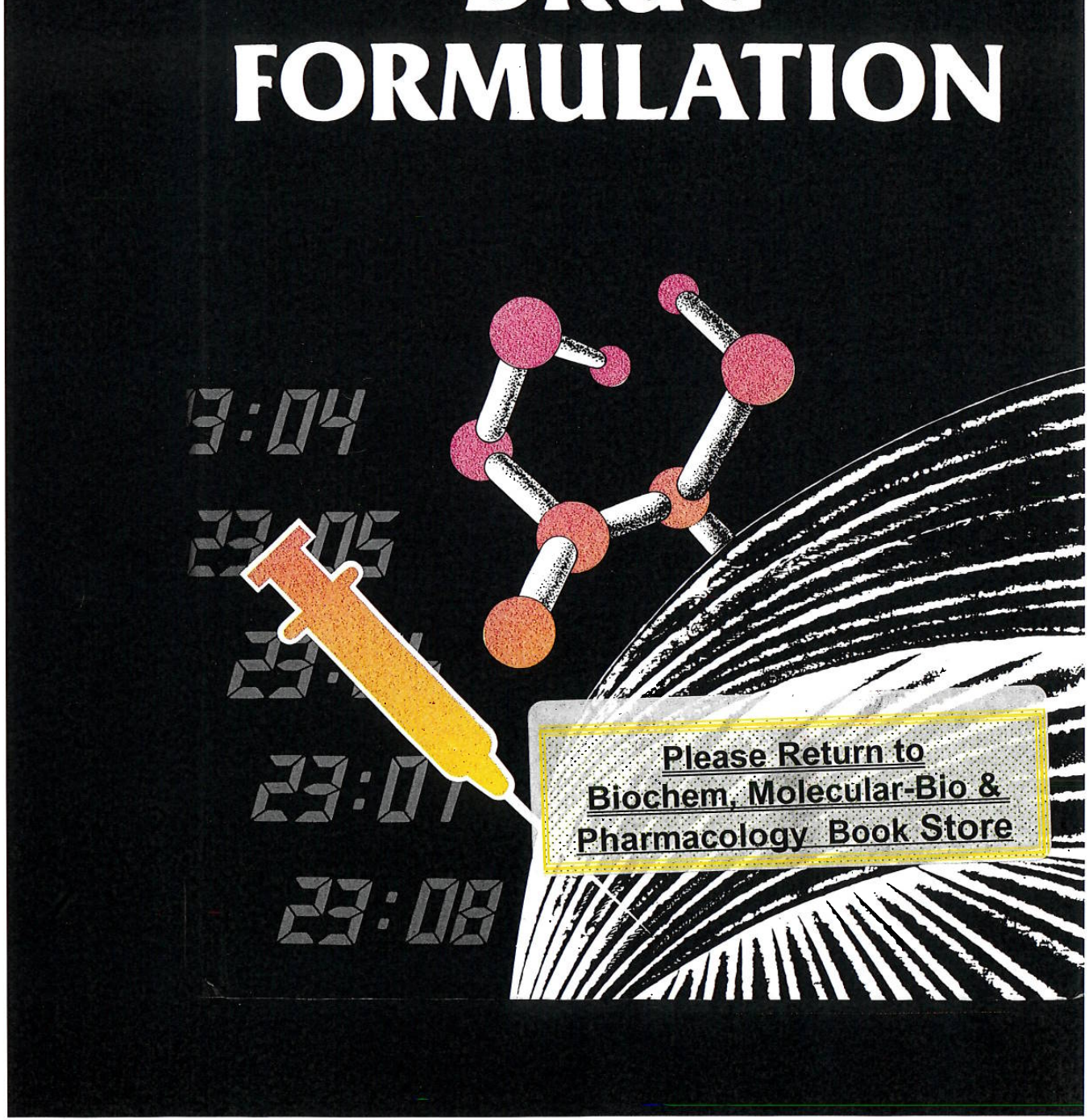

FORMULATION

BY

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pharmacologists, physicians, mathematicians, economists, etc.) who work together to solve the emerging problems in a successful and reproducible manner.

