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HOUSE GUIDES - AN APPLICATION OF BASIC STATISTICS IN PHARMACEUTICAL QUALITY CONTROL

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Experience has shown that it is virtually impossible to assign limits for the release of pharmaceuticals by a single formula. The House Guides System is a method for assigning release limits which takes into account many of the significant variables. Assays are grouped into three categories by the statistic EVAL which is a function of assay precision, process variation, component stability, and width and symmetry of product specifications. Release limit formulae are assigned to the three respective groups in such a way as to achieve reasonable confidence limits.

INTRODUCTION

Every component of a drug product has some ideal value. If it is an active component which is claimed on the label, and if

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it is stable, this value should be 100% of label claim for every batch tested. If the component is unstable, it should contain 100 + X%, where X is the margin required to keep the product within specifications through its shelf life.

To provide for manufacturing and assay variation, some tolerance is allowed on each side of the ideal, e.g. "not less than 90 percent and not more than 110 percent of the labeled amount." These tolerances may be set by the compendia, by FDA regulations, by commitments in an NDA, or by company policy.

Theoretically, any batch should be acceptable if its assay value falls inside these tolerances, i.e. between the Lower and Upper Product Specifications (LPS & UPS). However, if an assay is exactly on one of the specifications, there is a 50/50 chance that the true value is outside. This 50% risk is too great.

The FDA has suggested that a 5% risk would be more appropriate in setting in-house limits for testing drug products. Many attempts were made at establishing a single formula for determining these in-house limits, but this always ended in failure. The number of variables and their respective ranges were too great to be combined in a single relationship which would yield reasonable confidence limits. It was reasoned that the best approach was to classify component/product types and then establish respective House Guide formulae. This led to the definition of the statistic EVAL and ultimately to three sets of formulae for House Guides.

PROCEDURE

Development of EVAL

(For simplicity, the case of stable component/product systems will be described first.)

In our first attempt at establishing House Guides, the variability of individual assays was determined by performing many assays under routine conditions on single homogeneous samples. The estimated standard deviations found in this manner were labeled s_{assay}, or s_a. Using these s_a's, House Guides for component/product systems were established as:

Upper Product Specification - 1.7 s_a

Lower Product Specification + 1.7 s_a

This is illustrated in Figure 1.

For an assay falling exactly on the UHG, there is a 5% chance that the batch is above UPS. For one falling exactly on the LHG, there is a 5% chance that the batch is below LPS. For assays falling inside the House Guides, there is less than 5% chance that the batch is outside of specifications.

Control Charts have been kept for many years on most of our component/products. When we attempted to superimpose the proposed House Guides on the Control Charts, it became apparent

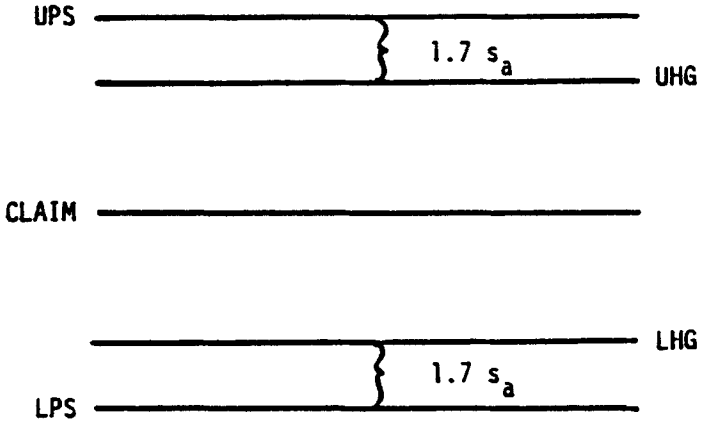

FIGURE 1

that we had a problem. When s_a was small compared with the specification range, the House Guides were usable. Where s_a was not so small, many assays fell outside the House Guides. The proposed system would only work when s_a was not more than about 1/8th of the available range. See Figure 2.

Most of our component/products had small enough s_a's, but for some, s_a was too large. The proposed system had only considered one variable, but it was obvious that others had to be included. To achieve this purpose, the statistic EVAL was devised.

$$EVAL = \frac{1.7\, s_a + 2\, s_c}{\text{Claim - Nearer Product Specification (NPS)}}$$

where: s_a has already been described.

