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Commentary

Current Challenges and Potential Opportunities for the Pharmaceutical Sciences to Make Global Impact: An FIP Perspective

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ABSTRACT

The chairs of each of the 8 Special Interest Groups of the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation have compiled opinions with regard to major challenges for the pharmaceutical sciences over the next 5–10 years. Areas covered are drug design and discovery, natural products, formulation design and pharmaceutical technology, pharmacokinetics/pharmacodynamics and systems pharmacology, translational and personalized medicine, biotechnology, analytical sciences and quality control, and regulatory science.

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Introduction

The International Pharmaceutical Federation (FIP) is a global organization representing 2 million pharmacists and pharmaceutical scientists, with 137 member groups, including the American

Association of Pharmaceutical Scientists. It sets standards through professional and scientific guidelines, policy statements and declarations, as well as by collaboration with other international organizations, including the World Health Organization (WHO).

In 2007, the President of FIP commissioned its Board of Pharmaceutical Sciences (BPS) to develop an article on the impact of pharmaceutical sciences, a reflection on progress over the last 50 years.¹ The aim was to acquaint fellow scientists with the contributions of pharmaceutical scientists and to increase awareness of the role that they have played in improving health care. Based on

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this review, a concise flyer was also produced to stimulate interest in the pharmaceutical sciences as a career choice for graduates.² Having looked back at past achievements, BPS now looks forward in an attempt to identify the main challenges across the spectrum of activities that comprises the pharmaceutical sciences.

Whereas the impact article was prepared by individuals who had witnessed the development of the pharmaceutical sciences over much of the last 50 years, the main contemporary challenges have been addressed in this article by a mostly younger generation. Accordingly, the chairs of each of the BPS Special Interest Groups (SIGs) were invited to seek the opinions of 5–10 global opinion leaders in their area as to the main issues and to use their responses to identify up to 5 key challenges. Currently, there are 8 SIGs with global outreach within FIP, namely Drug Design and Discovery, Natural Products, Formulation Design and Pharmaceutical Technology, Pharmacokinetics or Pharmacodynamics and Systems Pharmacology, Translational and Personalized Medicine, Biotechnology, Analytical Sciences and Quality Control, and Regulatory Science. It should be noted that other areas such as drug metabolism, pharmacoconomics, pharmacovigilance, and social and behavioral sciences are not represented as SIGs. Together with the Board of Pharmaceutical Practice within FIP, BPS is currently seeking to establish joint interest groups around the last 3 areas.

Drug Design and Discovery

The Need for New Drugs to Combat Diseases With Major Impact on Health and Economics

New Anti-Infective Drugs

For several years now, the world has been confronted with the rapid evolution of bacteria and other microorganisms resistant to current antimicrobial treatment (e.g., methicillin-resistant *Staphylococcus aureus* and carbapenem-resistant *Klebsiella pneumoniae*), many being unaffected by more than one compound. Once the efficacy of “reserve” antibiotics such as teicoplanin has been overcome, patients will begin to die and, indeed, are already dying from otherwise easily treatable conditions such as septicemia. Regrettably, few new antibiotics, especially ones with novel mechanisms of action, have yet to reach the clinic. They are urgently needed. Classical approaches to the development of antibiotics involving impairment of protein synthesis or cell wall formation may not provide sufficiently lethal agents; new strategies are required including those designed to inhibit efflux pumps and to impair the cellular penetration and dissemination of the microorganism. The development of new anti-infective agents capable of addressing major unmet needs in developing countries for the treatment of malaria, tuberculosis, dengue, Ebola, and other tropical diseases also remains a global health priority. In this context, a challenge is to develop alternative reimbursement models, to refine and evolve public-private partnerships with open access to relevant information across national borders, and, in common with all aspects of drug development, to ensure data integrity and scientific honesty.

