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AAPS Task Force Report

Value of pharmaceutical sciences

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As one of his key initiatives, then AAPS President Vincent H.L. Lee, Ph.D., created a Task Force on the Value of Pharmaceutical Sciences (VOPS) in 1996. The charge to this Task Force was 'to identify the major contributions of pharmaceutical scientists that have made a difference in our everyday life. The outcome of such a project would be a heightened awareness by the scientific community and public at large of the value of pharmaceutical sciences to society'. The membership of the Task Force included Ronald T. Borchardt, Ph.D., Chair; Daniel L. Azarnoff, M.D.; Harry G. Brittain, Ph.D.; Ho-Leung Fung, Ph.D.; David K. Knapp, Ph.D.; Michael P. Powell, Ph.D.; Tomi K. Sawyer, Ph.D.; George Zografi, Ph.D.; and Christine K. Carrico, Ph.D.; AAPS Staff Liaison.

The initial objective of the VOPS Task Force was to identify those areas where pharmaceutical scientists have made their most significant contributions as well as those areas where the contributions of pharmaceutical scientists have arisen primarily through collaborations with other basic scientists (e.g., medicinal chemists, cellular and molecular biologists, immunologist, pharmacologists, toxicologists) and–or clinical scientists. These so-called core and collaborative contributions include: (a) What are prodrugs? How have they helped? (b) Physical pharmacy—Preformulation; (c) Drug analysis; (d) Dosage form design; (e) Manufacturing technology; (f) Drug disposition—What the body does to a drug? (g) Toxicokinetics; (h) Therapeutic evaluation; and (i) Pharmaceutical scientists = Significant savings and enhanced value.

In addition, the VOPS Task Force identified breakthrough technologies by which pharmaceutical scientists will make significant scientific contributions to society in the future. These breakthrough technologies include: (a) Combinatorial chemistry; (b) In vitro pharmaceutical techniques; (c) Molecular aspects of drug metabolism; (d) Analytical technology; (e) Biomaterials; (f) Gene transfer–Gene therapy; and (g) Live therapeutics.

In addition to input provided by the members of the VOPS Task Force, input was received from the AAPS Fellows and AAPS members. The preparation of the Task Force's Final Report was a team effort involving contributions from formal members (named above) as well as ad hoc members of the VOPS Task Force (Anthony Sinkula, Ph.D.; Michael Pikal, Ph.D.; Michael Akers, Ph.D.; Rodney Pearlman, Ph.D.; Grant Wilkinson, Ph.D.; and Zahra Shahrokh, Ph.D.).

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Christine K. Carrico, Ph.D., who was the AAPS Staff Liaison, was particularly helpful in editing the final report of the Task Force. Below is a summary of the Task Force's conclusions.

1. Core and collaborative contributions

1.1. What are prodrugs? how have they helped medicine?

Discovering a molecule with the optimum structure to interact with a receptor or enzyme may not result in a clinically useful drug if the body prevents the molecule from getting to that site of action. In the past decade, chemists and pharmaceutical scientists, working together, have designed prodrugs, or inactive derivatives of an active drug, to circumvent this problem. Prodrugs remain inactive, and unacted upon, in the body until they reach their site of action where they are converted by a natural bodily process into their active form. Prodrugs have been used to improve drug delivery, decrease side effects, prolong the duration of action of a drug and even improve the taste of a medicine.

Many drugs are not absorbed well after an oral dose either because they don't cross the cellular membranes well or because they are metabolized by enzymes in the liver before they have a chance to get to their site of action. The prodrug approach has been used to link a fat-soluble, not easily metabolized chemical group to the drug to help it cross into the bloodstream and get past the liver's metabolizing enzymes. Once the prodrug passes the liver, this group is chopped off and the active drug is available to do its work. There are many examples where the oral bioavailability of drugs has been improved by starting with prodrugs, including the antihypertensive ACE inhibitors, some antibiotics, anti-viral agents, peptide drugs, clotting inhibitors, and bronchodilators.

A wide variety of side effects are due either to having to give large doses of the drug so that enough of the active drug will eventually reach its site of action, or to having the drug act at places other than where it is desired. Using the prodrug approach, the antiepileptic drugs phenytoin and valproic acid have been made less irritating following IV administration and less toxic to the liver and developing fetus. Corticosteroids, highly effective anti-inflammatory drugs, also have toxic effects on many different systems. By designing a prodrug that relies on bacterial enzymes in the colon to chop off the inactive part, it is now possible to ameliorate many of those toxicities and get more drug to the site of action.

One area where severe systemic toxicity can limit treatment is in cancer chemotherapy because the drugs themselves are so toxic. Prodrugs of certain types of anticancer drugs have been created which rely on the fact that tumors don't have the same oxygen supply as normal tissue. These prodrugs are not toxic, but once they get to the tumor, the low oxygen level causes them to change their state and become toxic. An exciting new direction is a two-step targeted chemotherapy, called antibody-directed enzyme prodrug therapy (ADEPT). In this approach, an enzyme that will activate the prodrug is actually attached to the surface of a tumor using an antibody to the tumor surface. The non-toxic prodrug of the chemotherapeutic agent is harmless to the body until it gets to the tumor where the newly attached enzyme converts it into the toxic drug right at the site of action.

Prodrugs have already given many older drugs a new lease on life by decreasing side effects, decreasing the required dose, and increasing their effectiveness. New approaches to prodrug design offer even more promising avenues to improve drug therapy in the future.

