process validation studies or by lot release testing.

In general, products for which the presence of live cells cannot be excluded or which have little downstream purification (for example, some conventional live virus vaccines) will need such characterization of the cell substrate. The utility of tumorigenicity testing and chromosomal analysis for new cell substrates for unpurified products should be evaluated on a case-by-case basis. Use of cell lines known to be tumorigenic or to possess abnormal karyology should be evaluated in terms of risk-benefit for each product application when the product contains cells or when not highly purified.

Products that are manufactured in genetically unmodified MRC–5 or WI–38 cells do not need characterization of these cell substrates by karyology or tumorigenicity since extensive characterization has already been performed and published for these cell lines. However, for each MRC–5 and WI–38 WCB generated, manufacturers should confirm, once, that the cells grown in the manner to be used in production are diploid and have the expected lifespan.

For new or previously uncharacterized diploid cell substrates, confirmation of diploid karyology should be presented and tumorigenic potential should be established, using cells from the MCB.

3.0 Glossary

Cell bank—A cell bank is a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell line—Type of cell population that originates by serial subculture of a primary cell population, which can be banked.

Continuous cell line—A cell line having an infinite capacity for growth. Often referred to as ''immortal'' and previously referred to as ''established.''

Diploid cell line—A cell line having a finite in vitro lifespan in which the chromosomes are paired (euploid) and are structurally identical to those of the species from which they were derived.

Host cells—See parental cells.

In vitro cell age—Measure of time between thaw of the MCB vial(s) and harvest of the production vessel measured by elapsed chronological time, 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.

Metazoan—Organism of multicellular animal nature.

MCB (Master Cell Bank)—An aliquot of a single pool of cells which 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 original MCB unless justified.

Parental cells—Cells to be manipulated to give rise to a cell substrate or an intermediate cell line. For microbial expression systems, it is typical to also describe the parental cells as the host cells. For hybridomas, it is typical to also describe the parental cells as the cells to be fused.

WCB (Working Cell Bank)—The Working Cell Bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

Appendix 1

Primary Cell Substrates

I. Introduction

The principles contained in this document apply in general to biotechnological/biological products prepared from characterized banked cells. However, a number of biological products, in particular certain viral vaccines, are prepared using primary cells.

Because primary cell cultures are used within the first passage after establishment from the tissue of origin, it is not possible to carry out extensive characterization of the cells prior to their use as is done for banked cell substrates. In addition, biological products produced using primary cell substrates often do not undergo extensive processing (e.g., purification). Despite these differences, the approach taken to ensure the suitability and safety of primary cell substrates for production of biologicals is analogous, in many respects, to that outlined in this document and in other guidances.

This annex outlines cell substrate-related information that should be included in marketing applications for biological products prepared using primary cells. This information falls into three general categories: (1) Information concerning the source tissue (or organ) and other animal-derived raw materials used for the establishment of primary cell substrates, (2) information concerning the preparation of primary cell substrates, and (3) testing performed on primary cell substrates to ensure the safety of the product.

II. Source Tissue and Other Raw Materials

Information should be provided about the animals used as a source of tissue for the preparation of primary cell substrates. Tissue should be derived from healthy animals subjected to veterinary and laboratory monitoring to certify the absence of pathogenic agents. Whenever possible, donor animals should be obtained from closed, specific pathogen-free (when available) colonies or flocks. Animals used as tissue donors should not have been used previously for experimental studies. Animals should be adequately quarantined for an appropriate period of time prior to use for the preparation of cells. In some countries, animals may need to be quarantined in the country where the primary cells are prepared. Manufacturers should consult with national/regional authorities for specific requirements.

Information on materials and components used for the preparation of primary cell substrates should be provided, including the identity and source of all reagents of human or animal origin. A description of testing performed on components of animal origin to certify the absence of detectable contaminants and adventitious agents should be included.

III. Preparation of Primary Cell Substrates

Methods used for isolation of cells from tissue, establishment of primary cell cultures, and maintenance of cultures should be described.

