include plaque assays where each plaque counted corresponds to a single infectious unit. Both quantal and quantitative assays are amenable to statistical evaluation.

2. Variation can arise within an assay as a result of dilution errors, statistical effects, and differences within the assay system which are either unknown or difficult to control. These effects are likely to be greater when different assay runs are compared (between-assay variation) than when results within a single assay run are compared (within-assay variation).

3. The 95 percent confidence limits for results of within-assay variation normally should be on the order of $\pm 0.5 \log_{10}$ of the mean. Within-assay variation can be assessed by standard textbook methods. Between-assay variation can be monitored by the inclusion of a reference preparation, the estimate of whose potency should be within approximately 0.5 $\log_{10}$ of the mean estimate established in the laboratory for the assay to be acceptable. Assays with lower precision may be acceptable with appropriate justification.

4. The 95 percent confidence limits for the reduction factor observed should be calculated wherever possible in studies of clearance of ''relevant'' and specific ''model'' viruses. If the 95 percent confidence limits for the viral assays of the starting material are +s, and for the viral assays of the material after the step are +a, the 95 percent confidence limits for the reduction factor are

$$\pm\sqrt{S^2+a^2}.$$

B. Probability of Detection of Viruses at Low Concentrations

At low virus concentrations (e.g., in the range of 10 to 1,000 infectious particles per liter) it is evident that a sample of a few milliliters may or may not contain infectious particles. The probability, p, that this sample does not contain infectious viruses is:

$p = ((V-v)/V)^n$

where V (liter) is the overall volume of the material to be tested, v (liter) is the volume of the sample and n is the absolute number of infectious particles statistically distributed in V.

If V >> v, this equation can be approximated by the Poisson distribution:

$p = e^{-cv}$

where c is the concentration of infectious particles per liter.

or, $c = \ln p / -v$

As an example, if a sample volume of 1 mL is tested, the probabilities *p* at virus concentrations ranging from 10 to 1,000 infectious particles per liter are:

c	10	100	1,000
p	0.99	0.90	0.37

This indicates that for a concentration of 1,000 viruses per liter, in 37 percent of sampling, 1 mL will not contain a virus particle.

If only a portion of a sample is tested for virus and the test is negative, the amount of virus which would have to be present in the total sample in order to achieve a positive result should be calculated and this value taken into account when calculating a reduction factor. Confidence limits at 95 percent are desirable. However, in some instances, this may not be practical due to material limitations.

Appendix 4

Calculation of Reduction Factors in Studies to Determine Viral Clearance

The virus reduction factor of an individual purification or inactivation step is defined as the $\log_{10}$ of the ratio of the virus load in the pre-purification material and the virus load in the post-purification material which is ready for use in the next step of the process. If the following abbreviations are used:

Starting material: vol v′; titer $10^{a'}$;
virus load: $(v')(10^{a})$,
Final material: vol v″; titer $10^{a''}$;
virus load: $(v'')(10^{a''})$,
the individual reduction factors Ri are calculated according to

$10^{Ri} = (v')(10^{a'}) / (v'')(10^{a''})$

This formula takes into account both the titers and volumes of the materials before and after the purification step.

Because of the inherent imprecision of some virus titrations, an individual reduction factor used for the calculation of an overall reduction factor should be greater than 1.

The overall reduction factor for a complete production process is the sum logarithm of the reduction factors of the individual steps. It represents the logarithm of the ratio of the virus load at the beginning of the first process clearance step and at the end of the last process clearance step. Reduction factors are normally expressed on a logarithmic scale which implies that, while residual virus infectivity will never be reduced to zero, it may be greatly reduced mathematically.

Appendix 5

Calculation of Estimated Particles per Dose

This is applicable to those viruses for which an estimate of starting numbers can be made, such as endogenous retroviruses.

Example:

I. Assumptions

Measured or estimated concentration of virus in cell culture harvest = 10^6/mL

Calculated viral clearance factor = $>10^{15}$

Volume of culture harvest needed to make a dose of product = 1 liter (10^3mL)

II. Calculation of Estimated Particles/Dose

$$\frac{(10^6\ virus\ units/mL)\ x\ (10^3\ mL/dose)}{Clearance\ factor\ >10^{15}}$$

$$= \frac{10^9\ particles/dose}{Clearance\ factor\ >10^{15}}$$

$$= <10^{-6}\ particles/dose$$

Therefore, less than one particle per million doses would be expected.

Dated: September 16, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–25569 Filed 9–23–98; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the Advisory Committee To the Director, National Cancer Institute.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: Advisory Committee To the Director, National Cancer Institute.

Date: October 2, 1998.

Time: 2:00 pm to 3:00 pm.

Agenda: To update committee on the progress of the NCI working groups.

Place: National Institutes of Health, Building 31, Conference Room 7, 9000 Rockville Pike, Bethesda, MD 20892.

Contact Person: Susan J. Waldrop, Executive Secretary, National Institutes of Health, National Cancer Institute, Office of Science Policy, Bethesda, MD 20892, 301/496–1458.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: September 16, 1998.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

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