s_c is batch assay variation, as shown on the Control

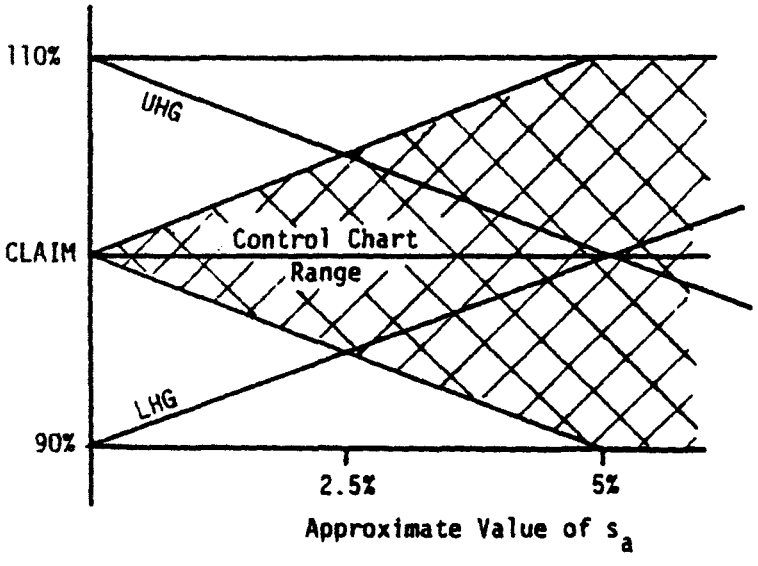

FIGURE 2

Chart. It includes assay variability, s_a, true batch variability, s_b, and other lesser sources of variation.

The denominator takes care of asymmetric product specifications, e.g. 90 to 115%.

To allow for unstable components, the margin for stability (Stab) was added in the denominator, and the EVAL formula became,

$$EVAL = \frac{1.7\, s_a + 2\, s_c}{(\text{Claim} + \text{Stab}) - \text{Nearer Product Specification}}$$

Using this formula, our component/product assays were divided into three groups, and the frequency with which the assays were done during the preceding year, not including replicates, was determined.

Group	EVAL	Frequency	Assay Classification
A	1 or less	78%	Precise
B	Between 1 and 2	16%	Intermediate Precision
C	Greater than 2	11%	Semi-quantitative

From EVAL to House Guides

Using the groupings shown above, the following House Guide formulae were established:

Group A

$$UHG = UPS - \frac{1.7\, s_a}{\sqrt{n}}$$

$$LHG = LPS + Stab + \frac{1.7\, s_a}{\sqrt{n}}$$

Group B

$$UHG = UPS - \frac{1.7}{\sqrt{n}}\,(2 - EVAL)\, s_a$$

$$LHG = LPS + Stab + \frac{1.7}{\sqrt{n}}\,(2 - EVAL)\, s_a$$

Group C For one assay: UHG = UPS

$$LHG = \frac{Claim + Input}{2}$$

For two or more assays:

UHG = UPS

LHG = LPS

Figure 3 illustrates the effect of following these formulae. It soon becomes apparent that this system allows maximum confidence consistent with the current state of manufacturing and testing technology. It also provides a logical and systematized approach to assigning House Guides.

In Group C, the House Guide limits are tightened for one assay, then set at UPS and LPS. Most of these are microbiological, and normally the compendia calls for two or more assays on different days.

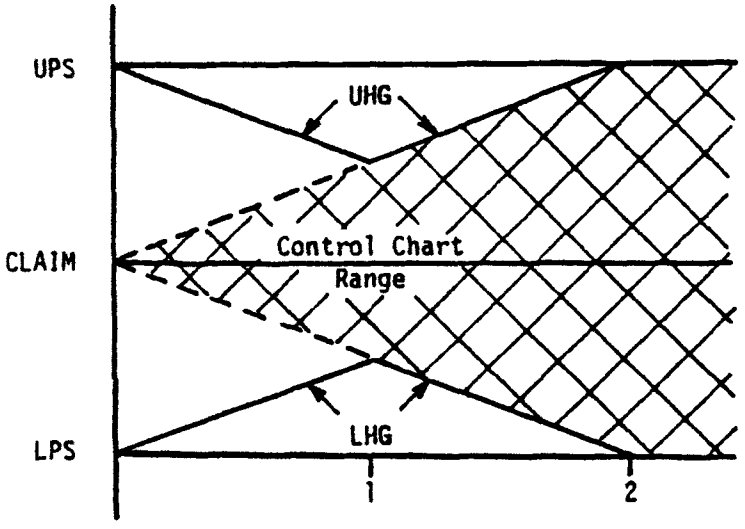

FIGURE 3

SUMMARY

A system of House Guides has been developed, based on the philosophy that assays on individual batches do not determine the precise quantity of any component present, nor do they have any effect on the quality of that batch of product. Quality is built in by Manufacturing, and no amount of assaying will change it. Replicate assays merely increase the cost to the manufacturer, and eventually to the consumer.

Assays perform three functions: 1. They should detect serious mistakes made in Manufacturing, 2. They should indicate whether or not the current batch differs significantly from previous batches of the same product, and 3. They should detect long-term trends in Manufacturing procedures or in assay techniques.

For these reasons, we attempted to devise systems which would minimize the frequency of replicate assays. With most of our component/product systems in Group A, our House Guide system achieves a high degree of assurance at minimum cost. For the other groups we have somewhat less assurance, but we have all that is warranted by the present state of the art.

In addition to the House Guides, we have a back-up assurance system in our Geometric Moving Average Control Charts.[1] These are probably the best Control Chart system for pharmaceutical products. Their use will be described in a subsequent publication.

[1] S. W. Roberts, Technometrics, 1, 239 (1959)