1.2. Physical pharmacy—preformulation

Many drugs can undergo chemical change when stored under various conditions in the pharmacy or in the homes of patients. When such chemical changes occur, drugs generally lose their therapeutic effectiveness or, in some cases, become toxic and harmful to patients. Chemical degradation of drugs can be greatly accelerated when the drug product is exposed to high temperatures and relative humidities, as one might find in hot and humid climatic conditions or even in a typical

bathroom where drugs are often stored. In some cases, drugs will undergo chemical degradation by exposure to normal sunlight and ordinary room lighting or by exposure to high levels of oxygen from the atmosphere. Often, the chemical change is easily detectable at low levels by a change in color or odor. For example, one can usually detect a distinct vinegar-like odor when opening a bottle containing aspirin tablets that has been stored for some period of time. However, in most situations, specialized analytical techniques developed by pharmaceutical scientists to allow detection of such chemical changes at low levels are the only way such changes can be detected.

To anticipate degradation and to develop strategies for preventing such changes, the pharmaceutical scientist carefully studies the chemical properties of all drugs in solution or as solids as early as possible in the development process. Conditions of temperature, relative humidity, light, oxygen, and even acidity and alkalinity of water, are utilized to mimic conditions that the drug might encounter throughout its handling, storage and use. A typical severe and accelerated test of stability might be exposure to 40°C (104°F) and 75% relative humidity for 12 months without evidence of significant chemical change.

To be able to set conditions under which drug products are to be stored and to establish the expiration date, i.e. the date on the label after which the drug should not be used because of possible chemical degradation, pharmaceutical scientists have developed techniques to measure small changes in the chemistry of drugs under various conditions and have used such data to better predict the likelihood of practical problems in this regard. Great emphasis is placed on detecting and identifying the products of such chemical reactions and testing these products for any possible therapeutic or toxicological effects. In this way, the pharmaceutical scientist provides assurances that a therapeutically efficacious and safe drug product is delivered to the public, and that it is maintained in that way for all types of approved storage conditions throughout the period between manufacture and use.

1.3. Drug analysis

Every person who has ever taken either an over-the-counter or prescription drug does so without thinking that the dosage form will hurt them in any way. It is assumed that the pill will have exactly the proper dosage strength and that it will be totally free from harmful substances. These assurances would not exist without the modern science of drug analysis, which has become the tool whereby pharmaceutical scientists guarantee the quality of their drug products.

Analytical separation methods are routinely developed which can detect and measure virtually any impurity species which is present at levels exceeding 0.1%, and often can be used at even lower levels of detection. This use of strict specifications to control drug quality is only possible when suitable analytical methodology exists. However, the rigorous control maintained on the quality of drug substances and products in this country has now become so routine and accepted that few even pause to consider the strides which have been made in this area. Twenty years ago, before the advent of modern analytical separation techniques such as high-performance liquid chromatography (HPLC) and gas chromatography (GC), impurity levels of a few percent were considered acceptable. Now that the methodology exists to accurately determine the levels of impurity species at significantly lower levels, it has become the industry and regulatory norm to require detection and quantitation on a daily basis. There is no doubt that the lowered impurity specifications in place for all recently filed drugs provide a higher degree of protection to the public than would otherwise exist.

Equally important to the development of modern pharmaceutics has been the ability of scientists to develop methods to follow the metabolic paths of drugs in the human body. It is certain that a full understanding of the action of a drug substance cannot be obtained without a determination of the concentration of the active form of the drug in the body as time progresses. The development of a drug dosing regimen cannot be undertaken without knowing how long the compound remains in circulation at therapeutic levels,

and this information can only be gleaned from studies of drug concentration levels in body fluids. This situation has become even more important when one considers that drug substances are becoming progressively more potent, making it essential that workers fully understand the kinetics of drug action. This type of work requires both high degrees of sensitivity as well as extraordinary selectivity, which fortunately has become available through the marriage of two analytical techniques, HPLC with mass spectrometry (HPLC-MS). The use of HPLC-MS methodology has become routine in the analysis of substances in body fluids, but its use has permitted the development of drugs for which the information could not have been obtained by any other method.

1.4. Dosage form design

The rational (scientifically-based) design of dosage forms that deliver the proper amount of active drug substances to the site of action in the human or animal over a defined period of time to elicit a therapeutic (and not toxic) response has been, and continues to be, one of the major challenges of pharmaceutical scientists since the advent of drug therapy. Effective drug therapy from a dosage form standpoint is highly dependent upon the route of administration. The conventional dosage forms such as tablets and capsules are used predominately via the oral route of administration and constitute the great majority of unit dosages in use today. Where oral drug administration is not feasible, parenteral (injectable) administration is the next route of choice. The route of administration in many cases determines the choice of dosage form and is based on certain physicochemical characteristics of the drug molecule, e.g. aqueous solubility at physiological pH, chemical stability, molecular weight, etc. While the physicochemical approach to dosage form design has served the pharmaceutical sciences well in the past, the advances in our understanding of the cell biology, physiology, immunology and biochemistry of drug delivery promise new and novel approaches to the design of dosage forms based on this new knowledge.

A better understanding of the various physiological, enzymatic–metabolic and cellular barriers affecting the delivery of drugs are leading pharmaceutical scientists into interdisciplinary collaborative efforts with biochemists, cell biologists, physiologists, medicinal chemists and clinicians in order to produce dosage forms and drug delivery systems that deliver drugs more efficiently and safely. This increased understanding of the drug delivery also allows pharmaceutical scientists to exploit many routes of administration not previously considered feasible. Such routes as the skin (transdermal), lung (inhalation), mucosal surfaces (mouth, nose, vaginal), ocular (eye) and others are presently being re-examined as promising routes of administration in light of new information in the biological sciences. Indeed, products are already available that are exploiting the unique characteristics of these non-oral routes, e.g. nicotine patches and gum, metered dose inhalers for asthma. The recent discoveries in polymer science have opened new avenues in exploiting a wide variety of polymers and polymer systems for the design of dosage forms and drug delivery systems that allow for the controlled release of drugs over long periods of time in the organism to enhance the safety and efficacy of drug therapy and to make it easier for the patient to take their drugs as prescribed.

