February 8, 1996.

Alan M. Rulis,

Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 96–4062 Filed 2–22–96; 8:45 am]

BILLING CODE 4160–01–P

[Docket No. 95D–0216]

International Conference on Harmonisation; Final Guideline on Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration is publishing a final guideline on the quality of biotechnological products entitled ''Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products.'' The guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant deoxyribonucleic acid (r-DNA) derived proteins.

DATES: Effective February 23, 1996. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the guideline are available from the Division of Communications Management (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Elaine C. Esber, Center for Biologics Evaluation and Research (HFM–30), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0641.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input

from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the Federal Register of August 21, 1995 (60 FR 43496), FDA published a draft tripartite guideline entitled ''Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products.'' The notice gave interested persons an opportunity to submit comments by October 5, 1995.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held on November 29, 1995.

The guideline presents guidance regarding the characterization of the expression construct for the production of r-DNA protein products in eukaryotic and prokaryotic cells. The guideline is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce r-DNA derived proteins. The guideline is not intended to cover the entire quality aspect of r-DNA derived medicinal products.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Although this guideline does not create or confer any rights for or on any person and does not operate to bind FDA, it does represent the agency's current thinking on the production of r-DNA derived protein products.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the Federal Register.

Interested persons may, at any time, submit written comments on the final guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guideline follows:

Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products

I. Introduction

This document presents guidance regarding the characterization of the expression construct for the production of recombinant DNA (r-DNA) protein products in eukaryotic and prokaryotic cells. The document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce r-DNA derived proteins. The document is not intended to cover the entire quality aspect of r-DNA derived medicinal products.

The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. Segments of the expression construct should be analyzed using nucleic acid techniques in conjunction with other tests performed on the purified recombinant protein for assuring the quality and consistency of the final product. Analysis of the expression construct at the nucleic acid level should be considered as part of the overall evaluation of quality, taking into account that this testing only evaluates the coding sequence of a recombinant gene and not the translational fidelity nor other characteristics of the recombinant protein, such as secondary structure, tertiary structure, and posttranslational modifications.

II. Rationale for Analysis of the Expression Construct

The purpose of analyzing the expression construct is to establish that the correct coding sequence of the product has been incorporated into the host cell and is maintained during culture to the end of production. The genetic sequence of recombinant proteins produced in living cells can undergo mutations that could alter the properties of the protein with potential adverse consequences to patients. No single experimental approach can be expected to detect all possible modifications to a protein. Protein analytical techniques can be used to assess the amino acid sequence of the protein and structural features of the expressed protein due to posttranslational modifications such as proteolytic processing, glycosylation, phosphorylation, and acetylation. Data from nucleic acid analysis may be useful because protein analytical methods may not detect all changes in protein structure resulting from mutations in the sequence coding for the recombinant protein. The relative importance of nucleic acid analysis and protein analysis will vary from product to product.

Nucleic acid analysis can be used to verify the coding sequence and the physical state of the expression construct. The nucleic acid analysis is performed to ensure that the expressed protein will have the correct amino acid sequence, but is not intended to detect low levels of variant sequences. Where the production cells have multiple integrated copies of the expression construct, not all of which may be transcriptionally active, examination of the transcription product itself by analysis of m-RNA or c-DNA may be more appropriate than analysis of genomic DNA. Analytical approaches that examine a bulk population of nucleic acids, such as those performed on pooled clones or material amplified by the polymerase chain reaction, may be considered as an alternative to approaches that depend on selection of individual DNA clones. Other techniques could be considered that allow for rapid and sensitive confirmation of the sequence coding for the recombinant protein in the expression construct.

The following sections describe information that should be supplied regarding the characterization of the expression construct during the development and validation of the production system. Analytical methodologies should be validated for the intended purpose of confirmation of sequence. The validation documentation should, at a minimum, include estimates of the limits of detection for variant sequences. This should be performed for either nucleic acid or protein sequencing methods. The philosophy and recommendations for analysis expressed in this document should be reviewed periodically to take advantage of new advances in technology and scientific information.

III. Characterization of the Expression System

A. Expression Construct and Cell Clone Used to Develop the Master Cell Bank (MCB)

The manufacturer should describe the origin of the nucleotide sequence coding for the protein. This should include identification and source of the cell from which the nucleotide sequence was originally obtained. Methods used to prepare the DNA coding for the protein should be described.

The steps in the assembly of the expression construct should be described in detail. This description should include the source and function of the component parts of the expression construct, e.g., origins of replication, antibiotic resistance genes, promoters, enhancers, and whether or not the protein is being synthesized as a fusion protein. A detailed component map and a complete annotated sequence of the plasmid should be given, indicating those regions that have been sequenced during the construction and those taken from the literature. Other expressed proteins encoded by the plasmid should be indicated. The nucleotide sequence of the coding region of the gene of interest and associated flanking regions that are inserted into the vector, up to and including the junctions of insertion, should be determined by DNA sequencing of the construct.

