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IMPACT OF THE PHARMACEUTICAL SCIENCES ON HEALTH CARE

A REFLECTION OVER THE PAST 50 YEARS

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As we engage, at any ever increasing pace, in our daily lives it is all too easy to forget the improvements in healthcare that have been experienced by citizens of the world over the decades. This thought was the stimulus behind the decision of the Board of Pharmaceutical Sciences (BPS) of the International Pharmaceutical Federation (FIP) to task a group of leading pharmaceutical scientists to reflect and document the many and significant contributions that in particular pharmaceutical sciences, and implicitly pharmaceutical scientists, have made to these improvements over the past 50 years, with a focus on medicines. The aim was not only to make fellow scientists aware of our contributions, but also to increase public awareness of the role that the pharmaceutical sciences plays in healthcare, as well as to stimulate interest in the pharmaceutical sciences as a career choice for young graduates.

Fifty years serves as a useful dividing point. Reflect that, in the early '60's, there were no safe and effective treatments for such common conditions as essential hypertension and atherosclerosis, both of which increase the chance of premature death. Nor were there such remedies for a whole host of debilitating and lethal parasitic diseases that have afflicted many millions, especially in the developing world. Indeed, the majority of today's most commonly prescribed medicines such as the statins, calcium channel blocking agents, bisphosphonates, oral contraceptives, and the whole class of monoclonal antibodies did not exist then, while improvements has been seen in many other classes, such as antibiotics and antimalarials. Also, the surgical treatment of peptic and duodenal ulcers with its attendant risks was relatively common before the advent of the proton pump inhibitors. In the first half of the 20th century most medicines were prepared extemporaneously, whereas today this practice accounts for less than 1% of all prescriptions. Such changes did not occur by chance.

This report is divided into six sections (drug discovery, ADME (absorption, distribution, metabolism, and excretion), pharmacokinetics and pharmacodynamics, drug formulation, drug regulation and drug utilization), each describing key contributions that have been made in the progressions of medicines, from conception to use. A common thread throughout is the application of translational science to the improvement of drug discovery, development and therapeu-

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tic application. Each section was coordinated by a leading scientist who was asked, after consulting widely with many colleagues across the globe, to identify "The five most influential ideas/concepts/developments introduced by 'pharmaceutical scientists' (in their field) over the past 50 years?" However, it is recognised that separation into sections is artificial as inevitably there is considerable overlap in the sciences underpinning progress in the six sections. To assist in the visualisation of the events in each section is a timeline on which are identified the important landmarks that occurred during the past approximately 50 years. The format of the timeline varies as best fits the section. While efforts have been made to identify the earliest key publication(s) associated with a seminal discovery or development, sometimes more current reviews are appropriate. Furthermore, omissions may have inadvertently arisen. Also, while highlights in the progress of basic sciences can often be accredited readily to specific individuals, those in drug discovery, development and regulation are frequently the result of complex teamwork over extended periods, making individual attribution of merit very difficult.

The meaning of the term pharmaceutical science is in the eye of the beholder. Here, it is defined as the 'science of medicines', the science underpinning the discovery, development, production and use of medicines, arguably one of the most complex and sophisticated endeavours of mankind. However, it is recognised that the science enabling these subjects often requires competencies from different traditional fields of sciences, and that there are many important contributors to pharmaceutical sciences who would not consider themselves as 'pharmaceutical scientists'. Nonetheless, in most of the seminal references provided in this report at least one of the authors would regard themselves as such.

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DRUG DISCOVERY

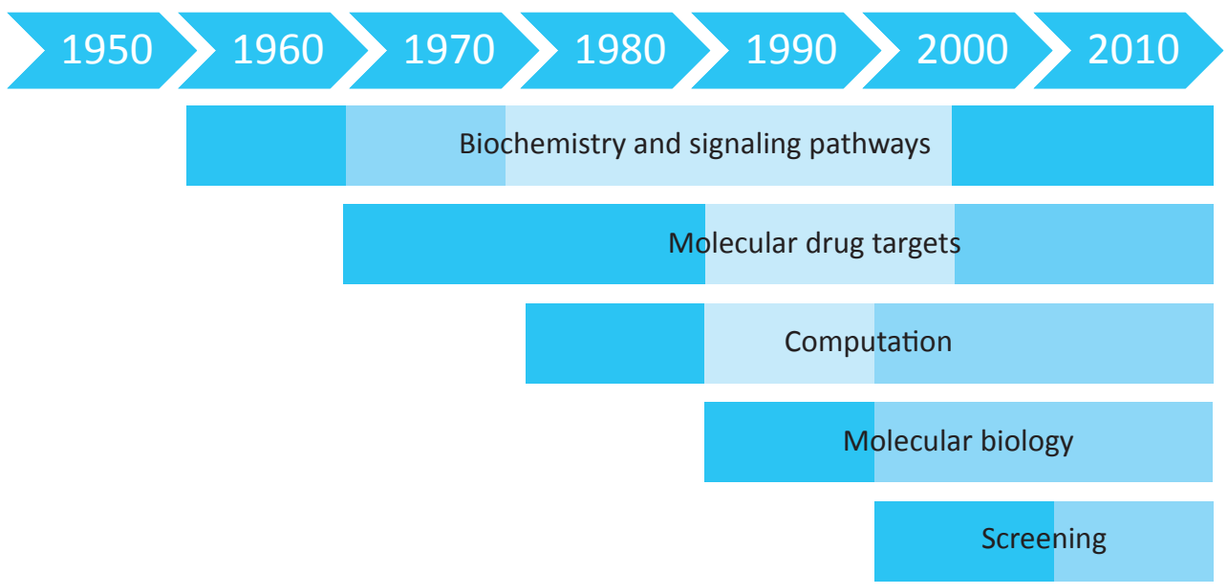

Figure 1. Timeline of introduction of some key concepts and developments in drug discovery

"Nothing has remained as it was!" This short sentence reflects the fundamental changes that drug discovery has undergone during the last 50 years, mostly induced by major paradigm shifts in the progress of science in general, some of them associated with the formation of entirely new scientific disciplines. An amazing sequence appeared in five areas of scientific breakthrough, which roughly arrived one by one, decade by decade over this half century (Figure 1).

1. Biochemistry and signalling pathways

The launch in 1960 of the first oral contraceptive, a prelude to the first life-style changing class of designer drugs, and the invention of levodopa therapy for Parkinson's Disease[1], among others, heralded a new phase in drug discovery, with a paradigm shift from organic chemistry to biochemical pharmacology as lead discipline in drug discovery. In both cases the design of the drug had been guided by a precise understanding of metabolic function, which has remained an indispensible part of drug discovery ever since. Levodopa relied on its active transport into the brain and subsequent conversion there to the neurotransmitter dopamine. Thus it was, in addition, an impressive example of the "prodrug" concept. Also in 1960 a new therapeutic category was created: the "tranquilisers", with chlordiazepoxide and diazepam as first representatives[2].

The Nobel Prize winning elucidation of the "arachidonic acid cascade"[3] revealed fundamental biochemical mechanisms underlying pain and blood coagulation, and provided the basis for a better understanding of the action of then established drugs, such as the non-steroidal anti-inflammatory agents and corticosteroids. Other major therapeutic breakthroughs related to a key metabolic pathway followed in the area of antifungals that inhibit vital steroid biosynthe-

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sis[4], and the statins, which lower cholesterol by inhibition of hydroxyglutaryl-coenzyme A reductase. Although the discovery of cyclosporine, which prevents the rejection of organ transplants, was serendipitous, it paved the way for the discovery of a host of effective immunosuppressant drugs.

2. Molecular drug targets

The term "receptor" was coined at the end of the 19th century. Although major receptor classes had been long defined by the 1950's, the role of "receptors" as central elements of drug discovery (target based strategies) could only evolve with progress in biochemistry, which provided the ground for a precise interpretation of functional pharmacological data. Exploratory testing now shifted from animal pharmacology to molecular pharmacology, with radiopharmacology serving as a central method and molecular parameters used to classify pharmacological action.

Identification of receptor subtypes and understanding of the receptor machineries rendered possible the identification of potent and selective ligands, which formed the basis for the great successes in drug discovery during the second half of the 20th century. Extensive research took place first in the field of adrenergic receptors, with the ß-blockers becoming medicines of major importance, and in the field of acetylcholine receptors. Many other key medicines then followed from this "fine tuning" paradigm. Targets include membrane receptors, above all G-protein coupled membrane receptors (GPCRs) and ion channel proteins, as well as nuclear receptors and enzymes. H2-receptors antagonists have been in competition with proton pump inhibitors. The blockbuster status of both in ulcer therapy was later challenged by the finding that Helicobacter pylori is a major cause for this disease.

Much of these successes would not have been possible without advances in analytical techniques, such as X-ray crystallography and high resolution NMR spectroscopy that provided detailed structural information at target sites.

During the same period organic synthesis developed into an "art" allowing the precise molecular design of ligands at more and more precisely defined binding sites of receptor proteins. Stereochemistry evolved into a prominent topic due to the chirality of the drug targets. Many design strategies have been worked out to optimize drug target interactions. An efficient "machinery" for the design of drug candidates has thus grown up.

3. Computation in drug design

First "indirect" examples of computer use in drug research were their applications in complex analytical techniques, like NMR or X-ray, and for theoretical calculations of structures. Computer use directly for drug design was at first limited to calculation of physicochemical parameters (QSAR)[5,6], molecular modeling of small molecules and drugs[7,8] and pharmacophore modeling[9]. However, with the advent of more powerful computers that 'allowed' visualization and analysis of complex molecules, like proteins, "rational drug design"[10,11], involving computer assisted (stereo)controlled design of drug candidates based on structure activity relationships, became of age. Although results of this first phase of "rational drug design" did not meet the high expectations, there is nowadays no relevant drug discovery without input from molecular modelling. Applications of computers range from studies on ligand-target interactions to virtual screening and high throughput docking. Computers are also an indispensable tool for storing and analyzing the vast amount of biomedical data, essential for progress in systems pharmacology.

4. Molecular Biology – "Tools and Drugs"

Without doubt, molecular biology has been the "dominating" science of the last quarter of the 20th century. Swiftly and comprehensively, this science opened up the understanding of the genomic level of life. Not surprisingly, the rapid growth of molecular biology with impressive landmarks, such as the human genome project[12] or the discovery of oncogenes[13] has had a huge overall impact on pharmaceutical sciences. However, the announced paradigmatic full replacement of "small molecule drugs" by genome-based therapies has not occurred.

