the viscosity of the medium, and R is the particle radius. Since the effect of laminar shear is independent of the particle density, the conclusions of Reich and Vold are also applicable to pharmaceutical suspensions. They calculated that for a shear gradient of 100 sec.$^{-1}$, J/I is 10^{-2} for 0.1-μm. diameter particles, 10 for 1.0-μm. diameter, and 10^{4} for 10-μm. diameter. This shows again that, at around a diameter of 1 μm., orthokinetic effects assume a greater importance in comparison with perikinetic.

Discussion—To produce a pharmaceutical suspension that will sediment to give an open-structured redispersible coagulum, two processes are necessary: (*a*) particle collisions in the suspension, and (*b*) controlled particle adhesion on contact.

This communication has indicated that, in the absence of Brownian motion, sedimentation and shear effects can cause the former and the magnitude of the latter can be estimated by calculating energy of interaction curves (13).

Coagulation could be produced in a pharmaceutical suspension by the application of controlled shear, but care would be necessary since shear can also reverse the process and cause a breakdown in the structure. The formulator must design the suspension so that shear forces induced by shaking the container achieve this purpose. The sedimentation effect is inherent in the nature of the system, provided that there is a density difference between the phases and the suspension is polydispersed. Most pharmaceutical suspensions containing finely milled powders may be expected to have a proportion of particles in the region where Brownian motion is operative, and this proportion can be significant if calculated by number. Brownian coagulation eventually produces aggregates which are large enough to take part in sedimentation coagulation.

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Received January 10, 1972.
Accepted for publication October 5, 1972.

Compendial Dissolution Tests: Merits of Sequential over Standard Inspection Plans

Keyphrases ☐ Dissolution tests, compendial—statistical analysis, proposed sequential analysis inspection of dosage units ☐ Sequential analysis inspection—application in dissolution testing ☐ Inspection of tablet and capsule lots—sequential analysis plan for dissolution rate testing ☐ Sampling of tablet and capsule lots—sequential analysis inspection plan.

Sir:

Dissolution rate tests for tablets and capsules are destructive tests, so any acceptance inspection plan for this property that is included in a compendial monograph must be based on the results of the complete analysis of one or more randomly selected samples. All sampling inspection plans carry two inherent risks because the quality of the chosen sample or samples may not truly reflect the absolute quality of the lot. The first risk is that a lot whose absolute quality is acceptable will have to be rejected. This risk, designated α, has its greatest influence on the economics of production. The second risk is that a lot whose absolute quality is unacceptable will pass inspection. This risk, designated β, has its greatest effect on the therapeutic effectiveness of the lot and, hence, on the consumer.

This communication is concerned with computing the values of α and β that are inherent in the dissolution tests in USP XVIII (1) and NF XIII (2) and with proposing the adoption of an alternative test based on a sequential analysis plan (3). No attempt is made to address the equally important question concerning the meaningfulness, in terms of the bioavailability, of the presently defined criterion of good and bad dissolution behavior which is based on the time it takes for 60% of the drug to dissolve from its dosage form. Regardless of what criteria may be laid down to ensure bioavailability, it is essential that the inspection plan used is one that carries values of risks α and β that are consistent with production economy and therapeutic effectiveness.

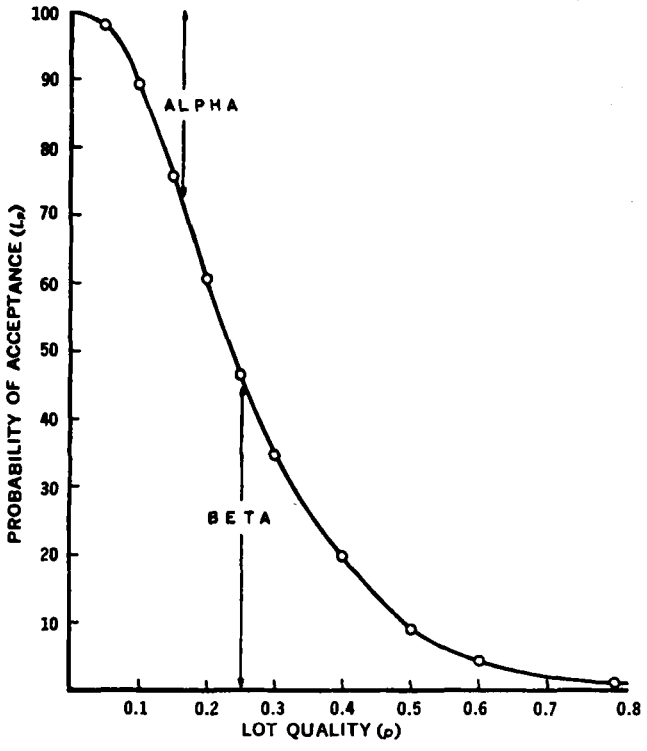

Figure 1—*Operating characteristic curve for the current compendial dissolution test.*

The current compendial dissolution tests (1, 2) are based on a standard double-sampling inspection plan. They require that an initial sample of six dosage units be individually subjected to a standardized dissolution test. The lot can then be accepted if all six units meet specified requirements but must be rejected if three or more units do not meet these requirements. If one or two units fail to meet the requirements, a further sample of six units must be examined. The lot can then only be accepted if no fewer than 10 of the 12 units meet the requirements. The overall probability, L_p, that a lot will be accepted under this plan is given by the sum of the probabilities that: (*a*) there are no defective units in the first sample of six, (*b*) there is one defective unit in the first sample of six and one or none in the second sample, and (*c*) there are two defective units in the first sample and none in the second.