The experiments within individual phases (zero to four) described in Table 1.1. do not necessarily proceed in exact sequence. Results from one experiment may determine the extent of parallel examinations. So, for example, if pharmacologic screening of an active ingredient during the zero phase did not show any biologic activity, no pre-formulation experiments would be performed unless the former result could be changed (e.g. by the addition of a substance which increased absorption). Pharmaceutical formulation experiments in phases zero to three are indispensable. However, these experiments must not be regarded as simple, routine tasks since the development of marketable products is highly dependent on the expert's scientific knowledge and creativity during these experimental phases. The complete development of a drug to the marketing stage may take ten to twelve years [2] depending primarily on the resourcefulness of the manufacturer and on the legal rules of the given country.

1.1. PRE-FORMULATION STUDIES

Pre-formulation studies in pharmacy are sometimes defined as those that precede product development. The investigator should critically consider the physical–chemical data even prior to animal testing to provide the development pharmacist with some key facts. These facts will bear upon such things as *(a)* preparing drug samples for animal tests in a way that optimizes chances for the compound to exert its pharmacological action, *(b)* ways to solubilize the compound, *(c)* determining photosensitivity or other aspects of its chemical stability, etc. These studies commonly take a month or two to perform.

Pre-formulation studies [18] in a broader sense, and applied to a broader spectrum of special chemical products, may be defined as those preceding the actual establishment of the final formula and working directions for product manufacture. These may take years to carry out. In this book emphasis is on formulation of drug products, but pre-formulation is addressed in broad sense. It discusses the approach to formulation work in pre-development, development, pilot scale-up studies, and pre-manufacturing development. It tries to show what studies are required and how to perform them in order to get uniformly good drug products of high quality [16].

When a potentially marketable new active ingredient is identified, it is important to find the most satisfactory and efficacious pharmaceutical dosage form. Such preparations must be stable, compatible, bioavailable and able to be manufactured in an economical manner. Pre-formulation experiments are designed to answer these basic questions on a small scale [21].

The most important is that the active ingredient possess appropriate biological activity or at least be a chemical analogue which has advantageous actions or therapeutic properties when compared with the parent compound. When favourable results have been reported from the pharmacological and acute toxicity tests, the

Table 1.1. Outline for the development of a new active ingredient into a pharmaceutical product

PHASE 0
0.1. Conception, synthesis, synthesis of radio-labelled compound.
0.2. Physicochemical investigations.
0.3. Preliminary analytical studies on the active ingredient.
0.4. Screening for biological activity.
0.5. Acute and subchronic toxicity tests.
0.6. Pre-formulation experiments.
0.7. Marketing prognosis.

PHASE 1.
1.1. Clinical phase I. Examination of tolerance in healthy human volunteers. Selection of a suitable pharmaceutical dosage form and strength. Determined from preliminary short-term ADME tests and estimated pharmacokinetic parameters.
1.2. Investigation of metabolic pathways of the drug.
1.3. Chronic toxicity tests.
1.4. Investigation of mutagenic, teratogenic and carcinogenic effects.
1.5. Investigation of the active ingredient–DNA repair system.
1.6. Synthetic chemical experiments concerning scale up and manufacture of the experimental industrial product.
1.7. Drug formulation experiments (stability, compatibility, biopharmaceutics, dosage regimen design, etc.).
1.8. Total analytical investigation of the active ingredient, elaboration of stability testing methods and assays for specific measurements of metabolite(s).
1.9. Elaboration of marketing plans.

PHASE 2.
2.1. Clinical phase II. Randomized double blind, controlled clinical trials to verify the pharmacological effect in the patient population indicated. Long-term ADME tests and estimation of pharmacokinetic parameters.
2.2. Drug formulation experiments. Determination of bioavailability. Elaboration of production guidelines. Pharmaceutical pilot plant experimental work. Scale up experiments. Middle scale production of clinical samples.
2.3. Analytical investigation of pharmaceutical product.
2.4. Administrative work in accordance with marketing plans.
2.5. Marketing.

PHASE 3.
3.1. Wide-spreading clinical trials. Evaluations of the side-effects and possible drug interactions.
3.2. Large-scale manufacturing of the pharmaceutical products. Determination of the shelf-life.
3.3. Elaboration of quality norms for the product.
3.4. Administrative work in accordance with marketing plans. Registration certificate.
3.5. Detailed marketing for estimation of claims and requirements.

PHASE 4. (Summarizing, evaluation)
4.1. Data concerning the synthesis.
4.2. Analytical data.
4.3. Manufacturing data.
4.4. Clinical data (field of indication, directions for use).
4.5. Registration.
4.6. Marketing data.
4.7. Production data.
4.8. Patent situation.

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