New Drugs for the Treatment of Diseases of CNS Disorders

As people live longer, the number of patients with dementia is increasing rapidly. Although acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, and NMDA receptor agonists, such as memantine, have been developed to treat the symptoms, compounds such as amyloid β inhibitors that delay disease progression are needed.³ The same applies to other major neurological diseases such as Parkinsonism and schizophrenia. Development of new CNS drugs is particularly challenging, while the mechanisms underlying disease remain obscure and the clinical assessment of efficacy is difficult.

Drug Discovery Based on New Understanding of Mechanism of Action

Selective Agonists at (Oligomeric) G-Protein–Coupled Receptors

In the past, it has been very difficult to activate G-protein–coupled receptors (GPCRs) selectively to avoid off-target side effects mediated by other receptors or receptor subtypes. This reflects the fact that the orthosteric pockets of cognate receptors and receptor families are structurally very similar. However, it is evident from recent X-ray analysis of the structure of GPCRs that many of them exhibit allosteric binding that could be addressed in developing more selective compounds. Dualsteric or bitopic ligands occupying both the allosteric and orthosteric binding sites can enhance agonist activity or can trigger partial agonism. Understanding the functional consequences of the oligomerization of GPCRs is a further challenge. If a single receptor can form multiple homo- or hetero-oligomers, drugs designed to bind to the monomer may still interact with the oligomers, resulting in multiple unintended responses. Therefore, in designing and screening compounds that target a specific oligomer, it will be vital to elucidate the location of the oligomer interface and the distances between respective ligand-binding pockets in the receptors.⁴

Epigenetic Inhibitors

The development of inhibitors of epigenetic events mediated by DNA methylation or histone modification is in its infancy but is a potentially fruitful area for new drug development.⁵ Challenges include elucidation of downstream signaling pathways and crosstalk mechanisms between DNA methylation and histone modification and understanding of individual epigenetic enzyme isoforms.

Protein-Protein Interactions as Drug Targets

Protein-protein interactions (PPIs) have been recognized as key features of diseases such as cancer and HIV.⁶ For example, HDM2 is responsible for the ubiquitination of p53 tumor suppressor, and the complex is a potential anticancer target; the LEDGF/p75 integrase interaction is a target for anti-HIV therapy. Although PPIs were originally thought to be undruggable targets, advances in systems biology and the application and improvement of techniques such as surface plasmon resonance and nuclear magnetic resonance as well as the elucidation of crystal structures should accelerate drug design against them. Challenges include how to inhibit the PPIs directly or allosterically, which interface to be targeted and how much of it, and how to maximize bioavailability.

The Application of Systems Biology and Organ- and Body-on-a-Chip

Through the understanding of signaling pathways and metabolic networks, systems biology is being applied to the elucidation of biomarkers of disease and drug response and is expected to expand its role in the design and development of small molecules by targeting key network nodes and by exploiting the use of drug combinations to offset homeostatic mechanisms and enhance synergy.⁷ The emerging technology of organ- and body-on-a-chip also promises to open new opportunities in drug discovery with respect to target identification and validation, target-based screening, and phenotype screening.⁸

Increased Use of Human Tissue

In those cases where animal models are of limited use for establishing proof-of-concept for efficacy in humans, a challenge is to expedite the development and application of *in vitro* test systems based on human tissue, with due regard to ethical, legal, and

logistical issues.^{9,10} In this context, the use of differentiated cells from human stem cells is expected to increase significantly.¹¹

Improvements in Process Chemistry

Major challenges for process chemists in the pharmaceutical industry include the development of more efficient reactions with respect to yield, cost of raw materials and stability of synthetic intermediates, and safer synthetic routes using less-hazardous materials. This extends to a responsibility to increase the adoption of “green chemistry” to minimize the environmental impact of disposal of medicines through contamination of water and food chains.

Synthesis of Oligosaccharides as Building Blocks for Antibody Drug Conjugates

Scale-up of the regioselective and stereoselective syntheses of oligosaccharides remains a challenge in the pharmaceutical industry with regard to the provision of sufficient yields, selectivity, and quality. The combination of chemical and enzymatic synthesis will help to access the structural complexity of glycoconjugates, thereby enhancing the manufacture of oligosaccharides.

