

INGREDIENT REQUIREMENTS

§ 113.50 Ingredients of biological products.

All ingredients used in a licensed biological product shall meet accepted standards of purity and quality; shall be sufficiently nontoxic so that the amount present in the recommended dose of the product shall not be toxic to the recipient; and in the combinations used shall not denature the specific substances in the product below the minimum acceptable potency within the dating period when stored at the recommended temperature.

[38 FR 29889, Oct. 30, 1973]

§ 113.51 Requirements for primary cells used for production of biologics.

Primary cells used to prepare biological products shall be derived from normal tissue of healthy animals. When prescribed in an applicable Standard Requirement or in the filed Outline of Production, each batch of primary cells used to prepare a biological product shall be tested as prescribed in this section. A batch of primary cells found unsatisfactory by any prescribed test shall not be used. A serial of biological product shall not be released if produced from primary cells that are found unsatisfactory by any prescribed test.

(a) Final container samples of completed product or samples of the final pool of harvested material or samples of each subculture of cells used to prepare the biological product shall be shown free of mycoplasma as prescribed in §113.28. The sample for testing shall consist of at least 75 cm² of actively growing cells or the equivalent in harvest fluids; *Provided*, That all sources of cells in the batch of primary cells are represented.

(b) Final container samples of completed product or samples of the final pool of harvested material or samples of each subculture of cells used to prepare the biological product shall be shown free of bacteria and fungi as prescribed in §113.26 or §113.27 (whichever is applicable).

(c) A monolayer at least 75 cm² from each batch of primary cells or each subculture of primary cells used to pre-

pare a biological product shall be shown free of extraneous agents as prescribed in this paragraph.

(1) The test monolayer shall be maintained using the medium (with additives) and under conditions similar to those used to prepare biological products.

(i) Monolayers of avian origin shall be maintained for at least 14 days and shall be subcultured at least once during the maintenance period. All but the last subculture shall result in a new monolayer of at least 75 cm². The last subculture shall meet the minimum area requirement specified in §§113.46 and 113.47.

(ii) Monolayers not of avian origin shall be maintained for at least 28 days and shall be subcultured at least twice during the maintenance period. All but the last subculture shall result in a new monolayer of at least 75 cm². The last subculture shall meet the minimum area requirement specified in §§113.46 and 113.47.

(2) Monolayers shall be examined regularly throughout the required maintenance period for evidence of the presence of cytopathogenic agents. If evidence of a cytopathogenic agent is found, the batch of primary cells is unsatisfactory.

(3) At the conclusion of the required maintenance period, monolayers shall be tested for:

(i) Cytopathogenic and/or hemadsorbing agents as prescribed in §113.46;

(ii) Extraneous viruses by the fluorescent antibody technique as prescribed in §113.47.

[50 FR 442, Jan. 4, 1985, as amended at 60 FR 24549, May 9, 1995]

§ 113.52 Requirements for cell lines used for production of biologics.

When prescribed in an applicable Standard Requirement or in a filed Outline of Production each cell line used to prepare a biological product shall be tested as prescribed in this section. A cell line found unsatisfactory by any prescribed test shall not be used. A serial of biological product shall not be released if produced from a cell line that is found unsatisfactory by any prescribed test.