The first generation biopharmaceuticals included recombinant blood factors[14]. Here, the decisive improvements have been in production, resulting in efficient industrial scale quantities of high quality human(ized) proteins. The largest growth however has been in the number and variety of monoclonal antibody drugs with their unique potential for specific target recognition thereby broadening and revolutionizing therapeutic options for many previous untreated or poorly treated diseases. Monoclonal antibodies have been used alone, coupled with small-molecule cargo, or as derivatives. Like nucleic acid derived compounds, namely oligonucleotides, siRNA and miRNA, they are at the same time potential therapeutic modalities and important tools in functional genomics.

5. Automated Screening

The "return of the small molecules" after the molecular biology hype was triggered by the development of combinatorial and parallel synthetic methods, which allow synthesis of a vast number of compounds in one run[15,16]. However, it was the development of automated high throughput screening that has allowed fast hit identification from the resulting large compound libraries, applying mostly recombinant pharmacological test systems. Moreover, automated screening was not just a new technique, but signaled the advent of a new scientific approach of general relevance: robotics and artificial intelligence in experimental research, a fast growing trend. High throughput screening of very large libraries aiming at fast hit identification, whose success has not been very convincing, has been replaced by more focused screening of target libraries, as well as fragment

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based approaches[17]. The result has been an enormously increased efficiency in hit identification, lead finding, and lead optimization, exemplified by the recent "triumph" of the new class of protein kinase inhibitors, possibly the most impressive progress in cancer treatment within the last decade. The increased efficiency in drug design due to the screening option also facilitated consideration of druggability features within the discovery phase (see ADME section).

Novel developments in mass spectrometry, microscopy[18] and imaging techniques are playing an increasing role not only in screening based drug discovery, but also in drug research in general. Imaging is swiftly evolving into a tool in drug research with several methods on molecular, cellular, tissue, organ and whole body level. PET, SPECT, fMRI and CT are the most widely used techniques at present. Fluorescent-based bioassays are now playing an increasing role there. Biomarkers are also helping to provide precise interpretation in diagnosis and therapy.

1960 – 2011: THE WAY WE WERE AND WHERE WE ARE NOW

From signalling pathways to metabolic networks: Despite the enormous scientific progress over the past 50 years, and the huge number of identifiable targets, there is general concern about unacceptably high attrition rates, especially in late stage drug development, often due to lack of clinical efficacy. This has led to a remarkable change of paradigm in drug research: from reductionist to systems approaches. While biochemistry and signalling pathways – as well as the other new achievements in drug discovery – have been important components of the drug discovery process, increasingly they are being complemented by advances in systems biology – combining proteomics, genomics, metabolomics and bioinformatics – above all by adding the genomic level and creating multidimensional metabolic and signaling networks[19,20]. The associated rising field of systems pharmacology is forecast to provide precise mapping of disease biology, opening up metabolic network based avenues of drug discovery, including design of drugs with 'individualised' therapeutic properties.

Competence in drug discovery: It is evident that the complexity of drug discovery has grown significantly over the last 50 years. It may be expected that research in drug discovery will soon result in task defined profiles of scientists with focus on target discovery, lead discovery or on lead optimization, respectively. Apart from that, traditional technical elements of preclinical development already appear now in the discovery phase, while, on the other hand, active compound manufacture is subject to regulatory control. Pharmaceutical research and development can no more be organized just via inter-disciplinary co-operation, but has to be considered as the science of medicines, i.e. the pharmaceutical sciences with its full and broad scope. Scientists in drug discovery will need both a broad systems view and a repertoire of knowledge and techniques from different disciplines to be able to carry out their complex work.

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ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME)

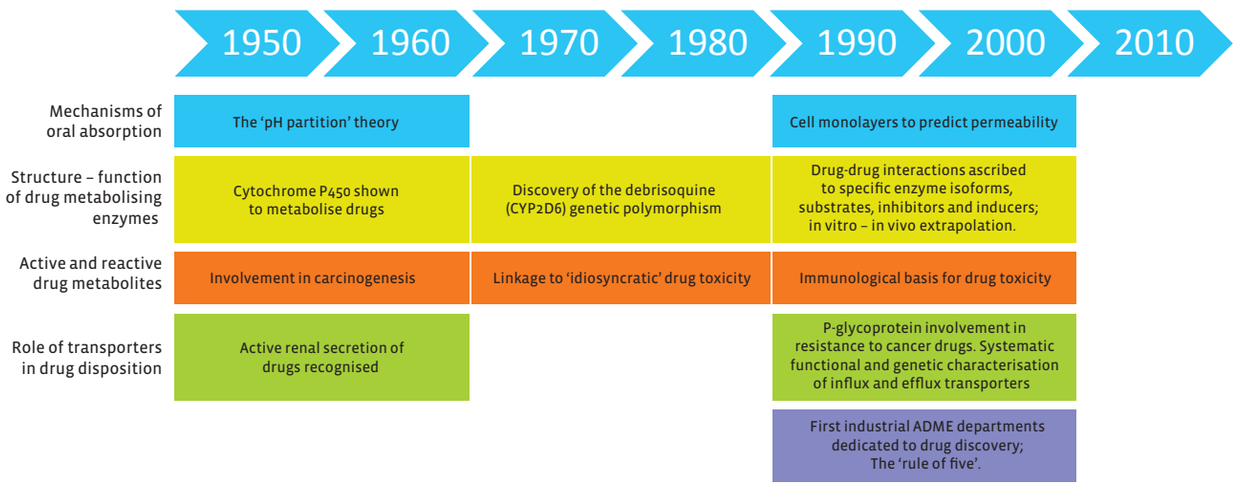

Figure 2. Timeline of introduction of key concepts and developments in absorption, distribution, excretion and metabolism (ADME)

Fifty years ago relatively little attention was placed on the relationship between the structure and physicochemical properties of a chemical and its handling and fate within the body. Much has happened since.

1. Mechanisms of oral drug absorption

To achieve therapeutic concentrations systemically an oral drug needs to be reliably absorbed. Compounds can cross biological membranes by two passive processes, transcellular through the intestinal cell membrane and paracellular through aqueous pores formed by the tight junctions between the cells. These aqueous pores limit absorption to small drug molecules with a molecular weight of usually less than 300 daltons[21]. For a drug to cross by the transcellular route it must be lipophilic, although an alternative for some highly lipophilic compounds is lymphatic uptake following association with lipoproteins in the enterocytes[22]. Since small intestine transit time is only 3-4 hours and many compounds are not absorbed efficiently from the colon, which has a mean transit time of up to 12h, the available "window" for drug absorption is limited. This has important implications for the design of delayed- and prolonged-release dosage forms.

Many drugs have polar and non-polar characteristics and are weak acids or bases. In the 1950's Brodie et al.[23,24] proposed the pH-partition theory to explain the influence of gastrointestinal pH and drug pKa on the extent of drug absorption. They reasoned that when a drug is ionized it will not be able to pass through the lipid membrane, and that the non- ionized drug is the absorbed species. Actual lipid permeability was found to be dependent on the degree and type of hydrogen bonding functionality in a molecule in addition to ionisation and lipophilicity. As lipoidal permeability declines transporter proteins (see below) have an increasing impact on the absorption process. Much of the role of passive membrane diffusion and transporter interplay was identified with cell monolayers. Monolayers of a well differentiated human intestinal epithelial cell, Caco-2, were the first cell line used as a model to study passive drug absorption across the intestinal epithelium. A good correlation was obtained between data on oral drug absorption in humans and the results in the Caco-2 model.[25,26] To discover and develop drugs whose targets required high hydrogen bonding capacity in vitro screening systems proved vital to define the absorption potential of new drugs. These same screening systems were also highly predictive of gastrointestinal drug-drug interactions caused by inhibitory concentrations of one drug increasing the flux of another across the gastrointestinal membrane by inhibiting drug efflux transporters. With the developing knowledge of gastrointestinal drug absorption, the attraction of the oral route in terms of patient conveni-

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ence and flexibility of dose size drove innovative strategies to enhance the absorption of both poorly soluble and of poorly permeable drugs (such as peptides and proteins). These strategies have included the use of liposomes, microtablets, pellets, chitosan capsules, nanocapsules, nanoparticles, mucoadhesive polymers, microemulsions and adhesive drug delivery systems[27] (see Drug Formulation Section).

2. Structure-function of drug metabolising enzymes

The search for orally effective drugs means that unless the target receptor accepts small drug molecules (MW < 300 daltons) the emerging compounds need to be lipophilic and lipid permeable. Such drugs cannot be efficiently excreted by the kidney and the liver via the bile because of extensive passive tubular reabsorption. Therefore, they must rely wholly or partially on metabolism for their clearance from the body, by a system of enzymes that were probably evolved originally to protect the body against toxic chemicals ingested in the diet. Many enzymes are involved in drug metabolism but the principal system is cytochrome P450. The name cytochrome P450, or CYP for short, arose from the discovery that a liver microsomal CO-binding pigment capable of metabolising exogenous chemicals was a haem protein having a strong UV absorption peak at 450 nM[28]. Further historical details of the discovery of cytochrome P450 are documented by Estabrook.[29] The central role of cytochrome P450s in the metabolism of xenobiotics was first established with the observation that various carcinogens were activated by the enzyme[30] shortly followed by studies of Axelrod[31] in the early 1950's that linked the enzyme to the metabolism (oxidation) of a range of compounds. Eventually it was recognised that cytochrome P450 is in fact a superfamily of enzymes as emerging in vivo data, enzyme purification and fundamental studies to elucidate the topography of their active sites revealed isoforms with different substrate selectivity and inhibitory potential.[32] Identification of genetic sequences led to the multiple forms of CYP450 being classified into a number of families – CYP1 enzymes catalysing the metabolism of many carcinogens and drugs, CYP2 and 3 enzymes effecting the metabolism of many drugs and CYP4 enzymes metabolising lipids, plus a number of other forms involved in steroidogenesis. The latter families have provided drug targets for cancer and fungal infections.