While the role of the dosage form cannot be minimized in its importance in rational drug therapy, it still represents the presentation of the drug to the real drug delivery system which is the living organism that receives the drug. The challenge to pharmaceutical scientists is one of learning the language of fellow scientists whose research contributes to our understanding of the biological and immunological aspects of the delivery of drugs in ways that at present may appear to be science fiction. The creative and collaborative combination of the physicochemical, biological, chemical and clinical approaches to understanding and solving these seemingly insurmountable problems, and the scientific design of dosage forms for the delivery of drugs, represents the next frontier in the pharmaceutical sciences.

1.5. Manufacturing technology

The discovery of a new therapeutic entity is normally preceded by years of scientific effort and considerable financial investment. However, unless this new entity can be manufactured and distributed in a dosage form and package that can be successfully used by the health care professional or patient, the scientific advance creates no benefit to human health. In addition, it is becoming more obvious that unless the entire development process proceeds efficiently, thereby bringing important new products to the market quickly, costs become prohibitive.

For both safety and efficacy, a product must remain stable during manufacture, distribution, and use. That is, product degradation must be minimized. The application of sound chemical principles to pharmaceutical systems coupled with engineering advances have generally allowed the manufacture of stable products on a commercial scale. Many of the new products of biotechnology, such as therapeutic proteins, present special stability problems. As with most labile molecules, removal of water to form a solid generally improves stability during distribution. Freeze drying, also termed 'lyophilization', is a drying process employed to convert solutions of labile materials into dry solids of sufficient stability for distribution. However, many proteins suffer degradation during freeze drying, and stability of the dry product is often less than needed. Recent advances in process engineering and rational formulation design have resulted in protein products stable at room temperature for years, whereas the corresponding solutions may suffer excessive degradation in weeks, even if refrigerated.

A critical quality attribute for any injectable product is sterility (i.e. the absence of contamination by microorganisms). Since the consequence of injecting a product contaminated with even a low level of microorganisms may result in patient death, injectable products must be produced using complex and highly exacting procedures designed to assure sterility, but yet be capable of producing an affordable drug product on a commercial scale.

Steady advances in aseptic, or sterile, processing technology over the years have met this goal. A notable recent advance is the application of barrier technology to aseptic processing. Traditional aseptic processing techniques involve processing in a clean room with the personnel trained in aseptic techniques needed to run the process. Since the major source of microbial contamination in a traditional aseptic process is people, it is obvious that a process which places a physical barrier between the people and the product would be a great advance. Aseptic processing with barrier technology does just that. The net result is potentially greater sterility assurance without significant additional process complexity and cost.

While it is obvious that a miracle drug does no good unless the patient actually takes the medication, it is perhaps less obvious that patient compliance with the prescribed administration schedule is often much less that optimal. Thus, convenience and ease of use may be a major quality attribute for a product. A controlled release tablet that can be taken once a day is much more likely to be properly administered than a tablet that must be taken four times daily. Likewise, an injectable drug, such as insulin, can be administered more conveniently if provided in a fully automated pen-injector than with a conventional vial and syringe system. Drugs injected by infusion in hospitals and home health care situations can be more conveniently administered by a variety of new delivery systems such as intravenous controller devices, ADD-VantageAE®, CRIS AE®, syringe pumps, and implantable devices. Such systems are examples of drug dosage forms and delivery systems that improve health care through improved user convenience and patient compliance.

1.6. Drug disposition—what the body does to a drug?

Until the 1960's, drug administration to humans was largely a haphazard affair. Drugs of natural origin or through chemical synthesis, although shown to have pharmacological properties when tested in isolated organs and tissues, were given to humans mostly in oral forms (pills,

tablets, capsules) generally without knowledge of how much of the drug would be absorbed, how frequently the drug should be given, and how individual dosages should differ. There was little appreciation of the genetic and environmental factors that affect drug availability to the relevant tissue site where the drug is expected to exert its actions. When drugs are available through multiple commercial products, e.g. as was (and still is) the case for a popular drug like aspirin, there was no knowledge not only of how effective one such product was relative to another, but also (obviously) the critical factors that govern such efficacy.

Over the past 30 + years, pharmaceutical scientists have made important strides in understanding these phenomena. First, these scientists developed sensitive and specific methods for the determination of the concentrations of drugs and their metabolized products in biological fluids, such as blood and urine. Then, they developed mathematical relationships that could provide various important quantitative parameters to describe the drug behavior in a human body. They could now answer these crucial questions—How much drug is absorbed? How fast is the drug eliminated? How frequently should the drug be given? How do ethnic background, diet, personal habits (e.g. smoking) and other drugs affect circulating drug levels? Are generic products biologically equivalent to the brand name? They began to understand that certain drugs are not active by themselves, but have to be biologically transformed to exert their action. These understandings led to the development of newer, safer and more effective drugs.

Pharmaceutical scientists then used this knowledge about drug disposition to improve drug therapy. They found out, for many drugs, the range of therapeutically effective blood concentrations vs. toxic levels. They invented the discipline of clinical pharmacokinetics with which they design the proper dosage regimens for individual patients based on the way the drug acts on the body and is acted on by the body in different populations and in different individuals. This application benefits patients treated for heart diseases, asthma, infections, and transplant rejections, to cite a few examples.