Application of Flow Reactor Systems (Microreactors)

This automated technology can facilitate mass production, enabling more direct transfer of laboratory-optimized conditions to production scale with the use of less energy. The challenge is the optimization of reaction conditions in the flow system.

Genotoxic Impurities

The toxicological assessment of genotoxic impurities and the determination of acceptable limits for such impurities are difficult. A Threshold of Toxicological Concern with respect to carcinogenicity of 1.5 µg/day intake of the impurity is currently considered to be associated with an acceptable risk.¹² Heavy metal contamination from catalysts and reagents poses a particular risk that should be minimized by increasing use of organic rather than inorganic catalysts.

Natural Products

Production and Evaluation of the Quality of Source Plants and Identification of Their Constituents

A systematic approach to standardization of the cultivation of plant sources for natural products and the identification of their constituents will require increasing application of modern techniques in plant biology, agricultural sciences, genomics, molecular biology, and analytical and information sciences. This should lead to improvements in the sustainability and appropriate use of limited natural resources and the discovery of compounds with new therapeutic applications. Metabolomics will be applied increasingly in the evaluation of the highly complex mixtures present in natural products, and genetic modification will allow the creation of new medicinal plants.

Innovation in the Evaluation of the Pharmacology of Natural Medicines and Provision of a Robust Evidence-Base for Their Efficacy

Although the complexity of the composition of natural medicines sets them apart from conventional medicines, this complexity brings potential benefit with regard to synergistic pharmacological effects from multiple compounds and the metabolites formed from these compounds once they enter the body. A challenge in this context is the application of the principles and methods of systems

biology to understand and exploit this synergism (“yin and yang”). Clearly, complexity also imposes increased requirements for the standardization of dosage and the rigorous evaluation of clinical efficacy. In this context, cultural and commercial aspects of the use of natural medicines will have to be considered with appropriate sensitivity.

The Interface With Regulatory Science

The use of natural medicines is an integral part of traditional medicine. International consensus is being sought increasingly, notably through the WHO and the International Standardization Organization. The former is currently making efforts to classify traditional medicines within the framework of the International Classification of Diseases (International Classification of Diseases–11 is expected to be issued in 2017), whereas the latter is trying to establish international standards for a group of products used mainly in traditional Chinese medicine.¹³ These initiatives should go some way to meet a desire for appropriate controls on natural medicines, especially with regard to their import-export between countries.

Formulation Design and Pharmaceutical Technology

Continuous Manufacture

Conventionally, large-scale production of medicines that are compliant with Good Manufacturing Practice involves a series of single steps or reactions followed by batch-specific, downstream processes. To improve control over quality and to enhance process safety as well as to reduce costs and time to market, the pharmaceutical industry is exploring fully continuous end-to-end processing.¹⁴ This implies that active pharmaceutical ingredients (APIs) are processed together with excipients, which will necessitate new approaches to tightly integrated processing technologies.¹⁵ In 2004, the US Food and Drug Administration (FDA) launched the concept of process analytical technology with the aim of encouraging real-time quality testing during production. Combined with continuous manufacturing that eliminates open manual handling of actives and excipients, this approach is predicted to increase safety and shorten processing times without compromising the quality of medicines.¹⁶

The pharmaceutical industry is reluctant to adopt new manufacturing approaches unless they are proven superior both technologically and financially. This represents a significant challenge for rapid implementation of continuous manufacture as only limited resources will be invested in new technologies to assess the viability of this seamless end-to-end processing concept. Several economic models have revealed that capital investment in continuous manufacturing technology could lead to substantial savings in API development cost in addition to reducing or eliminating scale-up risk.¹⁷ From a regulatory perspective, continuous manufacturing driven by a comprehensive understanding of in-process variables is widely viewed as full realization of the quality-by-design concept.¹⁸ The barriers to successful implementation of continuous manufacturing differ significantly from sector to sector (e.g., small molecule chemical synthesis vs. bioprocessing of therapeutic proteins¹⁹). In addition to unique process challenges that may require substantial modifications of production facilities, continuous manufacturing also places markedly different demands on organizational culture and workforce skills. Although there will still be a necessity for unique expertise in various areas, specialists will need to interact with experts from different content areas to a greater extent than they do presently in order jointly to advance process development. As a consequence, differentiation among process development teams will decrease.