Thus, progress in understanding the cytochromes P450 has been dramatic over the last 40 years. Of particular potential clinical relevance is the fact that some of these enzymes exhibit marked single nucleotide polymorphisms and different genotype frequencies across racial groups. Observations in the 1970's of bimodal distributions in the urinary ratios of debrisoquine[33] and sparteine[34] to their major oxidation products led eventually to the characterisation of several polymorphic forms of CYP2D6 associated with 'poor', 'intermediate', 'extensive' and ultrarapid' phenotypes[35] with respect to the metabolism of many important drugs such as beta-adrenoceptor blockers, class 1 antiarrhythmics and antidepressants. Subsequently, other CYPs were shown to exhibit genetic variants and polymorphs with decreased catalytic function, including CYP2C19 and CYP2C9,[36,37] with implications for the dosage of important drugs such as warfarin and losartan. Although rapid genotyping tests are now available for the common polymorphisms of drug metabolising enzymes, their uptake in medical practice remains controversial pending further evidence of clinical and pharmacoeconomic benefit[38].

The withdrawal of several drugs from clinical use over the last 15 years as a result of significant and clinically unmanageable drug-drug interactions relating to enzyme inhibition, particularly of CYP3A4, has established the need within drug development to screen for such interactions through in vitro studies with human hepatocytes, microsomes and recombinant enzymes (see Pharmacokinetic Section). A striking example of a serious metabolically-based drug-drug interaction is that between potent inhibitor of CYP3A, ketoconazole, and the non-sedating H1 antihistamine terfenadine leading to fatal cardiac arrhythmias as a result of excessive systemic accumulation of the parent drug.[39,40] This led subsequently to the replacement of terfenadine with its metabolite fexofenadine. The latter accounts for the non-sedative anti-histaminic properties of terfenadine since, under normal conditions, the parent drug is not systemically available because of extensive first-pass metabolism in the gut and liver and fexofenadine, being a zwitterion and actively effluxed from cells by P-glycoprotein, is excluded from the brain. Contemporary examples of highly clinically significant metabolically-based drug-drug interactions include time-based inhibition of the formation of the active metabolites of tamoxifen and clopidogrel by paroxetine and omeprazole, respectively, leading to therapeutic failure. Tamoxifen, used to treat breast cancer, is activated by CYP2D6[41] and clopidogrel, used to prevent strokes, by CYP2C19.[42]

3. Active and reactive drug metabolites

The role of metabolites in the safety and efficacy of drugs has been the subject of considerable research activity over the last 50 years. Stable metabolites can be detected in tissues, blood and excreta. Many contribute to the pharmacological activity of a drug, but their role in toxicity continues to be debated. Recent progress in the area has centred around understanding why metabolites can be pharmacologically active and what combination of structure and physicochemical properties can make them abundant in the circulation.[43,44] In contrast to stable metabolites the evidence for unstable and reactive species generated by metabolism and a role in toxicity is substantial.

The concept of reactive intermediates formed as metabolites of drugs followed pioneering work on the carcinogenicity of polycyclic aromatic hydrocarbons and other planar heterocyclic aromatic compounds.[45,46] Other early studies of liver necrosis in rodents demonstrated that enhanced toxicity was associated with induction and attenuated toxicity with the inhibition of drug metabolising enzymes.[47] This toxicity was accompanied by the irreversible covalent binding of drug-related material, and in the 1970's Gillette[48] formally

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proposed that cellular necrosis, hypersensitivity and blood dyscrasias could result from the formation of reactive metabolites. Since various drugs showed these toxicities in only a small percentage of patients, attention focussed on the possibility of the involvement of an immunological component. This idea was reinforced by the observation that the administration of drugs such as halothane and tienilic acid led to the development of circulating antibodies to drug or modified proteins (CYP2C9, which metabolises tienilic acid). The chemistry behind the formation of reactive metabolites and their adducts was explored in a detailed and comprehensive manner using leading-edge technologies available at the time of the investigations.[49] The metabolism of drugs, such as the sulphonamide antibiotics, which cause severe skin toxicities (Stevens-Johnson syndrome), was characterised, identifying reactive N-4 hydroxylamine metabolites that produced specific T cell responses, again supporting an immunological link.[50] The research on reactive metabolites has had two major influences on drug development and usage. Firstly, efforts to identify 'structural alerts', that is chemical groups that are associated with a high risk of reactive metabolite formation (e.g. aromatic amines, particularly when unsubstituted in the ring), are flagged out to the synthetic chemist.[51] The second influence relates to the "holy grail" of being able to pre-screen patients for drug toxicity. Human leukocyte antigen (HLA) class I alleles process reactive metabolite adducts. The protein adduct is attached to specific HLA molecules on the antigen presenting cells and recognised by effector T cells via the T-cell receptor to cause T-cell activation. HLA-B*5701 is carried by 100% of patients who are patch test positive for abacavir hypersensitivity and screening for this HLA is highly predictive of the toxicity. Gradually similar diagnostics are emerging for other toxicities, although the issue is confounded by genetic and racial differences such that several tests may be required for a single drug to cover these variations.[52,53]

4. Role of transporters in drug disposition.

Active drug transport has been known to occur in the kidney for a long time since the renal clearance of a number of polar drugs exceeds glomerular filtration rate. Although the specific transporters involved have only recently been established, competition for these elements afforded the first clear examples of mechanistic drug-drug interactions. A gradual unravelling of the complex system of uptake and efflux transporters in many organs, notably in the kidney, liver and brain, has occurred over the last 15 years.[54] The efflux transporters were the subject of considerable scientific attention in the early 1990's as a prime mechanism for tumour drug resistance.[55,56] Drug transporters can exclude drugs from the brain[57], explaining absence of CNS effects from drugs such as non-sedating H1 antihistamines, and they can contribute favourably to organ uptake, and hence selectivity, as seen with the statins in the liver.[58] Thus, the potentially serious side effect of myopathy with statins is greatly attenuated by their extensive active hepatic uptake relative to their passive diffusion into muscle. The main transporter of statins in the liver is anion transporting polypeptide 1B1 (OATP1B1, SLCO1B1). Like many proteins involved in drug disposition it exhibits significant genetic polymorphism which contributes to variable therapeutic outcome in patients.[59] The various anion transporters have their counterparts in cation transporters.[60] All transporters are to some extent promiscuous with often wide overlap of substrates. In vitro systems expressing specific uptake and efflux transporters have allowed selectivity to be probed and a better understanding of the contribution of transporters to drug-drug interactions.[61] Drug transporters also play critical roles in the biliary and renal elimination of drug metabolites, particularly the highly water-soluble products of conjugation reactions.[62]

5. ADME and drug design

As a testament to the contributions of scientists working in the area of ADME, it is now increasingly recognised that selectivity and potency are not the only ingredients of drug discovery. As target chemical space continues to drift away from chemical features associated with favourable ADME properties, it becomes even more important to recognise the impact of the latter in drug design. Landmarks along this way include the recognition of the importance of stereochemistry, the first incorporation of drug metabolism and pharmacokinetic studies routinely in early drug discovery, the publication of Lipinski's rules and the development of the Biopharmaceutical Classification System. Enantioselectivity in ADME processes was recognised in the 1960's and '70's to contribute to the fact that optical isomers (enantiomers) can have markedly different pharmacokinetics and pharmacological activity[63], such that today essentially all drugs, if they possess a chiral centre, are developed and manufactured as a single enantiomer. In the 1980's pre-clinical drug metabolism and pharmacokinetic departments in the pharmaceutical industry were aligned with pre-clinical safety evaluation. The major exception to this was at Pfizer's Sandwich Laboratories Department which, almost uniquely, reported into Drug Discovery. The incorporation of metabolite identification and plasma drug concentration data into pharmacological screening programmes aided these laboratories in discovering major drugs such as fluconazole and amlodipine, which succeeded clinically, in part, because of superior pharmacokinetic features relative to agents in the same or similar pharmacological class.[64] The role of physicochemical properties (lipophilicity, hydrogen bonding and molecular weight) in providing the boundaries for drug candidates with a high chance of success were defined by Lipinski[65] in his rule-of-five, which has been further explored and developed within the concept of ADME space.[66] The Biopharmaceutical Classification System (BCS)[67] and subsequent modifications such as the Biopharmaceutical Drug Disposition Classification System (BDDS)[68] have been highly influential in offering templates to understand and predict oral drug bioavailability as influenced by physicochemical properties and active transport and, more recently, likely clearance pathways (enzyme or transporter).

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1960 – 2011:
THE WAY WE WERE AND WHERE WE ARE NOW

In the 1960's drug metabolism was mainly about identifying excreted metabolites, with reliance on radiolabel studies in animals. Analytical techniques were the key to development of the science as the application of paper and thin-layer chromatography progressed to the use of gas-liquid chromatography, eventually being replaced by liquid chromatography – mass spectrometry and other hyphenated techniques into the '70's and '80's. Drug absorption and distribution were essentially thought of as passive processes until the explosion of interest in transporters in the '90's. In the last 15 years, as a consequence of greater fundamental understanding of all of the processes involved in drug absorption and disposition, the pharmaceutical industry has implemented a battery of systematic in vitro and in silico ADME screening procedures to support drug discovery, candidate selection and development into humans. Thus, ADME scientists are now recognised to provide vital information on drug exposure as a means of rationalising pharmacology and safety programmes and, ultimately, dosage in patients. This effort is reflected in drug labelling that provides rational guidance to the prescriber, particularly with regard to drug-drug interactions and genetic and environmental factors associated with changes in metabolic clearance and transport.