The value of L_p is, in turn, related to the absolute quality of the lot, p, that is presented for inspection (quality being expressed as the fraction of defective units in the lot). Since the individual monograph in the USP specifies a single criterion for a good or bad product (*i.e.*, the time required for 60% of the drug to dissolve), the sample appears to follow a binomial distribution. By employing the Poisson distribution as its approximation, L_p can be readily computed for any value of p. (Molina's table was used in this report. See *Reference 4* for more details.) A plot of L_p against p (operational characteristic curve) for the current compendial tests is shown in Fig. 1. It can be seen that these tests involve a probability or risk of 47% of accepting a lot of quality 3/12. This is the maximum value of the risk β of a lot that is really of unacceptable quality passing inspection. Similarly, it can be seen that the probability

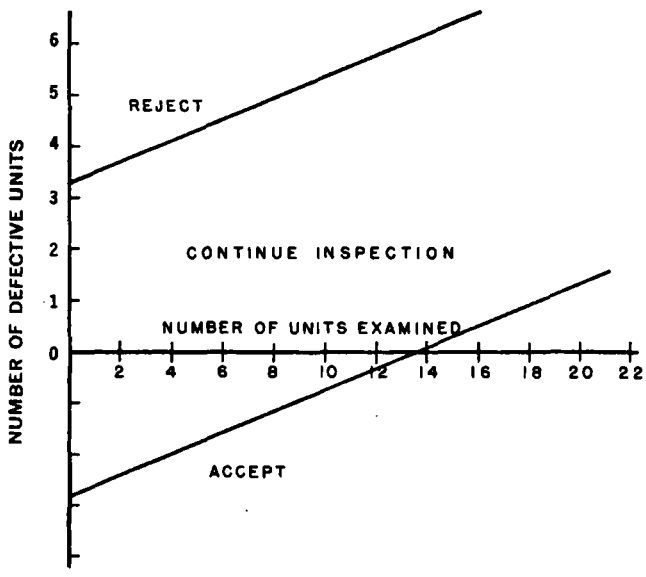

Figure 2—*Criteria for acceptance or rejection of a lot when the risks α and β are assigned to 15 and 20% and acceptable and unacceptable quality are specified as two or less defective units out of 12 and three or more defective units out of 12, respectively.*

of accepting a lot of absolute quality 2/12 is only 70%. Hence, the risk of rejecting an acceptable lot, α, using this plan runs as high as 30%. These risks seem extraordinarily high for a compendial test.

An alternative inspection plan based on sequential analysis appears to offer the possibility of a more meaningful test. A sequential analysis plan involves continuous analysis of units (or groups of units) from a lot until the inspector accumulates sufficient evidence to decide that, within certain predetermined values of α and β, the lot is of acceptable or unacceptable quality.

The criteria for acceptance or rejection of a lot under this type of plan are specified by two parallel oblique lines on a plot of number of defective units found against the total number of units tested. Such a figure is shown in Fig. 2 for a plan where α and β are assigned values of 15 and 20%, respectively, and acceptable and unaccept-

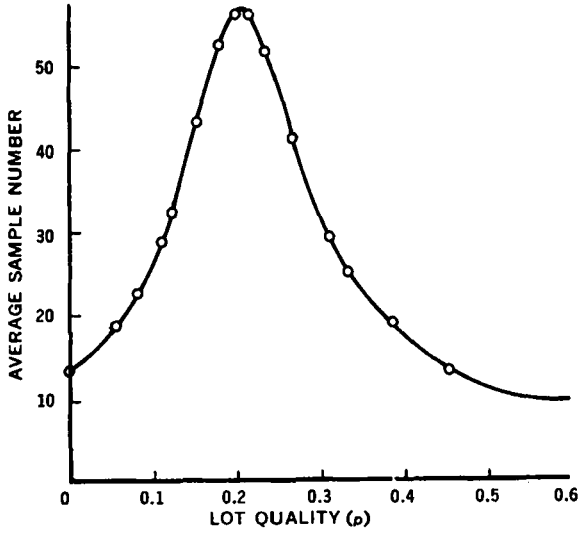

Figure 3—*Average sample of number as a function of the submitted lot quality under the same conditions as in Fig. 2.*

able quality are specified as two or less defective units out of 12 and three or more defective units out of 12. As the inspector tests units selected at random from the lot, he constructs a plot of number of defectives against number of units tested. If the plot intersects or crosses the lower line, the lot is accepted. Conversely, if the plot intersects the upper line, the lot is rejected. Inspection must, however, continue as long as the plot remains within the parallel lines.

The equations defining the parallel lines will not be developed here as they are well established in the literature (3). Suffice it to say that the slopes of both lines are uniquely defined by the limits set for acceptable or unacceptable quality, and the intercepts of the lines on the y axis are a function of both the quality limits and the predetermined values of risks α and β.

Some advantages of such an inspection plan over standard inspection plans are:

Flexibility—While it is anticipated that compendia would specify common quality criteria for all tablets and capsules, a sequential analysis inspection plan makes it possible to assign different values of the tolerable risks α and β to meet specific situations. For example, if it were known that the therapeutic effectiveness of Drug A was very much more dependent on the dissolution rate than that of Drug B, it may be advantageous to have a lower tolerable value of β for Drug A than for Drug B. This flexibility is not possible in a standard plan where the number of tests to be carried out is specified and, consequently, the values of α and β are fixed.

Number of Tests Required—To reach a decision on whether to accept or reject a lot within specified limits of risks α and β, a sequential analysis plan will always involve less testing than a standard plan (3). Consequently, such a plan will result in a production economy. Also, the number of tests required before a lot can be accepted can be minimized by a manufacturer who uses good quality control and only submits high quality material for inspection. This can be seen from the plot in Fig. 3 of the average number of tests required to reach a decision against the absolute quality of the submitted lot (computed as described in *Reference 3*).

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Received July 19, 1972.
Accepted for publication September 11, 1972.
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