These efforts of pharmaceutical scientists have led to safer and more economic use of drugs around the world. For example, we know how to choose a proper pharmaceutical product (generic vs. brand? sustained released vs. immediate release? transdermal patch vs. tablet?). We now know which groups of patients should receive a different dosage regimen for what drugs. We now know how to dose individual patients on certain drugs. We are beginning to devise strategies to minimize the time and resources needed to bring a promising and needed drug to the patient and yet assure its safe and effective use. In these aspects, pharmaceutical scientists have touched everybody's life, and drug administration is, by and large, no longer a haphazard affair.

1.7. Toxicokinetics

Before a potential drug is administered to human beings, toxicology (safety) studies in at least two species of animals are required to predict what type of toxicity to expect, and whether there appears to be an adequate safety margin between the proposed human dose and the dose causing toxicity in experimental animals. The dose of the drug and the timing of its administration (time of day, how frequently given, etc.) may have a profound effect on the actual dose the animal is exposed to and–or response to that dose. For example, a common method for orally-administering a drug in long-term toxicology studies in small animals is to mix it with the animal's food. Yet, rats eat primarily at night and in addition, they eat their dung. This dosing method hardly mimics the situation in humans. Similarly, to best mimic human exposure, should the size of the dose be based on body weight or surface administration? Answers to these and other questions are being answered by applying the principles of toxicokinetics to these animal safety studies.

Toxicokinetics is a relatively new approach to obtaining pharmacokinetic data during animal toxicity studies. Unlike pure pharmacokinetic studies where the purpose is to obtain information on what the body does to the drug, the objectives of toxicokinetic studies are to describe the systemic level of the drug in animals, the relationship

of this level of drug to the dose given and the dosing schedule, and to relate the level of drugs to any adverse side effects observed in the animals being given the drug. This information, when viewed together with studies of how the drug is metabolized and exposure data from studies in humans, will help in deciding which species is the best one to study for a given drug and what additional studies need to be done. Toxicokinetic studies may be an integral part of the safety study, or they may be undertaken separately to get specific information.

When a potential drug causes too much toxicity in the animal safety studies, it is usually dropped from further development and the money invested up to this point is lost. Toxicokinetic studies can prevent the premature discontinuation of potentially valuable drug development by indicating how the dosing regimen could be altered to avoid toxicity and still maintain therapeutic activity.

1.8. Therapeutic evaluation

Since no drug is totally safe, rational use is independent upon accurate knowledge of its effectiveness (efficacy), safety and the factors that affect each. In the early 1960's, Congress required a drug be effective as well as safe before it could be marketed. Since that time, a surprising amount of knowledge and the methods for obtaining this information have been accumulated. The well controlled clinical trials is now the Gold Standard to determine efficacy and safety in man, the result of significant advances in the scientific methods that have been, and are, evolving for designing and conducting therapeutic trials.

Both patients and investigators, either consciously or subconsciously, want medication to be effective. To eliminate this bias and other confounding factors, the well controlled clinical trial starts with a written protocol that clearly defines the objective(s) of the study and how it will be conducted. Attention is paid to many aspects of the trial to reasonably assure that the results obtained are a true answer. What criteria are used for selecting the type and number of patients enrolled? What is the dose of drug that will be given and how often will it be given? What will be measured to determine if the drug is effective (i.e. what are the therapeutic and–or pharmacodynamic endpoints)? What is the appropriate control group to measure treatment against? This is usually a group of patients that receive no drug, or placebo, whenever ethically appropriate. Is the trial double-blinded, i.e. neither the patient nor the investigator know whether the patient is receiving the drug or the control? How do you record adverse events and determine whether they are related to the drug? Is the clinical trial designed so that patients are selected at random for drug or control so that when the data is analyzed valid statistical analyses can be performed?

Obtaining concentrations of drug in the blood during a clinical trial is now common practice. These concentrations are used to determine compliance (i.e. whether the patient is taking the drug when he–she is supposed to), to effect of interactions with other drugs and food, and relationships between blood concentrations of a drug and the drug's effect, even with sparse data. Since many adverse drug responses are dose or drug concentration dependent, clinical trials should be designed to determine the minimal dose or blood concentration of drug that is effective without producing such adverse effects. Clinical trials also provide data on the incidence of adverse drug responses to compare with control group data. The incidence of many adverse drug responses is sufficiently low that the response will not be detected even in a large trial. Since symptoms and signs of an illness are often similar to adverse events associated with administration of a drug, it is important to develop methods that allow the care-giver to decide if the drug or the disease is responsible for the event. Stepwise mathematical procedures called algorithms have been developed and are being improved to facilitate this. Differences also exist among individuals in the adverse responses to drugs. One person may take a given dose of a drug with no side effects at all while another person exhibits a severe reaction. As our understanding of the bases for these differences increase, so will our ability to minimize adverse responses improve.

Improvements in the therapeutic trial are still needed. Improved methods are needed to determine if the patient took the test drug, and at the prescribed times, and to improve patient compliance if necessary. We also need to find ways to assess the effectiveness of a drug earlier in chronic diseases without having to wait for a long-term outcome so that large, extended, and expensive clinical trials are not required.

An important question to answer is whether the results from a trial with carefully selected patients can be generalized to all patients and what type of data are needed to define rationale use by age, gender and race, etc. Newer types of data that measure quality of life or cost of treatment are being demanded out of clinical trials and the methodology to obtain these data is improving and being standardized. Nevertheless, clinical trial methods have now improved to where they are steadily providing the data that will allow prescribers to achieve their ultimate goal—drug use tailored to the individual patient.

1.9. Pharmaceutical scientists = significant savings and enhanced value

The discussion of the value of the pharmaceutical sciences is not complete without recognizing the contributions made by many pharmaceutical scientists trained in the areas of economics, marketing, and management sciences. These scientists serve to link the efforts of scientists in drug discovery and development of pharmaceuticals with those involved in the distribution and consumption of pharmaceuticals and work toward measurement and assessment of societal contributions made by pharmaceuticals. Societal contributions made by pharmaceuticals are revealed through numerous economic evaluation and outcome assessment studies. These studies specifically address issues of identification, measurement, and valuation of costs (i.e., inputs or resources consumed) and the consequences (i.e., benefits or outcomes), and ultimately the determination of the value of drug therapy programs using techniques such as cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analysis.