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PHARMACOKINETICS & PHARMACODYNAMICS

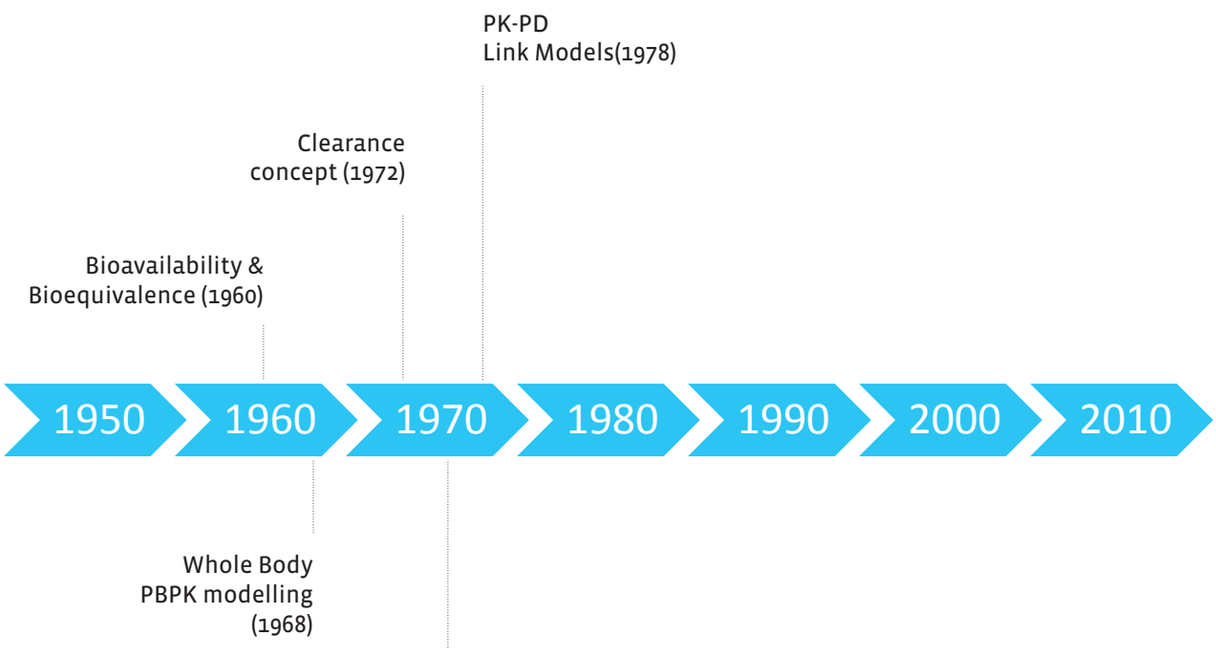

Figure 3. Timeline of introduction of some key concepts and developments in pharmacokinetics and pharmacodynamics

1. The Concepts of Bioavailability and Bioequivalence

The term bioavailability is commonly applied to describe the rate and extent of drug input into the systemic circulation. Formulation is an important determinant of the bioavailability of many drugs (see Formulation section). Formulations of the same drug giving rise to essentially similar plasma drug concentration – time profiles are said to be bioequivalent with regard to providing the same therapeutic effect.

Concern that slow disintegration and dissolution of drugs from tablets could be associated with clinical ineffectiveness was first raised as a significant issue in the late 1950's and early 1960's with respect to the bioavailability of riboflavin[69] and prednisolone.[70] At that time also, conflicting clinical reports concerning the relative advantages of plain and buffered aspirin tablets were ascribed to differences in dissolution rates amongst different products.[71] This formal recognition that formulation factors can influence the outcome of drug therapy was reinforced by two seminal reviews on this subject, termed biopharmaceutics[72,73] and subsequently by a greater realisation that biological factors (e.g. 'first-pass intestinal/hepatic drug metabolism) could also contribute to low bioavailability.[74-76]

The impact of bioavailability and bioequivalence concepts was manifest as a contribution to the better selection of candidate drugs and the design of oral (and other) drug products, and the regulatory requirement for evaluation of the equivalence of innovator and generic products (see 'Drug Regulation' section). Issues with regard to the design and statistical evaluation of bioequivalence studies are still with us today[77], and the area continues to have enormous economic relevance (see Drug Utilisation section).

2. Whole Body Physiologically-Based Pharmacokinetic Modelling

A whole body physiologically-based pharmacokinetic (PBPK) model connects the various organs and tissue of the body by the blood circulation in an anatomical and physiologically realistic manner. As such, it requires independent pieces of information (organ sizes, blood flows, and drug specific data on tissue: blood partition, metabolism and transport) within a generic model framework to provide a mechanistic, 'bottom-up' approach to predicting pharmacokinetic behaviour. Conceptually such models are quite different from so-called empirical and compartmental PK models which are driven solely by observed drug (usually in plasma) concentration –

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time data. In principle PBPK models allow the prediction of PK behaviour and the influence of patient variables before initial in vivo studies are carried out, thereby informing the optimal selection and design of such studies.

While the origins of the PBPK model can be traced back to 1937[78], their implementation had to await the development of computers and the first reports of their application began to appear in the 1960's and 1970's, first in the contexts of anaesthesia and environmental toxicology and then in the pharmaceutical sciences.[79-81]

Subsequent adoption of the PBPK approach within the pharmaceutical industry has been slow, limited by the need for extensive prior data, some of which (e.g. tissue:blood partition coefficients) had to be extrapolated for humans from animal data with great demands on experimental and analytical resources. These issues have now been largely resolved with the availability of comprehensive software and associated data bases and the development of methods for predicting human tissue uptake from physicochemical properties and tissue composition.[82,83] The incorporation of the principles of in vitro-in vivo extrapolation of drug metabolism[84-87] and transporter[61] data has also extended the power and utility of PBPK models, particularly with respect to the prediction of the extent of drug-drug interactions and the impact of age, genetics, disease and formulation[88], such that they are fuelling a radical paradigm shift in drug development that supplants the contemporary empirical R&D sequence of observation-intensive animal and human studies with a resource-sparing, predictive approach that emphasises limited human trials to confirm PBPK-based predictions.[89] In the future, the ability to link a real patient to his or her virtual twin through a PBPK model also offers a potentially useful educational and health care tool for the provision of advice on personalised drug dosage.

3. The Clearance Concept

While the concept of clearance as the proportionality factor between the rate of elimination of a compound and its plasma concentration and its relationship to organ blood flow was well understood in physiology, it was not until the early 1970's that it was appreciated and defined in the context of pharmacokinetics.[90-92] The importance of this development cannot be underestimated when it is realised that clearance is a critical determinant of the rate of drug administration needed to produce and maintain a desired effect that, together with parameters defining distribution, it controls the disposition kinetics of a drug, and that hepatic (and gut wall) clearance determines the extent of first-pass loss by metabolism when drugs are given orally.

By drawing together the major determinants of hepatic drug clearance (hepatic blood flow, free fraction of drug in blood and intrinsic hepatocellular activity and capacity), pharmacokinetic theory was moved on from empirical/compartmental modelling, casting it into a physiological context and thereby allowing a much improved understanding of the impact of physiological and pathological changes and drug-drug interactions on the elimination of drugs from the body. This also laid the foundation for the effective application of in vitro-in vivo extrapolation of data on drug metabolism and transport, and the utility of full whole body PBPK models in drug development.[89]

4. Nonlinear Mixed-Effect Modelling ("Population Pharmacokinetics")

At their inception, the application of PK or PK-PD models to the selection of a drug dosage regimen in an individual patient was often based on population mean values of the model parameters. Clearly, in order to reduce the error introduced by this assumption, as much of the inter-subject variance as possible must be explained by patient characteristics (such as age, weight, sex, renal function, relevant biomarkers). The traditional approach to solving the problem of defining covariates, sometimes called the 'two-stage method', involved intensive study of a relatively small number of subjects selected for a particular characteristic (for example, 'old age') – few subjects, many blood samples. Each set of individual data was fitted by the model and the mean and variance of the parameters was calculated. The difficulties with this approach are that the subjects studied were invariably not representative of the full spectrum of the patient population, that the model parameter estimates are biased, and that, by specifically excluding variables other than the one of interest (for example, age), the ability to detect the influence of other important variables by serendipity is minimised. The solution to this problem was not to consider separate subpopulations separately but rather to fit a population PK model (comprising the structural and variance models) simultaneously to the entire data (albeit sparse) from a wide spectrum of individuals, displaying all the important covariates, using mixed effect nonlinear modelling. This approach was pioneered in the mid-1970's and facilitated by the development of a specific computer programme called NONMEM.[93-95]

The population approach is now standard, with extension to pharmacodynamics, within all phases of drug development, under the label of pharmacometrics. It is applied to rationalising the dosage regimens of drugs in various patient populations and settings, and in bridging studies across different ethnic groups. With recent regulation requiring studies of new drugs in infants and children and the ethical need for minimising the burden of such studies, the 'population PK-PD' approach with sparse sampling is especially valuable. This also applies in the context of the evaluation of drugs in parts of the world where patient access and clinical research facilities may be less well-developed.

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5. Pharmacodynamics and Linkage to Pharmacokinetics

Most of the quantitative concepts in molecular pharmacology, including receptor affinity, intrinsic efficacy, agonism, and antagonism were established in the '50's. However, understanding and characterising the kinetic events between drug administration and response in vivo came later.[96] Commonly, the time-course of effect of a drug (pharmacodynamics, PD) lags significantly behind that of its plasma concentration (pharmacokinetics). In overcoming this problem when optimising drug dosage regimens, the important conceptual advance was to realise that the time-course of the effect itself could be used to define the kinetics of the link between a conceptually distinct 'effect compartment' and plasma. Hence, the development of linked PK-PD 'effect compartment' models, pioneered principally in the late 1960's and 1970's.[97-99] In its simplest form, the relationship between concentration and response within the effect compartment is defined directly by the Hill Equation (a basic equation in quantitative pharmacology) and kinetic events are defined by an exit first-order rate constant (keo), whose value is that which minimizes the hysteresis between the measured effect and the concentration in the effect compartment.[100]

Linked PK-PD models have provided a powerful tool for predicting drug response to multiple or continuous doses from single dose data, for apportioning pathophysiological influences on drug response between kinetic and dynamic causes, for understanding mechanisms of drug-drug interactions and tolerance, for correlating in vivo response with in vitro data on receptor binding, for comparing potencies across a series of drugs, and for designing dosage regimens.[101] In the latter context, for example, algorithms have been developed to optimise the dosage of intra-operative analgesics and other adjuvant drugs with computerised infusion pumps.[102]

More mechanistic 'physiological effect' PK-PD models have also been developed. These models accommodate for the many situations in which the observed response is distal to the direct interaction of drug with its target. This may arise either through complex cascading transduction mechanisms, some with feedback, or where the measured response, be it a change in the level of an endogenous substance or element of a system (e.g. white cell), results from the drug acting directly either on the production or loss of that substance or element.[103] One of the earliest examples was the development of a PK-PD model to characterise the temporal change in the plasma concentrations of clotting factors following administration of the oral anticoagulant, warfarin, the direct effect of which is to inhibit synthesis of the affected clotting factors.[104]

PK-PD models are now routinely used in drug development to inform rational drug dosage guidelines for clinical trials and therapeutic usage. With further advances in systems biology and in the development of biomarkers of disease severity and drug response, this capability is set to reach even higher levels of sophistication and utility.[105]

1960 – 2011: THE WAY WE WERE AND WHERE WE ARE NOW

In 1962 a landmark conference was held in Germany that synthesised all that had gone before in the development of pharmacokinetics.[106] At that time, however, a severe limitation on the practical application of the subject had been a relative lack of specific analytical methods for measuring drugs at relatively low concentrations in biological fluids, such that, in many ways, the theory outstripped the practice. This deficiency was soon to be addressed in the 60's by rapid developments in the application of chromatography, initially gas liquid chromatography and then high pressure liquid chromatography. Along with this development, several American pharmaceutical scientists created a major interest in pharmacokinetic theory and its application. Foremost amongst these were Ed Garrett, Milo Gibaldi, Gary Levy, Eino Nelson, Sid Riegelman and John Wagner.

