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ADVANCING THE CAUSE OF THERAPEUTIC ORPHANS

The problems associated with prescribing drugs for children were discussed previously on this page (*see June 1968*, "Therapeutic Orphans"). While knowledge concerning the actions and mechanisms of drugs is slowly unraveling, only a relatively few steps have been taken in a process that ultimately will require much study and research for a full understanding.

Determining drug actions and mechanisms in children is often complicated by different rates of metabolism, partially developed enzyme systems, and other factors associated with growth and maturation which are difficult to characterize and control under experimental conditions. In addition, for drugs not developed specifically for children and possibly having limited use in that age group, industry often may consider the expense of determining dosages and effects in children difficult to justify. Moreover, the legal problems and social ramifications involved with using children and infants in clinical trials further complicate the development of suitable criteria for children's doses.

Nevertheless, drugs *are* and *must* be used for children. Therefore, the most up-to-date information available is needed in a form that is easily used. For these reasons, the *1971 Pediatric Dosage Handbook: Usual Doses for Infants and Children* has been compiled by Dr. Harry C. Shirkey and published by the American Pharmaceutical Association.

The reliability or credibility of a reference source of this nature is associated primarily with the individuals and organizations involved with its compilation and publication. Dr. Shirkey, who earned his pharmacy and medical degrees from the University of Cincinnati, has practiced as a pediatrician since 1948; currently, he serves on the staff of several hospitals and also as a medical school faculty member, teaching courses in both pharmacology and pediatrics.

In addition, Dr. Shirkey serves as a member of the NF Board and Chairman of the NF Committee on Admissions. He is also Chairman of the Pediatric Panel of the USP and is a member of the Revision Committee. His American Medical Association activities include chairing the Drug Utilization Committee and serving as Vice-Chairman of the Council on Drugs.

The major feature of the *Handbook* is the comprehensive "Table of Pediatric Drugs, Their Dosage, Cautions and Contraindications for Use, and Their Available Dosage Forms." The material in this table reflects the most current and accurate information available concerning dosages for children and infants specifically.

While the need persists for more breadth and depth in research designed to elucidate drug mechanisms in adults as well as children, the publication of the *Pediatric Dosage Handbook* helps bridge the gap between research and practice as well as between research and consumer. Hopefully, this *Handbook* will aid in the effective and safe use of drugs with children and make them less "therapeutic orphans" and more like "foster children" at least.

Edward G. Feldmann

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COMMUNICATIONS

Objective Visual Evaluation of the Relative Content of Major and Minor Defects in Tablets and Capsules

Keyphrases ☐ Tablets, capsules—relative defect determination ☐ Defects, tablets and capsules—visual determination method

Sir:

Recently, it became desirable for our Quality Control Department to develop and subsequently implement a reasonably objective analysis for the evaluation of major and minor physical defects in tablets and capsules. The results would then be used to determine if additional processing was required prior to packaging.

Even though major and minor physical defects are routinely monitored by most pharmaceutical manufacturers, we were unable to find a reference regarding a test method in the literature. Consequently, a visual method has been developed which allows for the monitoring of major and minor physical defects in tablets and capsules.

Basically, the method consists of filling a rectangular plastic (Plexiglas) tray, a monolayer in depth, with the test tablets or capsules. The tray is placed on a workbench and positioned under a lamp containing a 100-watt incandescent lightbulb. The tray's width is placed parallel to the front bench edge about 7.62–15.24 cm. (3–6 in.) from the edge. The lamp is connected to a timer[1] that activates illumination of the lightbulb for a required amount of time.

Table I—Definition of Major and Minor Defects

Major Defects	Minor Defects
Surface spots	Polishing not uniform
Breaks or cracks	Feathered edges
Coated base tablet exposed	Chips
Foreign particulate matter[a]	Pitting or pimples
	Atypical mottling
	Nonuniform color
	Nonuniform size or shape
	Not smooth
	Smeared printing
	Thin-coated edges

[a] Detection of this major defect results in rejection of the lot until it is freed of any health hazard resulting from this defect.

Subsequently, the start button of the timer is depressed and the tablets are scanned for both major and minor defects (Table I); the defective tablets are marked, using a felt-tipped pen (or equivalent). Automatically, the light is turned off, signifying the end of the analysis. The number and types of defects are sorted, and the results are recorded on an assay report form. The report is designed so that the number and types of defects are identified.

An empty tray is superimposed over the tablet-containing tray, and the two trays are rotated 180° around the x- or y-axis so that the reverse side of the tablets are exposed. The original tray is removed, and the assay is performed on the new exposed side of the samples. The procedure is repeated until the total number of tablets or capsules required in the evaluation is assayed, and the results are recorded accumulatively.

The total number of units assayed is related to batch size and based on Military Standard 105D. Using the average tablet or capsule weight, the number of units to be tested are weighed into a beaker for subsequent transfer to the testing tray. A double sampling plan is used in which the acceptable quality level (A. Q. L.) is 0.65 and 4.0%, respectively, for major and minor defects.

Two sets of trays (two identical trays per set) are required to accommodate capsules, capsule-shaped tablets, and the conventional standard-shaped tablets. All the trays are 22.86 × 15.24 cm. (9 × 6 in.); however, the trays used for capsules and capsule-shaped tablets have an inner depth of 0.32 cm. (0.125 in.), and the trays used for the standard-shaped tablets have an inner depth of 0.16 cm. (0.062 in.).

Since the size of the tablet or capsule being assayed dictates the number of units in each tray load, the time interval (length of time light is illuminated) is correspondingly adjusted. In effect, the illumination duration is longest for the smallest tablet assayed. After a year of using this technique, we have developed the following formula for determining the time interval for a given sample:

$$P \text{ seconds/tablet} \times \frac{\text{total number of tablets to be assayed}}{\text{number of filled trays}} = \text{seconds/tray} \quad \text{(Eq. 1)}$$

The value of P chosen should reflect the desired rigidity of the inspection. In our laboratory, P has an average value of 0.035 sec./tablet. If 1000 tablets were to be tested and five filled trays were involved, the time interval would be 7 sec./tray. If the last tray is less than half a tray, half the time interval is used. Otherwise, the tray is considered a full tray.

We found that the number of tablets scanned per tray varies between analysts, and the formula attempts to compromise these differences. Otherwise, the natural tendency of the analyst is to become overcritical of the sample appearance.

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[1] Model M-1M, Industrial Timer Corporation, Parsippany, N. J.