Since 1991, academic pharmaceutical scientists have worked under a collaborative agreement with the FDA aimed at enhancing the drug approval process through three main initiatives: research, database development and education and training. The goal of the project has been to improve the drug approval process and the overall health care services for the country. This has been accomplished by reducing the time it takes to get drugs to the public while maintaining their safety and efficiency.

Once a drug has been approved for marketing, any changes in the manufacturing process, including scaling-up the production to produce sufficient quantities to sell to the public, have required a series of tests to demonstrate to the FDA that the drug produced by the new process is equivalent to the one originally approved. The overall mission of the research program is to establish a scientific foundation for new regulatory policies on such scale-up and post-approval changes (SUPAC) for oral solid disage forms. The research focuses on the possible influence formulation and process variables may have on both in vitro dissolution and in vivo bioavailability of dosage forms. The body of experimental data generated in the first research project on immediate release (IR) solid dosage forms not only indicated that existing policies were overly conservative, but also led to the adoption of new policies. This has resulted in a faster, more streamlined drug approval process based on requiring fewer, but more focused tests. It has been estimated that the number of pre-approval supplements required to be submitted by industry in support of SUPAC changes will be reduced by 20%, substantially reducing the regulatory burdens for both the industry and the FDA. This will save industry hundreds of millions of dollars which, in turn, will translate to lower costs to the public.

Research is now ongoing focusing on extended release oral solid dosage forms. A user friendly database has been developed to electronically represent and organize selected information from drug applications. This initiative makes possible faster and more effective application submissions by industry and more timely approval of applications by the FDA. The Bioequivelancy compo-

nent is now being used by companies to submit applications for review, and the Chemistry, Manufacturing and Control component will be operational by the end of the year. Reviewers report that the database reduces the time to write final reports by up to 70%. This will decrease the overall time required for the FDA to approve a drug, thereby again decreasing costs to the industry and the consumer. Not only will the database expedite the review process, but it will also allow the FDA to query the database for information which it was previously unable to access and to also track the history of the drug.

The education and training program originally focused on professional development of FDA's reviewers through various short courses and seminars. This program trained the review personnel, who are primarily chemists and biologists, in the general principles of pharmaceutics. This resulted in more effective and faster reviews through an enhanced ability to make informed, high quality decisions. Computer aided instructional programs allow reviewers to pursue training at their convenience. The educational program now provides training on the implementation of new regulatory guidelines, some of which have been directly derived from the research program.

This multifaceted approach to applying knowledge in the pharmaceutical sciences to policy development and regulation has resulted in significant cost savings and reduced regulatory burden for the industry and the FDA. Each day saved in the review process on a major drug can lead to up to $1 million in revenue, part of which is reinvested in research to provide better and safer drugs.

2. Breakthrough technologies

2.1. Combinatorial chemistry

An emerging breakthrough technology that pharmaceutical scientists are describing as a key factor in the so-called in drug discovery is that of combinatorial chemistry. A major theme underlying the science of combinatorial chemistry is that of molecular diversity, or the ability to create a significant number of compounds having randomized variation within their chemical structure at more than one site. The first examples of combinatorial chemistry were based on peptide mixtures in which synthesis was performed in such a manner to vary amino acid substitutions at multiple sites. Such studies illustrated this technology to be powerful in terms of both generating up to millions of chemically unique molecules and as a strategy to identify biologically active compounds using biochemical or pharmacology screens. Also impacting the technology of combinatorial chemistry has been engineering (e.g. various types of immobilized solid-phase polymer-assisted methods) and robotics to simplify and expedite the overall, synthesis and sorting processes.

Recent applications of sophisticated, yet challenging, synthetic chemistries are leading towards the creation of libraries of a plethora of small molecule types which are thought to be particularly promising for the discovery of novel drugs. Such advances in combinatorial chemistry are catalyzing drug discovery in proportions previously unknown in the pharmaceutical sciences. In this regard, combinatorial chemistry has been applied to both the discovery of promising new drug candidates (leads) and to their optimization to ultimately enhance their pharmacological properties in both in vitro and in vivo model systems.

Pharmaceutical scientists have discovered lead compounds and, in a few cases, drug candidates that range from enzyme inhibitors to compounds that bind receptors and either mimic or inhibit their natural function. Specific examples include antibiotic peptides, opioid receptor antagonists, thrombin inhibitors, and Factor X inhibitors. Many new discoveries are being made that will catalyze drug discovery in essentially all areas of pharmaceutical research.

Rational drug design is based on knowing the three-dimensional structure of the drug target and using computer-assisted molecular modeling to

predict an active drug structure. In concert with combinatorial chemistry, rational drug design is also providing an opportunity for focusing chemical modifications at key sites of a prototype molecule or lead compound. Therefore, synthetic, computational, biophysical and biological chemistry may be highly integrated in the application of combinatorial chemistry as directed to drug discovery. Beyond drug discovery exists enormous opportunities for the application of combinatorial chemistry to in vivo pharmacological and biopharmaceutical studies to optimize the in vivo properties of a drug candidate. Among the many intriguing avenues for such research are reducing the metabolism of the compound, improving its solubility, and enhancing its ability to cross cell membrane barriers.