Pharmacokinetic models in the 60's were mostly of the compartmental variety with first-order and zero-order connecting rate constants. Until 1968 concepts within the pharmaceutical sciences did not extend beyond the naive assumption of monoexponential elimination and the one compartment model with a single volume of distribution. This was all changed when Riegelman and his colleagues[107] pointed out that, indeed, the body was not a single, well-stirred compartment, and that it was permissible to graduate to at least a two-compartment representation with initial, steady state and pseudo-distribution equilibrium volumes of distribution. Henceforth, in the '70's, 'the data were fitted by a two-compartmental model' became a recurring theme in the literature, with progression to general treatments of linear mammillary models and non-compartmental approaches. However, these representations suffer from major drawbacks particularly in as much as they give little insight into the physiological determinants of the fate of drugs in the body. Thus, subsequent significant advances such as the introduction of the clearance concept, the development of whole body physiologically-based pharmacokinetic modelling and the linkage of PK to PD, discussed above, greatly enhanced the value of PK-PD modelling with respect to clinical utility and rational drug development. Today, the current modelling armamentarium in PK/PD is poised to make further substantial contributions to quantitative, systems pharmacology and toxicology and the rational and safe use of drugs.

(Those interested in a fuller history of pharmacokinetics/pharmacodynamics are referred to articles by Wagner[108], Tucker[109] and Csaka and Verotta[110]).

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FORMULATION SCIENCE (PHARMACEUTICS)

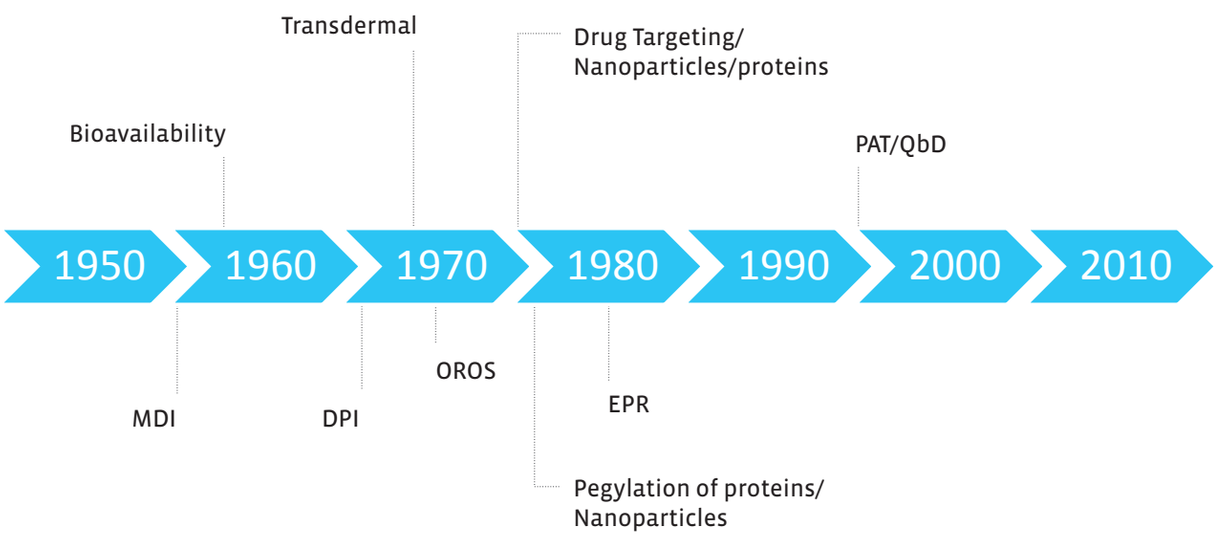

Figure 4. Timeline of introduction of some key concepts and developments in formulation sciences (numbers refer to references).

Patients don't take drugs, they take dosage forms containing them. This statement emphasizes that there is more to medicines than the active ingredient(s). The other constituents, excipients, while inactive pharmacologically themselves are essential in assuring the quality, stability and in many cases the in vivo performance of the active constituents. While formulation as an art form has probably existed for a millennium or two, only since the '60's was it broadly recognized that the formulation of a drug with excipients could impact its therapeutic value. Although, clear examples of successfully manipulating the release of drugs could already be found in the '50's, when different insulin zinc and protamine suspensions (for short, intermediate and long acting effects), and long acting penicillin formulations via complex formation e.g. with procaine, were introduced. In addition, the performance of drugs was being manipulated through the formation of inactive prodrugs, such as via esterification of sex hormones, which release the drug upon hydrolysis within the body to produce either short or long acting preparations depending on the stability of the ester.[111,112]

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1. Technological Progress and Quality Thinking

Nowadays, fast rotating instrumented tablet machines can produce up to 1,000,000 tablets per hour. Although the speed may not have increased much over the last 50 years the quality, in terms of weight control and content uniformity, certainly has improved enormously through the introduction of in-process quality control systems. The same is true for capsule filling machines and other processing equipment. Parallel advances in understanding the critical properties of powdered drugs and excipients – 'molecular and solid state pharmaceutics' – have strengthened the scientific basis of formulation design.[113] Moreover, 'computational pharmaceutics' i.e. the importation and application of optimization and decision-making tools (experimental design, artificial intelligence) has helped to move formulators away from trial and error approaches during development, the norm in the '60's, to rational, faster formulation development.[114-116]

As quality requirements became ever stricter, new analytical techniques were introduced to monitor and control the formulation process 'in real time' under the label of Process Analytical Technology (PAT)). Moreover, during the last decade the 'Quality by Design' (QbD) paradigm (establishing critical pharmaceutical quality attributes and defining the design space) has emerged to provide a full understanding of the relationship between the quality and therapeutic effect.[117, 118]

2. Bioavailability: a key element in modern formulation sciences

The impact of formulation on bioavailability and clinical performance was recognized early (see 'Pharmacokinetics and Pharmacodynamics' and 'Drug Regulation' sections). Certainly the 'digoxin case', involving inequivalence of digoxin preparations on the market brought the issue of excipient dependent drug release and absorption kinetics to the forefront.[119] Indeed, nowadays, no new formulation would be developed without carefully selecting the excipients, the manufacturing protocols and assessing its bioavailability performance.

The quantitative biophysical and physiological principles underlining the design of oral drug delivery systems were laid down in early '80[120] although the fuller understanding and impact of intestinal drug metabolising enzymes and transporters came later (see ADME section).

3. Modified release dosage forms

Many drugs are rapidly eliminated from the body often resulting in the need to administer the drug frequently in order to avoid excessively large differences between peak and trough plasma (and tissue) concentrations, a potential source of unacceptable adverse effects or ineffective levels, respectively. Moreover, frequent dosing is often inconvenient for both patient and nursing staff alike. The solution is to slow the release of drug from the formulation. In the introduction to this section examples were given of parenterally administered modified release systems that were already in use in the '50's and before. In those days the notion was already developed that oral absorption of drugs could be influenced by salt-selection or complex formation and that coating of tablets e.g. with shellac or (pH dependent) soluble cellulose derivatives led to retardation of drug release. Since then these technologies have become increasingly robust and their use in 'real life' optimized e.g., by exploring the sensitivity of modified release forms to food intake. Osmotic pump devices coupling semi-permeable coating with precision laser induced pin hole opening, to produce zero-order release dosage forms independent of the local environment, have also been developed.[121] Other oral modified release technologies are based on a non-biodegradable polymer matrix tablet with the drug embedded in the matrix. Later, granules and microcapsules, instead of tablets, with modified release kinetics were introduced. Nowadays there are many modified release dosage forms on the market.[122] A key factor in advancing our knowledge of oral absorption of drugs following ingestion of dosage forms came with the use of noninvasive imaging techniques, which shed light on the relationship between gastrointestinal physiology and function and product performance.[123]

A special development to enable less frequent administration, achieved by reducing elimination rather than prolong release, has been the family of long circulating PEG (polyethyleneglycol)-modified proteins particularly for proteins that are otherwise rapidly eliminated, such as interferon-alpha.[124] By masking sites recognized by the normal eliminating process of proteins PEGylation dramatically prolongs the interval needed between doses while retaining therapeutic activity.

To conclude, the introduction of well-designed modified release formulations has brought the patient advantages, not only in convenience but also, for some, in widening the therapeutic window by improving the pharmacokinetic profile of the drug (e.g nifedepine,[121]).

4. Site specific therapies

Therapeutic monoclonal antibodies often have a very high degree of selectivity but this property unfortunately is not conferred on many other drugs, leading often to undesirable adverse effects. Therapeutic monoclonal antibodies, target site specific as they may be, often lack potency. A potential solution, sought over many years, is to incorporate the native drug within a colloidal/nanometer sized carrier system that confers tissue selective targeting. Although this concept remains a challenge, first generation carrier systems are now part of some cancer and antifungal treatments.[125,126] The discovery in the 1980's of the Enhanced Permeability and Retention phenomenon (the leaky endothelium lining in the blood vessels in fast growing tumors) explains why nano-sized structures such as liposomes have some preference to localize in these cancer areas, with beneficial results.[127] Considerable effort has also been expended to make these nanostructures increasingly 'smarter', i.e. by including ele-

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ments that release or activate native drug in a temporal and spatial controlled manner down to the organ, tissue and/or cellular level, and by using surface modification for control of circulation times and site specificity, e.g. by monoclonal antibodies or fragments thereof.[128] However, while appealing, so far no breakthrough product has yet passed the regulatory hurdle. But it is just a matter of time.

