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THE CODEX OF PHARMACEUTICAL EXCIPIENTS: AN INTERNATIONAL COLLABORATIVE EFFORT

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The authors of a chapter on quality control in a recently published textbook (1) effortlessly succeeded in formulating a straightforward definition of excipients as "components of a finished dosage form other than the therapeutic ingredient." In describing these substances by what they are not rather than by what they are, a semantic solution to an ancient philological dilemma has been found. Continuing along this negative pathway, the readers are informed that excipients are considered to be "inert" but the authors fail to state whether this is their opinion or merely the repetition of a common historical convention. However, when they conclude with a warning that these "inert" materials can influence the quality of a drug product, the brevity of their definition provides a measure of insurance against inevitable criticism.

Leaning more heavily upon the origin of words as is the tradition among lexicographers, a standard US dictionary (2) defines an excipient as a pharmacologically inert, adhesive substance, as honey, syrup, or gum acacia, used to bind the contents of a

pill or tablet. Although the Latin derivation is more obvious in this definition, the meaning is too restrictive of modern usage and properties of excipients. The language problem becomes even more confusing when alternative words or expressions are substituted. Under the chapter heading of "Pharmaceutical Necessities", the current edition of Remington's Pharmaceutical Sciences (3) describes "substances which are of little or no therapeutic value, but which are useful in the manufacture and compounding of various pharmaceutical preparations". These necessities are separated into sections in accordance with their function in a formulation; i.e., antioxidants, coloring agents, flavors, solvents, etc. The compendia, dignified by the respect accorded to age, rest upon their regulatory authority and permit the addition of substances to a dosage form for improvement of stability, usefullness (sic!), pharmaceutical elegance, or for technological reasons.

Most of the additives in the Pharmacopeia (4) are described in approximately 110 monographs in the section on Pharmaceutic Ingredients although quite a few can be found as Pharmaceutic Aids in the section on Therapeutic Substances and Dosage Forms. The requirements for added substances in the National Formulary (5) are almost a mirror image of those in the Pharmacopeia except that they are described in about 100 monographs in the section on Pharmaceutic Aids or as Pharmaceutic Aids in the section on Therapeutic Substances. The actual "usefullness" of an additive is most clearly expressed by its intended function and the compendia require 54 words or expressions to cover the applicable functions.

Even a superficial historical view of excipients as defined by Lachman et al. (1) illustrates a surprisingly persistant attitude of indifference to their importance in dosage form design. The implication of "inertness" consistently tended to relegate the scientific investigation of the properties of these materials and their potential for interaction with drugs, other excipients, and packaging materials to a secondary role or to hazardous empirical judgements. Only during the past three decades has there been a slowly evolving change in this attitude with an accompanying increase in the volume and quality of research papers. With the rapid acceleration of investigational programs on bioavailability and bioequivalence, the relative magnitude and importance of problems involving the effects of excipients on the biological behavior of dosage forms have also gained increasing recognition.

Pharmacopeial monographs for excipients essentially deal with standards for identity, purity and assay but generally omit tests for physical properties and function. Criticism of compendial standards for excipients in the OTA Report on Bioequivalence (6) was limited to non-specificity of test methods, potential influence on bioavailability, and the number of important excipients excluded from official requirements. In view of the critical importance of potential interactions between excipients and drugs in dosage forms as well as the variables associated with manufacturing processes, the inclusion of official standards for many of the physical properties of excipients would be extremely difficult, if not actually undesirable.

However, the practical value of an encyclopedic type of compilation of excipients is beyond dispute and in 1974 a collaborative program organized by the major Swiss pharmaceutical companies resulted in the publication in the German language of a catalog of pharmaceutical excipients (Katalog pharmazeutischer Hilfsstoffe). This loose-leaf book contains descriptive information, names of suppliers, test methods and results for various parameters as obtained from the literature or measured in the laboratories of the collaborating companies, and the intended functional role(s) of the selected excipients in pharmaceutical dosage forms.

The advisability of publishing a similar type of codex in English was discussed with British academic and industrial pharmacists and quickly agreed upon provided that the scope of the publication would conform with formulation practices and current standards in the United States and United Kingdom. In April 1976, the APhA Academy of Pharmaceutical Sciences authorized the establishment of the Codex of Pharmaceutical Excipients project with implementation to be the responsibility of the Industrial Pharmaceutical Technology (IPT) Section. Shortly thereafter, the Council of the Pharmaceutical Society of Great Britain approved the request of their Industrial Practice Sub-Committee to collaborate with the Academy in the preparation of the Codex.

In the USA, the scientific direction of the project is the responsibility of a Steering Committee which, in addition to Jack Cooper as Project Chairman and Zak Chowhan as Project Vice Chairman,

is made up of four academic scientists from four schools of pharmacy and thirteen industrial scientists from ten pharmaceutical companies. John Hersey, Director of the Institute of Drug Technology Ltd. of Australia, Jerome Reinstein, Director of Laboratory Research for Vick International in Paris, Hans Hess, Director of Solid Dosage Form Research and Development for CIBA-GEIGY in Switzerland, B.T. Roufail, Bureau of Drug Surveillance in Canada, and Pierre Buri, Professor of Pharmaceutics and Biopharmaceutics at the University of Geneva, have agreed to serve as Corresponding Members of the Steering Committee. Other distinguished scientists from Italy, Denmark, Sweden and Japan have been invited to serve in the same capacity.

The preparation of monograph texts for the Codex will be handled by the members of the Monograph Committee, currently consisting of 22 pharmaceutical scientists from 15 schools of pharmacy and 62 pharmaceutical scientists from 38 pharmaceutical companies. An opinion survey involving recommendations for the selection of excipients and the spectrum of technical information to be included in the monographs has been conducted among the members of the Steering and Monograph Committees. Additional data from broader surveys involving the frequency of use of excipients is also available and will be used to provide an adequate data base for the selection process.

In the United Kingdom, a Liaison Committee responsible for the implementation of the project has been established under the chairmanship of Robert Weir, Manager of Technical Development for the Boots

Company Ltd. John Rees, Senior Lecturer in Pharmaceutics at the University of Aston, is Coordinator of Laboratory Testing, and John Bell, Pharmaceutical Development Manager for Fisons Limited, is Financial Controller and Technical Administrator. Surveys similar to those undertaken in the USA are currently under way and, in addition to the active volunteer collaborators, a number of specialists in pertinent aspects of pharmaceutics have agreed to serve as scientific advisors.

Although there is general recognition of the complex and difficult problems associated with the selection of the initial group of excipients for inclusion in the Codex from the 700-800 now present in marketed drug products, and in the collection of the widely scattered technical data for presentation in the monographs, the ultimate value of the Codex is obvious and explains the prompt and enthusiastic response of the collaborators. The latter represent a broad cross section of the various disciplines active in the pharmaceutical sciences whose training and experience can successfully overcome the difficulties and bring forth a compilation of great practical value to formulators, technologists, analysts and educators.

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