The future of combinatorial chemistry will undoubtedly provide a multitude of bona fide preclinical lead compounds and drug candidates, and it is expected that marketed pharmaceuticals having origins in combinatorial chemistry will make significant impact over the next 25 years of medical research. Such advances in combinatorial chemistry will continue to illustrate the paradigm shift in drug discovery from rather labor-intensive and time-consuming chemical synthesis of prototype drugs to that of accelerated chemical synthesis of millions of compounds that can be biologically screened to identify as well as optimize structurally novel drug candidates. Furthermore, combinatorial chemistry will likely provide a cost-effective strategy to accelerate this component of drug discovery.

2.2. In vitro biopharmaceutical techniques

Today's pharmaceutical scientists have many new technologies available to them that allow them to synthesize very potent and very specific drug candidates. Synthesizing these drugs candidates is only half the battle, however, since the human body has built-in barriers (e.g. the blood-brain barrier, the intestinal lining, the liver) that do not allow these new drug candidates to get to where they need to act. A major challenge confronting pharmaceutical scientists is how to design into new drug candidates not only potency and specificity, but also structural characteristics that not only allow, but actually facilitate, the molecule's ability to cross these physiological barriers to get to their sites of action.

Just as medicinal chemists now have available rapid techniques to tell them if they have made an active drug candidate, pharmaceutical scientists are developing techniques that allow for rapid characterization of the biopharmaceutical properties of these molecules. Molecular-based assays using cloned enzymes in test tubes mimic the body's ability to breakdown drugs in the liver and intestine. Such test tube assays allow pharmaceutical scientists to predict how the body will metabolize a promising drug candidate before large sums of money are spent developing and testing it in animals and humans. Cellular-based assays are actual cells that line the intestine or the micro blood vessels of the brain. These cells, grown in culture dishes, are used as models of the intestinal lining or the blood-brain barrier to measure how drugs cross this barrier. Both types of assays can be adapted to test large volumes of compounds in a short period of time. The availability of these assays will allow pharmaceutical scientists in collaboration with medicinal chemists to use an iterative process to achieve a drug that is not only very potent, but gets to where it needs to be in the body quickly and in greater amounts. One potential benefit of this is fewer unpleasant side effects because of having to give extra large doses of the drug in order to get enough at the site of action.

The development of these new biopharmaceutical techniques represents an exciting new advance in the pharmaceutical sciences, which not only can lead to an improved understanding of the biological barriers that limit the effectiveness of new drugs, but which can also expedite the process of drug discovery and drug development. This means that pharmaceutical companies will have more active drug candidates able to be developed in less time which ultimately translates into less costly drugs to the public.

2.3. Molecular aspects of drug metabolism

Imagine the physician's consternation when one patient exhibits a markedly different response from another patient when both are given the same dose of a particular drug. For some patients this dose indeed provides the desired effect(s), but for others it will not be an effective dose, and in the remainder there will be an increased propensity towards side-effects. Such variation in responses by different individuals to the same dose of a given drug is referred to as interindividual variability. One major factor in such differences is the way in which each drug is metabolized in an individual patient. Optimal drug therapy requires knowledge of each of these determinants, ideally before the drug is prescribed. A major breakthrough in pharmaceutical sciences and medicine has been an understanding of the molecular genetics of the enzymes which metabolize drugs and other chemicals. Each of the metabolizing enzymes appear to be very selective in terms of which drugs or chemicals it will metabolize, even if they are structurally closely related. Additionally, only a few or sometimes a single such enzyme is predominantly involved in a drug's overall metabolism.

For pharmaceutical scientists developing a candidate drug, it is important to have information on the enzymes that metabolize the drug candidate and the speed with which they do it as early as possible in the design phase. Historically, information on a drug's metabolic pathway (i.e. which enzymes are responsible) has been obtained from metabolism studies in animals, but this approach has now been largely replaced by techniques using human tissues or cloned metabolizing enzymes (e.g. different forms of cytochrome P450 and glucuronosyl transferase) to provide insights into the specific role and importance of individual forms of these enzymes. Using these tools, the qualitative and quantitative fate of a drug candidate can be predicted prior to its first administration to humans. As a consequence, the selection and optimization of desirable characteristics of metabolism are possible early in the development process, thus avoiding unanticipated toxicity problems and associated costs subsequent to the drug's clinical investigation. Moreover, the effect of one drug on another's disposition can be anticipated.

The interindividual variability in drug metabolism is usually due to both genetic and environmental factors, in particular, how the drug metabolizing enzymes are controlled. With certain enzymes, the genetic component predominates and variability is associated with variants of the normal, wild-type enzyme. An extreme example of this is genetic polymorphism, where the variant enzyme does not function properly and a sub-group of patients exist who are more prone to the concentration-dependent effects of a drug. This sub-group of patients may show toxic side effects to a dose of drug that is totally without side effects in the rest of the population. The recent understanding of the molecular genetic basis of such polymorphisms has resulted in the development of genotyping tests that allow identification of affected individuals. As a result, their atypical metabolism and likely response to a drug metabolized by the affected enzyme can be understood and predicted, thus permitting the physician to adjust the dose of drug they receive to achieve improved therapy. A similar approach is also becoming important in identifying risk factors associated with the development of various cancers. This is because the enzymes involved in drug metabolism are also responsible for the activation and detoxification of chemical carcinogens. Accordingly, an individual's susceptibility to cancer often involves the balance between these two processes, which is, in part, genetically determined and which can be screened by suitable genotyping tests.

2.4. Analytical technology

A major challenge facing scientists developing ever more potent drugs will be in developing new methods for analysis of these compounds. The situation will become especially critical for the analysis of impurities in the drugs, since the toxicity of these may be such that the impurities must

be controlled to extraordinarily low levels. For example, many new anti-cancer drugs are themselves cytotoxic, and their impurities equally so. The old rule to detect and quantitate impurity species at levels exceeding 0.1% cannot be applied to cytotoxic impurities, which might have to be measured at levels of 0.01% or even 0.001%. To reach such low analytical limits, new techniques and methodology will have to be developed.