Nonparenteral Formulations for Macromolecules

Clinical experience over the past decade has underlined the therapeutic value of macromolecules such as proteins for managing a diverse array of medical conditions. Considering recent advances in RNA and DNA technologies for therapeutic intervention, this sector holds tremendous potential for future growth.^{20,21} As patent protection on first-generation proteins begins to expire and innovators feel increasing market pressure from manufacturers of biosimilars and biobetters, development of nonparenteral formulations has become a more attractive tool for life cycle management.

Unfavorable physicochemical properties of macromolecules, including low lipophilicity and molecular size, combined with limited biochemical stability are a compelling rationale for the development of macromolecular entities as parenteral formulations. However, innovative drug delivery approaches offer new opportunities for nonparenteral administration by the nasal, pulmonary, and dermal routes.^{22–24} If proven effective, nonparenteral dosage forms of macromolecules are expected to capture a significant market segment as a result of the convenience of patient-controlled self-administration. Nevertheless, the challenge of unfavorable physicochemical properties and the biochemical instability of macromolecules remains, leading to limited systemic exposure after nonparenteral administration. Initial results from a few clinical studies suggest that advanced technologies such as microneedles²³ or improved delivery devices for nasal administration²⁴ can enable deposition of a sufficient dose of the macromolecule that translates into an effective therapeutic response. Further exploration of advanced delivery devices has the potential to augment the prospects for nonparenteral administration of macromolecules, although the regulatory pathway may require approval as combination products.

Commercial Manufacturing of Nanoscale Drug Delivery Systems

Nanosized drug delivery systems with a hydrodynamic radius of <20 nm have been shown to add value to existing therapies because of preferential accumulation in target tissue facilitated by active or passive targeting mechanisms.²⁵ However, clinical development of these promising formulations has been limited owing to technological challenges experienced during scale-up.

Conventional bottom-up fabrication technologies for structure- or function-controlled nanomaterials generally rely on noncovalent interactions between molecules causing self-association into supramolecular aggregates such as micelles, vesicles, and solid particles. Although the simplicity of this process seems highly advantageous for manufacturing, fabricated colloids show large variability in size, and particle shape is limited predominantly to spheres due to thermodynamically driven association kinetics. Furthermore, expensive and time-consuming separation processes are required before colloidal surfaces can be populated with suitable ligands facilitating target-specific delivery of payload.²⁶ To fabricate precisely defined nanoscale drug delivery systems suitable for clinical evaluation, advanced manufacturing technologies must be explored that enable more control over size and shape to allow surface modifications using covalent and noncovalent approaches without prior purification. Recently, several reports have highlighted the advantages of top-down fabrication methods including photolithography, microfluidic synthesis, and molding technology such as particle replication in nonwetting templates to overcome the limitations of conventional bottom-up fabrication technologies.²⁷ Future clinical studies will have to demonstrate whether nanocolloids fabricated using these advanced top-down

technologies produce desired efficacy while limiting undesired adverse events.

Formulations on Demand

Increasing understanding of genetic and other differences between patients emphasizes the need for personalized drug dosing. In contrast to solution and some semisolid dosage forms, conventional solid dosage forms such as oral tablets or capsules and standard drug delivery devices do not allow sufficient flexibility in dose adjustment. Patient groups likely to benefit most from the use of personalized dosage forms include children because of their rapidly changing physiology and metabolism and the elderly because of multiple drug therapy and the impact of coexisting diseases.²⁸ To date, coextrusion formulations²⁹ and various printing approaches³⁰ have been proposed as the basis for flexible oral drug delivery systems suitable for personalized dosing. Successful applications of tailored drug dosing may also facilitate safe manufacturing of drugs exhibiting high potency and the use of novel on-demand fixed-dose combinations.