IV. Testing of Primary Cell Substrates

Tests performed on primary cell substrates to qualify them for use in production should be described. As noted, the nature of primary cell substrates precludes extensive testing and characterization prior to use. Testing to demonstrate the absence of adventitious agents in these substrates is therefore conducted concurrently and may include: Observation of production or uninfected control cultures before, during, and beyond the period of production; inoculation of culture fluids from production and uninfected control cultures into various susceptible indicator cell cultures capable of detecting a wide range of relevant viruses, followed by examination for cytopathic changes and testing for the presence of hemadsorbing viruses; and other tests for specific agents (such as relevant retroviruses) as necessary. Additional information concerning specific viral tests may be found in the relevant national/regional/international guidances.

Appropriate testing regimens and test methods for cells used in the production of specific products will vary depending on the donor species used as a source of tissue, adventitious agents potentially present, the nature of the product, its intended clinical use, aspects of the manufacturing process, and the extent of testing performed on the final product. Applicants should explain and justify the approach taken with respect to their specific product.

Dated: August 28, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98–25108 Filed 9–18–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Medical Gas Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of workshop.

The Food and Drug Administration (FDA) is announcing the following workshop: Medical Gas Workshop. The topics to be discussed are good manufacturing practices (GMP's) issues for the medical gas industry, including air liquefaction, both process and computer validation, transfilling of both liquid and high pressure cylinders, and hospital installations.

Date and Time: The workshop will be held on Tuesday, November 10, 1998, 8:30 a.m. to 4:30 p.m.

Location: The workshop will be held at the Century Center, Convention Hall

C–South, 120 South Saint Joseph St., South Bend, IN.

Contact: Keith J. Jasukaitis, Food and Drug Administration, 1560 East Jefferson Ave., Detroit, MI 48207, 313–226–6260, ext. 114, FAX 313–226–3076, or e-mail ''kjasukai@ora.fda.gov''.

Registration: Send registration information (including name, title, firm name, address, telephone, and fax number, and the number of people expected to attend) to the contact person by Friday, October 23, 1998.

If you need special accommodations due to a disability, please notify Keith J. Jasukaitis by October 23, 1998.

Dated: September 11, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–25109 Filed 9–18–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee for Pharmaceutical Science; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Advisory Committee for Pharmaceutical Science.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on October 22, 1998, 8:30 a.m. to 5 p.m.

Location: Advisory Committee conference room, rm. 1066, 5630 Fishers Lane, Rockville, MD 20852.

Contact Person: Kimberly L. Topper or Angie Whitacre, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857–1000, 301–827–7001, or e-mail ''Topperk@cder.fda.gov'', or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12539. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss: (1) Bioavailability/bioequivalence (BA/BE) issues related to solid oral dosage forms; (2) progress reports on guidances pertaining to the biopharmaceutical classification system, other BA/BE guidances; and (3) criteria (average, population, and individual) to allow comparison of BE measures/parameters.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by October 5, 1998. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before October 5, 1998, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: September 11, 1998.

Sharon Smith Holston,

Acting Commissioner of Food and Drugs.

[FR Doc. 98–25106 Filed 9–18–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Joint Meeting of the Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on October 23, 1998, 8:30 a.m. to 5 p.m.

Location: Advisory Committee Conference Room, rm. 1066, 5630 Fishers Lane, Rockville, MD 20852.

Contact Person: Kimberly L. Topper or Tracy Riley, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7001, or e-mail ''Topperk@cder.fda.gov'', or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12539. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committees will discuss: (1) The draft guidance entitled ''Topical Dermatological Drug Product NDA's and ANDA's—In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies;'' (2) public comments received on the draft guidance; and (3) additional information.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by October 5, 1998. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before October 5, 1998, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: September 11, 1998.

Sharon Smith Holston,

Acting Commissioner of Food and Drugs.

[FR Doc. 98–25107 Filed 9–18–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (Ranch Hand Advisory Committee); Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Department of Health and Human