DIAGNOSTIC HYBRIDS
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QUALITY ASSURANCE STATEMENT
Cell Cultures and Media

Diagnostic Hybrids, Inc. (DHI) manufactures products in a facility certified to the ISO 13485:2003 quality system standard for medical device manufacturers and in conformance with the requirements of USA's Code of Federal Regulations title 21 (CFR), the requirements of Canada's Medical Device Regulations (CMDR), and the requirements of European Union's In Vitro Diagnostic Medical Devices Directive (IVDD).

CELLS:

- Cell types are from reliable, reputable, and traceable sources. Prior to acceptance into DHI's production facility, cell lines and strains are reviewed through documentation history and laboratory analysis to verify that no microorganisms (by sterility testing) and no viruses [as evidenced by the absence of cytopathic effect (CPE)] are known to be present.
- The various cell types are characterized as to species identity by isoenzyme analysis.
- Prior to shipment of each lot of cell culture, the culture medium is examined for clarity and pH, and monolayers are examined microscopically for morphology, confluence, and uniformity.
- During a cell product's lifetime, representatives of batches are evaluated according to defined performance criteria using appropriate indicator viruses or *Chlamydia* as inoculae.

MEDIA:

- The U.S.-origin fetal bovine serum (FBS) and bovine serum albumin (BSA) used throughout for these products, and the bovine-derived trypsin used in the preparation of cell cultures, are fully characterized and tested by the supplier(s) to demonstrate normal and specific levels of serum constituents (of the FBS) and to confirm the absence of *Mycoplasma spp*. and other organisms, in compliance with US-9CFR113. DHI tests and selects FBS prior to use to demonstrate that it is nontoxic to cells and supports normal cell growth.
- Media components are screened and/or selected based on relevant criteria, e.g., grade, activity, purity, toxicity.
- Media are prepared at a pH range of 7.0 to 7.6, which is generally characterized by an orange-to-red or pink color due to the incorporation of phenol red, a pH indicator dye. This pH value may change during the normal use of a Culture Medium-containing product (e.g., the pH will rise upon exposure to air, leading to a color change to purple; the pH may fall should the medium become contaminated with microorganism or exposed to a high CO_2 concentration leading to a color change to yellow).

STERILITY OF LOTS:

- At various stages of the manufacturing process prior to shipping, cell culture products and culture medium lots are screened for evidence of adventitious microorganisms.
- Upon receipt of all cell cultures, the uninoculated monolayer should be examined for appearance (e.g., dead or toxic cells, confluency) and morphology (e.g., atypical cells or CPE) prior to inoculation.
- Since cell cultures have a relatively short shelf-life, they cannot be tested for the required 14 days prior to shipment to verify absence of microorganisms. DHI continues to monitor representative samples from each lot of cell product for evidence of microorganisms for at least 14 days after first shipment.
- Media and frozen cell suspensions are screened for absence of microorganisms according to procedures described in the USP-XXIII for sterility testing of solutions.
- *Note concerning products with part number prefixes 46-, 47-, and 49-:* Fresh monkey primary cell cultures are known to occasionally harbor viruses or other microorganisms that were present in the source animal. Additional surveillance of these products is conducted in order to detect as soon as possible the presence of an endogenous agent that manifests itself either as a CPE in the cells or as turbidity of or flocculence in the culture medium; however, such detection often does not occur until the cells have been in a laboratory's hands for days or weeks. Due diligence is given this issue such that a laboratory that may receive an affected lot is notified as soon as we become aware of the occurrence and of its potential ramifications. The CDC-NIH manual, *Biosafety in Microbiological and Biomedical Laboratories*, 2007, recommends that primary primate culture be handled in the laboratory according to Biosafety Level 2 [BSL-2] practices.

PRODUCT SPECIFICATIONS:

Information beyond that provided by the Instructions for Use, Product Insert, Lot Specification Sheet or Material Safety Data Sheet on a particular product or product lot is available on request.

Karl E. Luke, PhD, Director, Quality Affairs

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Date