Novel Excipients

Most dosage forms comprise at least 1 API and a combination of pharmaceutical excipients, the latter being classified conventionally as pharmacologically inert. Increased understanding of the biopharmaceutical properties governing drug absorption has resulted in the selection of chemical entities as novel excipients that are critical enablers of desired drug product performance (e.g., permeation enhancers). However, regulatory challenges regarding the approval process of new excipients have limited introduction of these chemicals in commercial formulations.

Consistent with a recently introduced risk-based approach to the manufacture of drug products that applies the concepts of quality-by-design, process analytical technology, and design space, the development of excipients has also undergone more intense assessment with regard to the consistency of their composition and purity.³¹ Thus, the use of novel chemicals or new derivatives of currently used excipients in pharmaceutical formulations is now contingent on extensive pharmacokinetic and toxicological evaluation before regulatory approval. The high cost associated with these studies combined with the potential risk of failure after a long evaluation phase has had a negative impact on the development of new excipients and, in parallel, innovative drug delivery systems.³² To facilitate clinical development of innovative drug delivery technologies that significantly depend on performance characteristics of novel excipients, effective application of modern analytical tools in assessing critical quality and safety attributes of excipients is of prime importance.

Pharmacokinetics or Pharmacodynamics and Systems Biology

Physiologically Based Pharmacokinetic Modeling

The application of physiologically based pharmacokinetic (PBPK) modeling has come of age in drug development and regulation, reflecting significant advances over the last 15 years in the predictability of key pharmacokinetic parameters from physical chemistry and human *in vitro* data and in the availability of dedicated software platforms and associated databases.³³ However, although PBPK or PD modeling is more popular today than at any other time, significant challenges remain for its effective use in making critical decisions in early and clinical drug development, as well in the selection of individualized dosing regimens. With respect to understanding covariates and variability, focus in

applying PBPK has been on anticipating the quantitative impact of drug–drug interactions, age, genetics, racial differences, pregnancy, disease, food effects, and pharmaceutical formulations. These extensions of PBPK modeling, along with parallel simulation of the PK of biologics and moves toward linking PBPK to pharmacodynamic (PD) outcome, are clearly of benefit in understanding extremes of risk in different patient populations as part of the process of drug development. Indeed, mechanistic PBPK modeling is the only efficient methodology that can forecast the combined effects of many patient variables acting simultaneously. One current challenge is the effective application of proteomics, which is needed to measure the expression of low-abundance proteins that influence drug disposition and dynamics (e.g., tissue-specific transporters, FcRn, receptors, and enzymes). Bioanalytical and modeling advances are also needed, and efforts in these areas should improve the predictive performance of PBPK-PD models for subpopulations and individual patients.^{34,35}

An emerging challenge for PBPK-PD is its direct application in health care, concentrating on the individual rather than the population, as an educational tool and for the provision of computerized “point-of-care” advice on personalized drug dosage. The safe and effective management of multidrug treatment of the complex patient with multiple diseases and multiple prescribers requires an integrated view of pharmacology and therapeutics. In this context, linking the real patient to a “virtual twin” and the implementation of a PBPK-PD model in the cloud through a tablet is technically feasible and promises rapidly to predict appropriate individualized or stratified drug dosage and to avoid undesired complex multiple drug–drug interactions. Practical issues in making this proposition a reality include the routine availability of sufficient patient input data (demographics, genotypes, comedication, biomarkers), the availability of a sufficient range of unit dose preparations, physician acceptance, the relation of dose prediction (PBPK) to dose adjustment (therapeutic drug monitoring or adaptive feedback), evidence of cost-benefit to payers, and regulatory approval.