In addition, consciousness has been raised regarding drug compounds which are mixtures of enantiomers, that is, molecules that have the same chemical make-up but are mirror-images of one another. Often, one enantiomer is more effective than the other, and in such instances it is highly desirable to administer only the more active species. When compared to a dosage form consisting of the mixture of enantiomers, it has the effect of essentially halving the administered dose while retaining the full compound activity. The measurement of enantiomeric purity at ever-decreasing analytical levels will be a challenge for the future. Within the past years, the use of high-performance liquid chromatography (HPLC) has gone from being a laboratory curiosity to the current state where HPLC is the workhorse of all analytical facilities. In HPLC, an unknown mixture is forced through a solid matrix in a column, using liquid under pressure. Different components of the mixture are retained by the matrix based on their structure, size, and other physical properties. As liquid continues to push through the column, each molecular species is washed off, but at a different rate than other molecules with different properties.

Detectors measure what comes off the column over time. Vast strides have been made in detector and column technology, which have greatly improved the quality of this methodology. More recently, capillary electrophoresis (CE) has begun to be used by pioneers, who have reported that CE can reach even higher levels of sensitivity. CE involves using an electric field to further separate molecules based on their electrical charges. It is anticipated that new methods of separation and detection will continue to be developed by ingenious scientists, and that these advances will push our ability to detect minute levels of impurities even further.

It is highly likely that complicated analytical problems will be better solved by combining methodologies resulting in systems of increasing complexity, as reflected in their hyphenated names. For example, the combination of mass spectrometry (MS) with either gas chromatography (GC-MS) or liquid chromatography (LC-MS) is but the beginning of this trend. The union of superior separation methods with superior detection methods is a trend which will result in the generation of new methodologies of great power.

2.5. Biomaterials

Most drugs are administered orally as tablets, capsules or liquids and are absorbed into the blood system from the gastro-intestinal tract as part of the normal digestive process. With such an approach, however, it is often necessary for the patient to receive large doses of drug, perhaps two or three times a day, because of the relatively short residence time in the gastro-intestinal tract or because the drug is destroyed by various digestive processes. Taking a drug two–three times a day, is often inconvenient for patients, leading to missing doses, and therefore, to noncompliance in the use of the medication. For many patients with chronic diseases it would be much more convenient and efficient if all of the drug needed for a period of days, weeks, months, or even years, could be administered at one time and released over this time period at a therapeutic level. Such a strategy for drug administration has been accomplished through the implantation or injection of polymeric systems, i.e., large molecules, that contain the requisite amount of the drug to serve as a reservoir for the entire time course of therapy. These polymers control the rate of drug release, either by dissolving very slowly and thus slowly exposing the drug to body fluids for absorption, or by remaining intact throughout the period of use and releasing the drug slowly by some type of barrier mechanism.

What makes such an approach to drug therapy possible is the availability of various types of plastics known as biomaterials, i.e. materials that can be introduced into the body without being rejected and impaired in their properties by the normal immune system through the production of inflammation and deposition of biological materials on the surface of the material. Such deposition most often leads to the disruption of the drug-releasing mechanisms and thus to failure to deliver the appropriate amount of drug. The major breakthrough for the development of biocompatible materials for drug delivery first came from scientists attempting to develop artificial organs an organ parts, e.g. heart valves, artificial hips, etc., and the realization by pharmaceutical scientists that such systems could be applied to drug delivery. Today there are numerous examples of implants of such materials containing drugs being placed beneath the skin or into muscular tissue to deliver medication systemically over a period of years, or being placed directly into a local area like the brain for the treatment of brain tumors. Another breakthrough in this area came when it was realized that certain polymers mixed with drugs, after some time in the body, would very slowly dissolve, thus increasingly releasing the enclosed medication by enhanced exposure of drug to surrounding body fluids. This concept of biodegradation, originally used for the development of self-dissolving sutures, is now finding widespread use, for example, in the once-a-month delivery of non-orally absorbed proteins in microspheres injected intramuscularly. Intensive research by pharmaceutical scientists is now being carried out to further develop materials that are biocompatible over long periods of time, and with the properties that allow delivery of medication at controlled rates.

2.6. Gene transfer–gene therapy

Genes, which are present in almost every cell in the body, contain instructions used by each cell to make the various proteins needed for the body to function. Genes also carry hereditary information for the individual in germ cells. It is estimated that approximately 100 000 different genes represent the code for a human. To date, the unique identity of about 20 000–30 000 genes have been determined—yet the function (i.e. what each gene code is for) of only several thousand genes has been deciphered. Gene therapy is a means of supplementing defective genes with the correct genes. It holds the promise of being able to treat a wide range of diseases at their most basic level—that of the instructions encoded in the body genes.

The advent of biotechnology about 20 years ago has resulted in dramatic progress in our understanding of the molecular basis of how genes work. Some practical applications of biotechnology have included our ability to make human proteins in bacterial and cell cultures in large scale amounts. The pharmaceutical sciences played an important role in helping develop these agents into drugs by developing analytical methods, designing dosage forms, designing clinical trials, and developing the processes to produce stable, safe medicines. Some of these agents include life saving human medicines such as insulin, tissue-type plasminogen activator (TPA—used to dissolve blood clots formed in a heart attack) and erythropoeitin (EPO—used to build up a patient's blood cells during dialysis or cancer chemotherapy).