A description of the method of transfer of the expression construct into the host cell should be provided. In addition, methods used to amplify the expression construct and criteria used to select the cell clone for production should be described in detail.

B. Cell Bank System

Production of the recombinant protein should be based on well-defined MCB and Working Cell Banks (WCB). A cell bank is a collection of ampoules of uniform composition stored under defined conditions, each containing an aliquot of a single pool of cells. The MCB is generally derived from the selected cell clone containing the expression construct. The WCB is derived by expansion of one or more ampoules of the MCB. The cell line history and production of the cell banks should be described in detail, including methods and reagents used during culture, in vitro cell age, and storage conditions. All cell banks should be characterized for relevant phenotypic and genotypic markers, which could include the expression of the recombinant protein or presence of the expression construct.

The expression construct in the MCB should be analyzed as described below. If the testing cannot be carried out on the MCB, it should be carried out on each WCB.

Restriction endonuclease mapping or other suitable techniques should be used to analyze the expression construct for copy number, for insertions or deletions, and for the number of integration sites. For extrachromosomal expression systems, the percent of host cells retaining the expression construct should be determined.

The protein coding sequence for the recombinant protein product of the expression construct should be verified. For extrachromosomal expression systems, the expression construct should be isolated and the nucleotide sequence encoding the product should be verified without further cloning. For cells with chromosomal copies of the expression construct, the nucleotide sequence encoding the product could be verified by recloning and sequencing of chromosomal copies. Alternatively, the nucleic acid sequence encoding the product could be verified by techniques such as sequencing of pooled c-DNA clones or material amplified by the polymerase chain reaction. The nucleic acid sequence should be identical, within the limits of detection of the methodology, to that determined for the expression construct as described in section III.A., and should correspond to that expected for the protein sequence.

C. Limit for In Vitro Cell Age for Production

The limit for in vitro cell age for production should be based on data derived from production cells expanded under pilot plant-scale or full-scale conditions to the proposed in vitro cell age or beyond. Generally, the production cells are obtained by expansion of the WCB; the MCB could be used to prepare the production cells with appropriate justification.

The expression construct of the production cells should be analyzed once for the MCB as described in section III.B., except that the protein coding sequence of the expression construct in the production cells could be verified by either nucleic acid testing or analysis of the final protein product. Increases in the defined limit for in vitro cell age for production should be supported by data from cells that have been expanded to an in vitro cell age that is equal to or greater than the new limit for in vitro cell age.

IV. Conclusion

The characterization of the expression construct and the final purified protein are both important to ensure the consistent production of a r-DNA derived product. As described above, analytical data derived from both nucleic acid analysis and evaluation of the final purified protein should be evaluated to ensure the quality of a recombinant protein product.

Glossary of Terms

Expression Construct

The expression vector that contains the coding sequence of the recombinant protein and the elements necessary for its expression.

Flanking Control Regions

Noncoding nucleotide sequences that are adjacent to the 5' and 3' end of the coding sequence of the product that contain important elements that affect the transcription, translation, or stability of the coding sequence. These regions include, e.g., promoter, enhancer, and splicing sequences, and do not include origins of replication and antibiotic resistance genes.

Integration Site

The site where one or more copies of the expression construct is integrated into the host cell genome.

In Vitro Cell Age

Measure of time between thaw of the MCB vial(s) to harvest of the production vessel measured by elapsed chronological time in culture, by population doubling level of the cells, or by passage level of the cells when subcultivated by a defined procedure for dilution of the culture.

Master Cell Bank (MCB)

An aliquot of a single pool of cells that generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB, or WCB) should be the same as for the MCB unless justified.

Pilot Plant Scale

The production of a recombinant protein by a procedure fully representative of and simulating that to be applied on a full commercial manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Relevant Genotypic and Phenotypic Markers

Those markers permitting the identification of the strain of the cell line that should include the expression of the recombinant protein or presence of the expression construct.

Working Cell Bank (WCB)

The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

Dated: February 16, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–4064 Filed 2–22–96; 8:45 am]

BILLING CODE 4160–01–F

Advisory Committees; Notice of Meetings

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces forthcoming meetings of public advisory committees of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meetings and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

FDA has established an Advisory Committee Information Hotline (the hotline) using a voice-mail telephone system. The hotline provides the public with access to the most current information on FDA advisory committee meetings. The advisory committee hotline, which will disseminate current information and information updates, can be accessed by dialing 1–800–741–8138 or 301–443–0572. Each advisory committee is assigned a 5-digit number. This 5-digit number will appear in each individual notice of meeting. The hotline will enable the public to obtain information about a particular advisory committee by using the committee's 5-digit number. Information in the hotline