Systems Pharmacology Models

Empirical and semimechanistic population-based PK or PD models are now fully established components of model-informed drug development and adaptive feedback control of individual pharmacotherapy. These models typically contain a minimal number of identifiable parameters and are often used to determine patient covariates in a quantitative manner. However, the predictive power of such models can be limited by the nature of experimental and clinical trial designs and the collected data used to construct the models. These models are also rarely sufficient for capturing complex genotype–phenotype relationships and computationally integrating multidimensional omics data. In contrast, systems pharmacology models aim to develop formal mathematical and computational models that incorporate data at several temporal and spatial scales; these models will focus on interactions among multiple elements (biomolecules, cells, tissues, etc.) as a means to understand and predict therapeutic and toxic effects of drugs.³⁶ The effective integration of systems biology and PK or PD principles is needed to develop enhanced PD models that can be used to identify determinants of interindividual variability in drug response, patient subpopulations, rational drug combinatorial regimens, approaches to minimize the likelihood or circumvent drug resistance, biomarkers needed during drug development and after approval, and approaches to minimize or circumvent adverse drug reactions.³⁷ Analogous to the comparison between simple PK and PBPK systems, these more complex models will not replace the current empirical and semimechanistic PK or PD

approaches but rather will add complimentary information that can be used to inform critical decisions in drug development and ultimately individual therapeutics.

Qualification of PBPK and Systems Models

A wide range of established methods are available to qualify (validate) population-based and individual PK or PD models. However, it is well appreciated that such techniques are not appropriate for the qualification of complex systems pharmacology models.³⁸ The complexity of systems models, coupled with a large number of model parameters that are not all identifiable from a single data source, precludes the use of typical internal qualification methods. Sets of approaches need to be identified to provide guidance for qualifying complex models based on the characteristics of the models and their intended purpose. First and foremost, modeling and simulation development should begin with clearly stating the goals and objectives of the analysis. The type of model, its granularity, and what type of evidence would be considered sufficient for qualifying the model will depend heavily on the scope of the problem. Based on the regulatory, scientific, and clinical interests in the development and application of PK or PD systems models, further research and discussion is needed to establish best practices for this emerging field.

Translational Research and Individualized Medicines

The Clinical Value of Genetic Testing

A persistent challenge for the implementation of pharmacogenetic testing is the issue of its cost-benefit. Because the clinical value of such testing is affected by various medical, social, and financial factors, the cost-benefit balance varies between countries such that it is difficult to achieve international consensus.³⁹ Tests may be divided into those that aid the selection of drug and those that aid in selecting its dosage. In general, implementation of the former has been more successful, especially with regard to the choice of anticancer drugs based on tumor genetics.⁴⁰ Dose selection of anticancer drugs is largely based on tumor size, the extent of local invasion, and lymphatic and distant metastasis, such that pharmacogenetic tests predictive of exposure and response need to have significant added value. Although the gold standard of proof-of-value is a controlled clinical trial against standard of care, it is impractical to demand this level of assurance for every test, such that health care systems will have to consider other levels of evidence in deciding on implementation and reimbursement. Even when the results of randomized clinical trials are available, such as those on the impact of genotype on warfarin dosage, the outcomes may not always provide clarity with regard to clinical implementation.⁴¹ A further challenge for genetic testing in dose selection is to integrate this information with biomarker data and other sources of variability in drug exposure and response such as incomplete adherence, demographics, age, disease, and drug–drug interactions. Predictive PBPK-PD models may prove to be a useful vehicle for this, in association with a resurgence of “therapeutic drug monitoring,” linked to Bayesian adaptive algorithms.

The Role of Bioinformatics and “Big Data”

Omics techniques other than genomics, such as epigenomics, transcriptomics, and metabolomics, are becoming increasingly relevant to the implementation of stratified medicine, producing voluminous amounts of data. A challenge here is to integrate this information, alongside demographic and environmental data, with robust statistical analysis.⁴² Bioinformatics should play an

increasing role in finding meaningful spatiotemporal patterns in “big data,” including time-series analysis of associations between genetic and functional changes of relevance to drug exposure and response. There is also a need to increase access to “big data” held by both pharmaceutical companies and health systems.