5. Alternative routes of administration

Most systemically acting drugs are administered through the oral or parenteral route. Other routes of administration for such drugs have also been exploited with considerable success, including transdermal products with improved pharmacokinetic features (well controlled, slow release over days). First developed for motion sickness (e.g. scopolamine) and angina (e.g. nitroglycerin) others have followed, such as patches for hormone replacement therapy, fentanyl patches for severe pain management and nicotine patches for smoking cessation.[129] Another route where formulation science has made great strides is pulmonary delivery. This is mainly for local delivery of anti-asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis drugs. The introduction of pressurized metered dose inhalers (1956) and later powder inhalers (1971) improved delivery efficiency significantly and enhanced patient compliance.[130-132]

1960-2011: WHERE WERE WE AND WHERE ARE WE NOW?

Beyond any doubt, over the last 50 years pharmaceutical scientists engaged in formulation design have substantially improved quality (content, stability, reproducibility, impurity levels), convenience for the patient (dosage intervals, alternative routes of administration) and therapeutic benefit of dosage forms, through improved release time and even spatial control. Also, other than for very specialized products, fabrication of medicinal products has moved from extemporaneous preparation in local pharmacies and hospitals, to industry, subject to tight regulatory control. Here, as in the other sections, many external forces have influenced the course of events, including automation, enhanced analysis, and not least, advances in materials and material science. An excellent example is the introduction and lasting impact of basic physicochemical thinking in formulation sciences by the Higuchi brothers starting in the late 1950's and beyond.[133]

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DRUG REGULATION

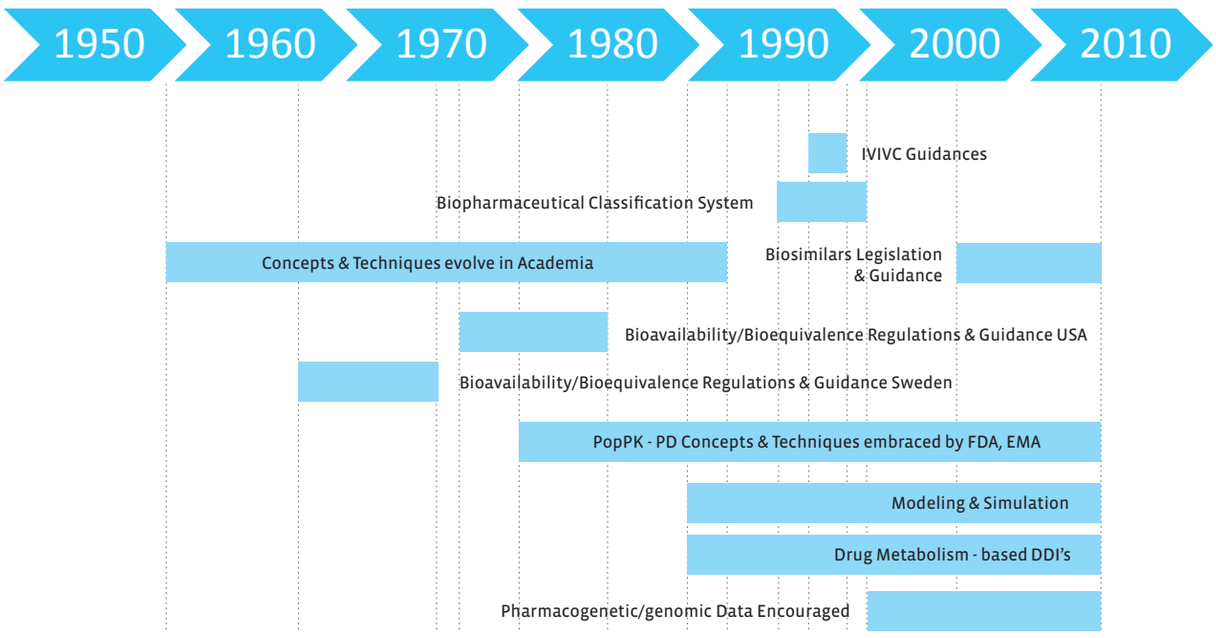

Figure 5. Timeline of introduction of some key developments and guidances in drug regulation

1. Formulation, Bioavailability and Bioequivalence

Regulatory attention to pharmaceutics, formulations and drug delivery systems stems from recognition of their deterministic biophysical influences on delivery, disposition, and clinical response. In order to assure consistency and reliability of non-parenteral, particularly oral, drug and device products and an ever-increasing variety of formulations and delivery systems, more than 20 published standards guidelines[134] have evolved, encompassing Good Manufacturing Practices, dissolution standards and residual drug in transdermal and related delivery systems. But this understanding and impact took time.

On the backdrop of the concept of bioavailability advanced by academic pharmaceutical scientists in the 1950's and '60's (see "Pharmacokinetics & Pharmacodynamics" section), by the late '60's, pharmaceutical researchers and regulators in Europe and United States recognized that different marketed oral drug products containing the same active ingredient and labeled dosage, especially those exhibiting a narrow dosage range, were not safely interchangeable, because of varying bioavailability absorption rate and extent parameters and systemic exposures. In Sweden, phenytoin intoxications related to vastly different bioavailabilities from different phenytoin formulations[135] led the Swedish drug regulatory agency to issue initial regulations in 1968, followed by a more detailed guidance in 1974. In the U.S. reports of high variability in the bioavailability of narrow therapeutic range digoxin products[136], with some providing essentially no drug at all, motivated FDA to publish a regulation in 1977 requiring drug manufacturers to investigate bioavailability of all new drugs, and to employ rigorous statistical procedures for assuring bioequivalence.[137,138] The bioequivalence concept and procedure became the critical basis for all generic drug approvals, and for bridging between different formulations of new drugs during development. This powerful contribution by pharmaceutical scientists formed the basis for the 1984 Drug Price Competition Act, providing statutory authority for FDA bioequivalence-based approval of all new generic drugs.[139] A similar approach was taken by European regulators.[140,141] The bioequivalence test is equivalent to a kind-of FDA-accepted "surrogate" clinical trial endpoint, substituting a small pharmacokinetic study, usually in normal volunteers, for an entire clinical development program as the basis for approval of a new generic drug product. In recent years, regulatory agencies have grappled with the more technically challenge of generic large protein therapeutics and other biological products – called "biosimilars". The EMA has

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published general and product-specific guidelines (http://www.gabionline.net/Guidelines/EU-guidelines-for-biosimilars) and has approved more than ten biosimilar products (http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe). Similar guidance is being developed by the FDA for implementation of the Biologics Price Competition and Innovation Act of 2009 (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm), but no biosimilar products have been approved for the U.S. market.

Further regulatory facilitation of generic drug development has resulted from pharmaceutical science procedures that allow bioequivalence determinations in some cases based on understanding of influence of drug substance water and lipid solubility properties, drug metabolism, and transporter biology within the gastrointestinal and hepatic systems as incorporated in the "Biopharmaceutical Classification System (BCS)" and "Biopharmaceutical Drug Disposition Classification System (BDDCS)"[67,142], enabling FDA and EMA "biowaiver" rules that permit regulatory acceptance of dissolution profile comparability in lieu of human in vivo bioequivalence tests of solid immediate release oral dosage forms.[143,144] A related technique that is useful for both regulators and drug developers is the In Vivo bioavailability – In Vitro dissolution test correlation procedure (IVIVC) for predicting bioavailability of extended release oral dosage forms.[145]

In 1960's, there were no regulatory requirements for ascertaining bioavailability and bioequivalence of drug products, nor could prescribers and patients safely switch between two drug products containing equal amounts of the active ingredient. Today, because of regulatory bioequivalence requirements, patients can expect equal efficacy and safety of generic equivalents of brand name products and of newly approved drug formulations that were tested only for bioequivalence with the product employed in confirmatory phase 3 trials. The history of evolution of bioavailability and bioequivalence concepts and requirements in FDA is summarized in detail by Skelly.[138]

2. ADME/PK-PD modeling concepts, and pharmacometric analysis and simulation techniques

Advanced concepts and techniques of PK and metabolism and linking of PK to PD evolved during the 1960's-1980's. In 1974, active participation of clinical pharmacologists in the regulatory process prompted Swedish regulators to employ PK/PD modeling and simulation concepts as a foundation for efficacy and safety evaluation[146], which was followed by more extensive guidance, published in 1980. In the US, population pharmacokinetic methods introduced by Sheiner et al in the 1970's[93] were first embraced by FDA in the early 1980's in the context of drug testing in the elderly and safety monitoring using a "pharmacokinetic screen" (see "Drug Safety and Risk-benefit Evaluation" below). Recognition of the potential power of population PKPD modeling and simulation methods prompted a national meeting of pharmaceutical and regulatory scientists in 1992 to discuss applications in drug development and regulation.[147] Around the same time, the European Medicines Evaluation Agency (EMEA, now called EMA), encouraged such applications in Europe.[148]

In the past 20 years FDA and its European counterpart EMA have encouraged ever wider usage of population PKPD[149-151] and more recently PBPK methods[89,152], which have advanced to realistic clinical trial simulation techniques.[153,154] During this same period, the culture of pharmaceutical sciences within Western regulatory agencies has expanded not only in staff and resources but in outreach initiatives to the pharmaceutical industry. For example, established in the mid-1990's, the FDA Office of Clinical Pharmacology and Biopharmaceutics implemented extensive pharmaceutical science-centric regulatory research, guidance[140] and review. Initiation of the FDA Advisory Committee on Pharmaceutical Science and Clinical Pharmacology followed shortly thereafter. Important regulatory pharmaceutical science initiatives include (a) the Clinical Pharmacology Question-based Review template, that identified key pharmaceutical science elements required for the review of a NDA[155], (b) the End-of-Phase 2a meeting for industry and regulatory scientists to review pharmaceutical science elements important to subsequent phase 2b and phase 3 trials[156], and (c) the recent establishment of the Division of pharmacometrics.[157] Pharmacometric integration of PKPD data from multiple trials in a drug development program is becoming a basis for multiple regulatory utilities, including dose-justification, investigation of multiple drug-drug interactions, labeling content, support for approval of pediatric and adult dosage regimens not confirmed in a phase 3 trial, and even as a basis for meeting the evidence of effectiveness requirement for marketing approval.[158]

By aggressively incorporating ADME/PK-PD modeling concepts, and pharmacometric analysis and simulation techniques, into the science base of drug regulation, as well as emphasis on drug metabolism, transporter, and drug-drug interactions, the field of pharmaceutical sciences has been stimulated to use higher research standards and to orient academic research towards applications that improve both drug development and regulatory practices. The impact on health and healthcare systems has come indirectly from the FDA and EMA influence on innovation and quality of the pharmaceutical industry R&D, manufacturing and timely access to drugs.