Using the tools of molecular biology, scientists have gained a greater understanding of the genetic basis of a wide range of diseases. Many diseases are a result of a malfunction in the gene controlling the production of a specific protein. For example, a number of diseases have a genetic origin, wherein a certain gene is defective at birth—including diseases such as cystic fibrosis (which primarily affects the lungs) and sickle cell anemia (which affects red blood cells). In other cases, disease results from damage to genes caused by an external source such as radiation, chemicals or a fault in the body's repair mechanism. The most apparent example is the array of diseases called cancer where genetic damage causes the effected cells to proliferate out of control.

The goal of gene therapy is to affect the outcome of diseases by administering the correct gene and have it taken up and utilized by the target cell. The cell will then be able to produce the correct protein, which will override the effects of the defective protein and cure the disease. It is important to note that gene therapy is involved in augmenting or overriding defective genes in the patient and not changing the germ line (i.e. the therapy will not affect the children of the recipient).

Gene therapy to date has involved two basic technologies. The first approach involves inserting the correct gene into an inactivated virus, and causing the delivery of the genetic information to occur as a consequence of viral infection of certain cells. In some applications, the target cells (such as blood forming cells or cells of the immune system) are removed from the patient's body, exposed to the viral gene delivery system and returned to the patient. In other cases, the viral gene delivery system is administered directly to the patient—an example is the use of viral delivery systems injected into melanomas to help the body reject the tumor.

Another approach to gene therapy uses synthetic molecules such as lipids to introduce the gene into the body. Such systems are being used to treat cystic fibrosis by applying the gene delivery product directly to the patient's lungs via an aerosol spray. These systems may have advantages over the viral systems because of a better safety profile and ease of manufacture. In addition, scientists are investigating the use of gene based vaccines, where the gene alone is injected into muscle cells of patients.

There are numerous challenges that need to be overcome for successful gene therapy. First, the correct gene has to be isolated, its expression optimized, and then produced in large amounts by fermentation techniques. Next, the gene has to be incorporated into a stable delivery system that is capable of getting into the correct cell type, either outside the body or after direct administration to the patient. These processes are very complex and are pushing the limits of our knowledge and understanding of genes and their function. Because of the enormous complexity of the procedures, they require the skill and expertise of scientists from many disciplines. The role played by pharmaceutical scientists is one of being able to provide the gene in a stable form, being able to help design targeting of the gene and providing the final dosage system in a form where it can be safely administered to the patient.

2.7. Live therapeutics

Most people recognize drugs as non-living entities, and they are correct—most therapeutics today are chemical entities designed to block a particular receptor or trigger a cascade of desired biological events. An exciting new field of live therapeutics is on the horizon, with the possibilities of curing certain cancer forms, beating AIDS and arresting Alzheimer's disease to name a few.

You might ask, how can one possibly make a drug that is alive or living? Well, it has already been done several times, and you have probably taken one or more of these! For example, a few of the childhood vaccines are made of living viruses that have been made non-pathogenic by growing them under selective conditions. Examples include the live viral vaccines against polio, smallpox, measles, and chickenpox. To protect against these diseases, one is injected with a live (but non-pathogenic) virus that looks like its disease-causing cousin, which signals your immune system to mount an immune response in readiness for the actual disease causing virus should you ever come into contact with it.

Research using live organisms to make better vaccines continues, ranging from a vaccinia-based herpes vaccine to prevent cold sores and sexually transmitted herpes, to expand weakened salmonella vaccines to prevent food poisoning.

Viruses may be used for other purposes than just making better vaccines. They are also used as efficient delivery vectors, where viruses can be designed to carry, target, and deliver pieces of DNA that encode for proteins that have a beneficial therapeutic effect. For example, cystic fibrosis is caused by a deficiency in the CFTR gene (this is the gene that encodes for a protein that keeps the lungs moist), and researchers have used the adenovirus to carry and incorporate the CFTR gene

into the lung tissue in an attempt to increase the CFTR gene product level and concomitantly cure cystic fibrosis. This approach is also being used for other disease states, such as the introduction of adenosine deaminase (ADA) into mature lymph cells of patients with ADA deficiency.

Another exciting area is the implantation of live cells that have been genetically altered to produce the desired drug, such as nerve growth factor for the treatment of Alzheimer's disease. Often these cells are not of human origin (for example, they might be Chinese Hamster Ovary cells, commonly used in biotechnology) and so must be encapsulated within semipermeable hollow fibers to guard against destruction by the human immune system. Such permeable fibers let nutrients in and the drug out, but do not allow passage of immune cells that would kill the drug-producing cells. The advantage of such a system is clear-cut; once implanted it would continuously deliver the drug for several years, forgoing difficult and repeated surgery to organs such as the brain. Such a treatment may be used for other indications including chronic pain, Parkinson's disease and other neurodegenerative disorders.

Using live therapeutics is also gaining a foothold in the war against cancer. It is possible to give our own immune systems a helping hand to destroy cancerous cells by increasing their number and cancer killing ability. This can be done using different types of immune cells, but the approaches are similar. For example, lymphocyte-activated killer (LAK) cells are removed from the patient, and grown up to high number density outside the body (ex vivo) using cytokines such as Interleukin-2, and then these cells are returned to the patient. Similarly, ex vivo expansion of tumor infiltrating lymphocytes (TIL therapy) has been demonstrated to be effective, for example, against metastatic melanoma.

Because cancer cells are remarkably like our own cells (indeed, they are our own cells that have lost the ability to specialize in their function), the mechanism to defeat cancer cells must be sophisticated and able to differentiate self from non-self, exactly what our immune system is designed to do. The exciting therapeutics mentioned above are quite diverse in their nature and disease targets but have a common thread—they are live therapeutics comprised of living viruses, cells or tissue, and are quite different from our standard repertoire of chemical and biochemical entities we call drugs. The development of this class of therapeutics has several hurdles to overcome, but also tremendous potential to cure infectious diseases, AIDS, and cancer.

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