Ethical, Legal, and Social Implications of Stratified Medicine

The increasing availability of genomic information at decreasing cost means that more patients will seek such information and that physicians must manage the process of informed consent to allow useful decisions to be made.⁴³ Because knowledge of an individual's genome will bring information on susceptibility to disease, such information collateral to that which may guide drug and dose selection will require careful management from an ethics point of view.⁴⁴ It will also be important to find appropriate compromises between safeguarding access to an individual's health information and sharing that data for the good of public health with guaranteed anonymity. Clearly, continuous health technology assessment will be essential to the success of stratified medicine. Behavioral aspects of the impact of genomics-based risk assessments are in need of further research.

Educational Barriers

To prepare health care providers for clinical decision making based on the implementation of stratified or personalized medicine, there is an urgent need for coordinated education and training programs. These should range from general courses for a broad range of health care staff to more in-depth instruction for researchers, physicians, pharmacists, and nurses. The Internet should be exploited increasingly as a low-cost means of transferring information and the provision of continuously updated education. It will also be important to develop innovative ways of educating the public, both directly and through the news media, about the possibilities and limitations of precision medicine.

The Application of Pharmacogenetics in Drug Development

Although the marketing departments of pharmaceutical companies have perhaps been less interested in stratified or personalized medicine after drug approval, due to pricing inflexibility and market loss, there is increasing acceptance of the principle of no payment for nonresponders. The challenge is to accelerate the change from a “product-” to a “patient-”-oriented mindset in drug development and to offer integrated drugs and diagnostics. In addition, in postmarketing surveillance programs, reverse translational research involving retrospective genetic and metabolomic analysis of data from patients suffering serious side effects has the promise of finding novel drug targets and better clinical outcomes. Any practical application of personalized medicine will require scale-down in the size of formulations (“mini-pills”) to allow flexible provision of a sufficient range of dose sizes. An alternative solution is the provision of variable and accurate doses through the application of inkjet 3D printing technology.^{29,45,46}

Biotechnology

New Therapeutic Advances

In the past 20 years, some of the most important therapeutic advances have involved the development of biological agents that enable the manipulation of disease pathways in a manner not possible with traditional small drug molecules. Biologics now represent 25% of new drug approvals.⁴⁷ More recently, there has

been a coming together of biologics and small drug molecules to exploit the advantages of each type of molecule. Because biologics can provide a highly selective capacity for drug targeting, they will be used increasingly as carriers for cytotoxic payloads (e.g., antibody drug conjugates). These and other therapeutic protein modalities, such as fusion proteins, will be developed increasingly, especially to exploit immunotherapy in the treatment of cancer. However, these molecules pose specific challenges with respect their characterization, control of the bioprocess, yield, cost of goods, and the stability of both substance and product.

Process, Manufacturing, and Impurities

In contrast to small molecule drugs, therapeutic proteins are highly complex structures that must be produced in living organisms. As a result of this complex production process, these products may contain a variety of process- and product-related impurities and degradation products, some of which have the potential to impact on patient safety or efficacy. For example, the presence of impurities such as host cell proteins or protein aggregates formed during processing may trigger immune reactions in patients,⁴⁸ whereas potency can be impaired by degradation in binding regions of proteins by oxidation.⁴⁹ For this reason, it is commonly considered that “the process is the product.”

The development of monoclonal antibodies causing cell death extends the definition of a cytotoxic or cytostatic beyond the inclusion of chemostatic small molecules. Cytotoxic products have to date been required to be produced in a segregated facility. This raises the question of the safety of manufacturing in multipurpose facilities with attendant consideration of cleaning validation, carryover, and patient risk.

In general, there is a need for more flexible and adaptive manufacturing (“on demand”) to add to market availability, and more “on-line/at-line testing” for rapid release and multi-attribute testing of biological products.

Comparability and Biosimilars

The advent of patent expiry on biological drugs poses the question as to whether the traditional understanding of generic medicines is appropriate for these products. Central to this issue is the concept of comparability, requiring the demonstration that 2 products of the same biologic are essentially similar with regard to efficacy and safety (and quality). Comparability is usually assessed during the development of a new biological drug and also needs to be considered with regard to the demonstration of the biosimilarity of generic and reference products. This is a multistage process, starting with the analytical comparison of parameters indicative of quality. However, it is widely acknowledged that current analytical techniques are not capable of characterizing biological products completely. Accordingly, the continuing challenge is to progress this assessment to preclinical evaluation involving, for example, pharmacokinetic studies in appropriate animals and, often, to efficacy trials in patients.