In the last 50 years, because of contributions by pharmaceutical scientists of ADME/PK-PD modeling concepts, and pharmacometric analysis and simulation techniques, regulatory agencies have replaced inefficient, empirical non-scientific approaches[140,141,159,160] with efficient model-based, quantitative scientific techniques. A more detailed history of the impact of pharmaceutical sciences on drug regulation in the U.S. can be found.[161]

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3. Personalized Medicine and Pharmacogenomics

Regulatory interest in pharmacogenetic influences on drug metabolism dates to the early 1990's, when CYP metabolic enzyme polymorphisms were recognized as determinants of metabolic related drug-drug interactions. Recognizing that individual differences in treatment responses depend in part on the influence of genetically determined metabolic characteristics, as well as disease-specific genetic differences, passive regulatory interest turned to championship in the early 2000's when FDA convened a series of public workshops to coordinate utility of pharmacogenomic techniques of mutual value to the pharmaceutical industry and FDA.[162] Shortly thereafter, to stimulate non-binding genomic data gathering, FDA published a guideline on voluntary genomic data submissions (VGDS)[163], which led to vigorous productive exchanges between industry and FDA pharmaceutical scientists concerning 'safe harbor' exploratory genomic data gathered in drug development activities that were exempt from IND (Investigational New Drug Application) and NDA/BLA (New Drug Application/Biologics License Application) reporting requirements.[164] These "voluntary exploratory data submissions" (VXDS) were expanded to include non-genomic biomarker data submitted to FDA and EMA.[165] The 10-year experience of FDA with VGDS was recently reviewed[166], as was the 5-year experience with more than 40 FDA and EMA VXDS submissions.[167] Additionally, the International Transporter Consortium has provided regulators with an important data source for consideration of regulatory implications of transporter-related influences on drug disposition.[168]

Regulated, gene-based diagnostic products have been advanced that can identify patients who may enjoy greater benefit or suffer higher risk. For example, patients with breast cancer evincing HER2/neu overexpression can expect benefit from trastuzumab (Herceptin) therapy, while genotyping for CYP2C9 and VKORC1 enabled labeling instructions for safe initiation of warfarin dosing.[169]

Pharmaceutical scientists in academia and the pharmaceutical industry have been greatly inspired by the advent of pharmacogenomics techniques and by regulator's encouragement. Although still in the early stages of implementation, the evolution of personalized medication, presaged by individualization of therapy using population PK has informed dosage optimization and therapeutic drug monitoring. Examples of increased safety and targeted benefit have provided strong stimuli for further applications.

Although the knowledge of gene biology was already evolving fifty years ago, many pharmacogenomic research and development tools that were not available then, have since been developed. Gene based targeted diagnostic and therapeutic products that were unthinkable then, are increasingly being applied in pharmaceutical science research, pharmaceutical development and regulation.[140,141,170]

4. Drug Safety

Appreciating the PK foundations of bioavailability and bioequivalence concepts, in the early 1980's FDA first embraced population pharmacokinetic methods introduced by Sheiner et al in the 1970's[93] by encouraging the "pharmacokinetic screen", a term coined by Bob Temple at FDA in a discussion paper on studying drugs in the elderly, as a potential means of explaining unexpected outcomes in phase 3 trials.[171,172] Realization of the importance of drug metabolism and drug-drug interactions by FDA came in the late 1980's when it became aware of sudden deaths in patients taking the antihistamine terfenadine (Seldane) along with the antifungal agent, ketoconazole, mentioned previously (see ADME). Recognizing that ketoconazole strongly reduced CYP3A4-mediated terfenadine clearance, elevating terfenadine levels, life-threatening QT-intervals and risk of fatal arrhythmias, regulators published requirements for knowledge of a drug's metabolism[173,174] and potential for drug-drug interactions[175], moving from a time (up to the mid-1990's) when the metabolism of drugs was frequently untested and drug-drug interactions were largely unrecognized, to recent years in which metabolism and interaction potential are invariably evaluated.

Drug-drug interactions are mediated not only by metabolic enzymes but also by transporters.[176] For example, the interaction of cerivastatin with gemfibrozil induced severe rhabdomyolysis and lead to the regulatory withdrawal of the drug. It was later elucidated that both metabolic enzymes and transporters account for this drug-drug interaction.[58] Recently, the FDA has been using PBPK modeling in predicting drug interactions especially when it involves both metabolic enzymes and transporters, and when several inhibitors, or an inhibitor and inducer are coadministered, as may arise in clinical practice.[152]

Pharmaceutical scientists pioneered the science of drug-drug interactions, which drove its regulatory significance. Uptake by both regulators and industry scientists has enabled identification, evaluation and guidance concerning drug related risks, thereby facilitating safety labeling, approval decisions and post-approval risk management procedures.[177] Fifty years ago, adverse reactions occurring when several medicines were taken simultaneously was not well understood. Today, not only is the pharmaceutical science understanding much more complete, but adverse drug interactions can often be predicted and so avoided.

1960-2011: WHERE WERE WE THEN AND WHERE ARE WE NOW?

The impact of regulatory encouragement of optimization of formulations, drug delivery systems, and dosage regimens by regulatory scientists on the field of pharmaceutical sciences has been to excite invention new dosage forms, formulations, and delivery systems, as well as advancement of IVIVC prediction procedures. The impact on the healthcare system has been extensive by achieving therapeutic success by overcoming dispositional barriers heretofore considered impenetrable with individualized dosage regimens.

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DRUG UTILIZATION

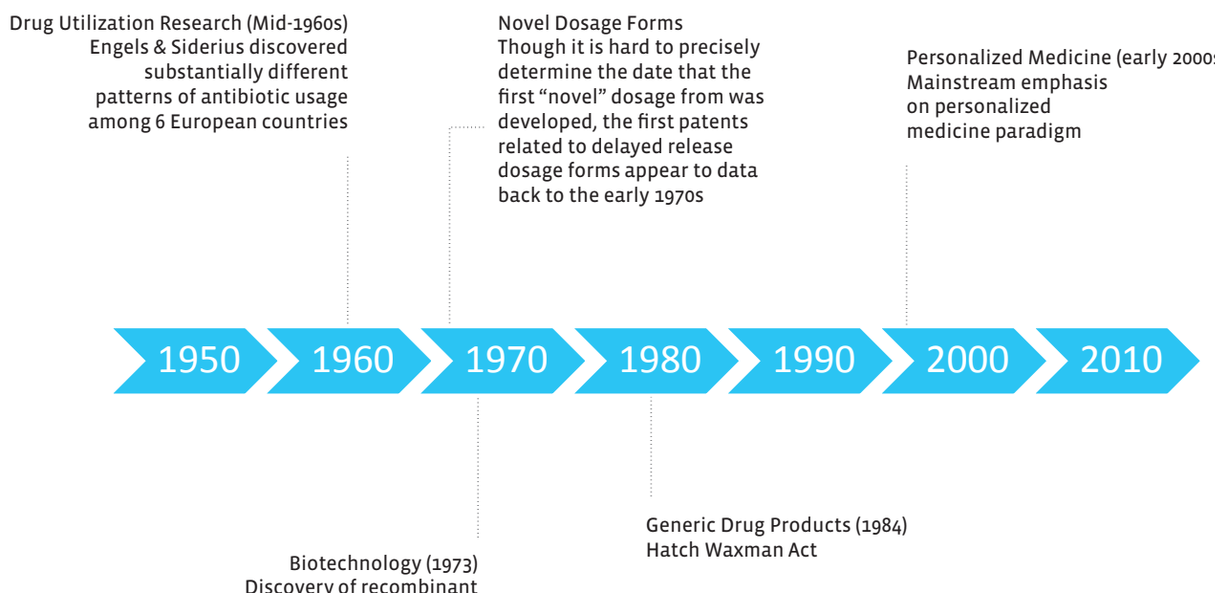

Figure 6. Timeline of the introduction of key concepts and developments in drug utilization.

Fifty years ago, imperfect drug-delivery relied upon crude powders and non-bio-equivalent formulations, and even the blunt parenteral delivery by clysis. Today, because of pharmaceutical and bioengineering advances in pharmaceutics, coupled with regulatory standards and facilitations, patients and caregivers have wide choice of effective and safe approaches to drug administration.

1. Drug Utilization Research

Drug utilization research is defined by the World Health Organization (WHO) as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[178] The origin of drug utilization research can be traced back to the mid-1960's when Engels and Siderius discovered substantially different patterns of antibiotic usage among six European countries.[179] This early work stimulated the interest of WHO in drug utilization research.

When combined with its associated disciplines, pharmacoepidemiology, and pharmaco-economics, drug utilization research provides the basis to determine the best drug therapy for patients with a particular disease. In this context "best" is defined as maximizing the therapeutic benefit while minimizing the adverse effects from drug therapy, at the lowest overall cost to the patient/healthcare system. Aspects of drug utilization are among the newer areas where pharmaceutical scientists have been engaged.

The total patient experience for drugs undergoing development is rather limited when compared to the experience gained once a drug is approved for marketing. It is the aim of drug utilization research and its associated disciplines

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to capture and analyze post marketing data in an effort to guide its rational use going forward. Such work can provide valuable information that was not available during the drug's development such as the efficacy of the drug in specific patient sub-populations that may not have been studied during its development, the existence of uncommon side effects, its relative effectiveness compared to other treatment modalities and the effects of drug overdoses.[180]

A large aim of drug utilization research seeks to curb the occurrence of adverse drug reactions (ADR) which are a major cause of morbidity, mortality and healthcare expense globally. Through global efforts such as that spearheaded by the WHO International Drug Monitoring Programme, submitted data can be analyzed and published in an effort to promote the rational use of drugs in as close to a real time fashion as possible.[181]

The field of drug utilization research is multidisciplinary in nature, with many types of biomedical research scientists, including pharmaceutical scientists, and allied healthcare professionals playing important roles. Through the conduct of pharmacoeconomic studies, scientists and healthcare practitioners can compare and contrast the therapeutic benefits and economic impact of different pharmaceutical treatments or other forms of therapy. The results from these studies can provide much needed guidance on the most efficacious and cost effective manner in which to manage disease.[182]

Another substantial contribution that pharmaceutical scientists have made to drug utilization research relates to the identification and evaluation of drug interactions. This work has ranged from early investigations of the effects of environmental factors, age, diet and other drugs on a drug's pharmacokinetics[183] to more recent investigations that explain the genetic basis for serious adverse drug interactions for some of the most highly prescribed drugs.[184] The identification and detailed understanding of the mechanistic basis of these types of interactions provides much needed information to healthcare professionals, so that safe and effective use of these medications is possible. In addition, this information can be leveraged by drug research and development scientists by taking advantage of the desirable characteristics of existing drugs, in an effort to develop safer and more effective medicines moving forward.

2. Generic Drug Products

The innovation that drives the drug R&D process, bringing novel medicines to the marketplace to address unmet medical needs, often with enormous benefits, comes at a cost. The current estimate is approximately $1 billion to develop and bring a new medicine to the marketplace. Bioequivalence procedures advanced by pharmaceutical scientists, have enabled the development of multiple source products (generics) of innovator drugs that have lost patent protection, permitting effective treatment of disease at a greatly reduced cost. Within the USA generic drugs account for 7 out of 10 prescriptions written today (with the percentage higher in some other countries), and offer therapy comparable to the innovator drug at 15-20% of the cost, saving financially burdened health care systems billions of dollars each year.[185,186] The National Association of Chain Drug Stores, for example, reported that the average 2007 retail price of generic prescription drugs was $34.34 compared to $119.51 for prescribed innovator's drugs.[187] While, in 2009 Aitkin et al[188] reported that the typical U.S. formulary now charges $6 for generic medications, $29 for preferred branded drugs, and $40 or more for non-preferred branded drugs.

Generic products have an interesting history. Though attempts to prevent adulterated or misbranded drugs from entering the marketplace date back to the late 1800s[185], concerns specific to generic drugs date back to the late 1920s, when the company that manufactured Bayer aspirin lost a heated battle to keep generic versions of aspirin off the market.[189] This paved the way for generic versions of a drug to be marketed. During that time, little or no testing was performed to assess the comparability of the generic drug to its branded counterpart. Then in 1984, legislation was passed in the United States that paved the way for generic drugs, as it allowed generic versions of a drug to be marketed without the need to repeat safety and efficacy testing.[185]

In recent years there has been an increased focus in the area of biosimilar development. Though this is still a relatively new field and guidance relative to what constitutes a biosimilar does not exist throughout the world, pharmaceutical scientists will play a key role in performing the formulation and characterization work necessary to ensure the comparability of the biosimilar to the branded product.

In addition, to the dramatic savings offered by generic drugs, the availability of generic drugs dramatically reduces the on-going use of the branded product, which provides a strong economic stimulus for the continual innovation that brings new drugs to market. Without the contributions of pharmaceutical scientists in the formulation of generic drugs and in assessing their bioequivalence, the very existence of safe and effective generic drugs would not be possible.

3. Biotechnology

Traditionally, the pharmaceutical industry had focused on the research and development of "small molecule" drugs. These drugs were chemically based molecules whose mode of action consisted of their association with an endogenous drug receptor that in turn elicited a pharmacologic response. These molecules were generally synthetic in nature and their ability to evoke a beneficial pharmacologic response may have been due to the structural similarity they bore to an endogenous molecule, as is the case for several therapeutic classes of agonists and "antagonists". Alternatively, a molecule's actions may have been totally unanticipated and discovered serendipitously.

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Then in 1973, with the discovery of recombinant DNA techniques[190], a revolution in therapeutics began – a biotechnology revolution that laid the foundation for future work in genetic engineering. These were the beginnings of the focus within the pharmaceutical industry on developing biotechnology-derived products for use in treating disease. This discipline is still in its infancy and will increase in its impact for many years to come. Though biologics such as vaccines had existed prior to the '70's, the development of therapeutic proteins to treat disease offer now new distinct possibilities, since these advances in recombinant DNA technology made it possible to produce large quantities of a desired protein in living organisms.

Though the hopes of "gene" therapy remain somewhat elusive, the use of vaccines, monoclonal antibodies and therapeutic proteins, and other biologics have contributed in a truly novel way to the pharmaceutical care of patients.

The scientific contributions that have made biotechnology a meaningful approach to disease treatment have come from a variety of scientific disciplines including molecular biology, immunology, microbiology and genetic engineering to name a few. Pharmaceutical scientists have made substantial contributions to the development of biotechnology-derived products through their knowledge of formulation sciences, pharmacokinetics/ pharmacodynamics, pharmacogenetics and analytics/bioanalytics.

Pharmaceutical scientists have made substantial progress in developing novel formulations such as "functionalized" nanoparticles to impart site specific delivery of biotechnology products (see section Formulation Sciences).[191] This technology will prove to optimize therapy by delivering drug only to the sites where activity is desired. Still others are developing enhancements to transdermal delivery platforms to make them amenable to delivering proteins.[192]

4. Adherence

With all of the technological advances in the pharmaceutical arena, focused on developing safer and more effective medicines, a patient's adherence to a prescribed drug regimen is in most instances the single most important cause of therapeutic failures. For example, approximately 50% of heart failure patients do not take their medications as prescribed post-hospitalization.[193] Similar dismal adherence rates have been observed in other disease states.[194] If progress can be made in improving such an alarming statistic, substantial progress in the degree of therapeutic success in treating disease should follow.

Pharmaceutical scientists have played a key role on this front in developing drug delivery platforms that release drug over extended periods of time, making less frequent administration of drugs, particularly those with short half-lives, possible. Such advances on the part of pharmaceutical scientists have made a difference as it has been shown that medical adherence to a prescribed dosage regimen increases as the frequency of administration goes down.[195]

The use of extended or modified release dosage forms can also serve to diminish the occurrence of bothersome side effects that result in a patient discontinuing therapy. In this regard the impact of the pharmaceutical scientist's work has been significant. In one study evaluating medical adherence to 2 different medications used to treat overactive bladder disease, medical adherence was improved greater than 50% for tolterodine and over two-fold for oxybutynin when extended release formulations were employed in the treatment regimens.[196] Similar results have been reported for transdermal patches in treating elderly patients with hypertension.[197]

In addition to improvements in medical adherence, pharmaceutical scientists have created novel dosage forms that produce a prompt therapeutic response in an outpatient setting when parenteral administration of a drug may be impractical. For example, cancer patients who experience break-through pain need immediate analgesic relief and are routinely treated with opioids such as morphine and fentanyl for this purpose. Several different types of buccal delivery systems including effervescent tablets have been developed by pharmaceutical scientists to produce such prompt onset of action.[198]

In addition to these innovations, much work has been done to develop delivery platforms that target specific sites in the body as has been described in the "Biotechnology" section of this manuscript.

5. Personalized Medicine

Traditional pharmaceutical research and development activities have focused largely on a "one size fits all" or "blockbuster" approach to therapeutics, where disease states were generally considered to be homogeneous and novel approaches to treating highly prevalent diseases were sought, as these had the greatest market potential within the industry. Historically, little attention was given during drug development activities to differential responses that may have occurred in sub-groups of patients with a particular disease. However, while there have been successes, as stated in the 'Drug Utilization Research' section, morbidity and mortality from adverse drug reactions is staggering in the US alone resulting in unnecessary costs to the health-care system and failure to effectively treat disease in individual patients.[180] There has also evolved over several decades increasing evidence for the role of genetic variation in the pharmacokinetics and pharmacodynamics of drugs.

At the present time, based on the considerable knowledge gained in the pharmacogenetics and pharmacogenomics areas, we now know that an individual's genetic make-up may determine in part how specific drugs are handled within

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the body. Additionally we have learned that many disease states are a heterogeneous mix of disease sub-types that may be ameliorated best through highly targeted "personalized medicine" approaches. These advances offer an unprecedented opportunity to improve the way we treat disease and are beginning to revolutionize the way that new drugs are developed.

The evolution of personalized medicine has been a multidisciplinary effort involving researchers from a myriad of disciplines, including basic and clinical pharmacology, genetics and the pharmaceutical sciences, in addition to those contributions made by practicing healthcare professionals. Collectively these researchers and practitioners have discovered a wide range of genetic variations in both the pharmacokinetics and the dynamics of drug action. Among the major contributions that pharmaceutical scientists have made are related to the virtualization of rational drug discovery paradigms, the identification of genetic variations in drug metabolizing enzymes and drug transporter systems as well as genetic variations responsible for differences in drug response.[184,199-201]

An increasing emphasis on the identification, validation and use of differential biomarkers and disease state modeling has begun and will continue in order to understand and quantify differences in response among disease sub-types, so that targeted therapies can be developed. These disciplines are at a relatively early stage in their development. Pharmaceutical scientists will continue to actively engage in the maturing of these disciplines and the personalized medicine paradigm as it continues to evolve.

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We have just begun to scratch the surface in the evolution of the personalized medicine paradigm. As this evolution begins to mature, the manner in which patients are treated will be changed, with a much greater reliance on the use of companion diagnostics to guide the selection of therapeutic agents to be used in treating individual patients. As a consequence, reimbursement for pharmaceutical care will narrow with third party payers reimbursing for only those pharmaceutical interventions proven to work as indicated on the basis of diagnostic testing. On this basis, drug utilization research will become more important than ever.

There are many challenges that remain for pharmaceutical scientists in the field of biotechnology. Biotechnology products are not suitable for oral administration due to their acid lability and high molecular weight and are currently delivered through injection, or inhalation. Pharmaceutical scientists are currently working to develop approaches to permit oral administration through the use of various strategies including controlled release.[202,203] Surmounting this obstacle will be difficult but will be considered a crowning achievement for pharmaceutical scientists once accomplished, as it will make chronic administration of biologics more practical and acceptable. Furthermore, biosimilars with play an increasingly prominent role in therapeutics moving forward, with the potential to add further cost savings to an overburdened health care systems globally.

GENERAL CONCLUSION

This report documents the critical importance of research in the pharmaceutical sciences over the past 50 years, and implicitly the contributions that pharmaceutical scientists have made, to the improved discovery, development, production and use of new medicines for the betterment of public health. But there is no room for complacency, with an ever pressing need to make drugs even safer and development more efficient and cost effective in order to provide society with affordable quality medicines to meet both unmet medical needs and improved drugs to replace existing suboptimal ones. While one cannot predict where the important breakthroughs will come, there can be no doubt that those engaged in the pharmaceutical sciences will make their contribution felt.

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