Administration Devices

Because biologics are generally given by parenteral routes, this creates challenges with regard to their administration, particularly in the management of chronic disease. Hence, there is a need to address technical challenges in the development of drug delivery devices including prefilled syringes, needle-safe systems, injector pens, and infusion pumps with improved capability for efficient and safe usage by the patient without the risk of misuse. The

availability of less-invasive delivery methods would also help with compliance.

Analytical Sciences and Quality

High-Throughput Screening

Current analytical tools such as automatic liquid handling systems are expensive to set up, run, and maintain. Therefore, a significant analytical challenge is to run screening assays with higher capacity, increased speed, and lower quantities of biological material. Further development of miniaturized systems with greater numbers of wells is anticipated, along with increased application of acoustic pipetting techniques for library transfers, microfluidics, and microarray printing.

New Analytical Methods

Improvements in the selectivity and specificity of on-line microanalysis and biosensing of drugs and biomarkers are in hand that should have major impact on many branches of the pharmaceutical sciences. In this respect, for example, the use of aptamers (ligand-binding nucleic acids with high affinity and selectivity) linked to electrochemical detection offers promise for the real-time evaluation of pharmacokinetics in animals and humans.⁵⁰

Biosimilars

Seemingly minor variations in the production of biologic drugs can result in large variability in macromolecular structure and, therefore, potentially in potency. Accordingly, the assessment and comparison of physicochemical and structural features of a biologic in order to demonstrate biosimilarity to the originator product is complex, requiring judicious selection of batches and the application of appropriate analytical techniques. This challenge also extends to comparison of the *in vivo* kinetics and immunogenicity of products.

International Harmonization of Bioanalytical Guidance

The bioanalysis of drug concentrations in biological matrices within a regulatory environment continues to be a key issue in drug development. Although the FDA Bioanalytical Method Validation guidance document⁵¹ has been widely adopted internationally, interpretation varies amongst scientists and regulatory agencies in different regions, especially in developing countries. In addition, some regulatory agencies are developing additional national guidelines. Standardization and harmonization on a global basis is complicated by technical, political, and economic issues in different regions but is expected to enhance the transparency and efficiency of the drug development process.

Diagnostics and Quality Medicines

Apart from the development of analytical methods for the measurement of new biomarkers for disease, there is a need to widen the availability of convenient and cheap diagnostic tests both at the point of care and within the patient's home. The latter consideration is a particular imperative in developing countries where patient access to hospitals and clinics and electricity and water are often limited. Development of methods that simply require addition of sample to paper ("lab-on-a-paper")⁵² offers promise in this direction.

The growing availability of counterfeit medicines, including those accessed through the Internet, also poses a challenge with respect to the development of convenient and cheap analytical methods that can be applied at all stages of the supply chain.

Regulatory Science

The Biopharmaceutical Classification Scheme

Differences between regulatory agencies with regard to the definition of compound characteristics need to be harmonized to clarify the Biopharmaceutical Classification Scheme (BCS).⁵³⁻⁵⁵ Although the European Medicines Agency (EMA) defines "highly soluble" with respect to "the highest single dose" recommended in prescribers' information, the US FDA refers to the "highest dosage strength" available on the market. This discrepancy causes an issue with the classification of drugs that can meet the requirements for "highly soluble" at the highest dosage strength which fail to meet them when information for prescribers indicates that 2 tablets can be taken at once. Some drugs with these borderline properties can be found on the WHO Essential Medicines List. The definition of "high permeability" is also currently inconsistent; the EMA and WHO have adopted a criterion of 85% absorption of the dose, whereas the original FDA criterion was 90%. Unlike the solubility criterion, no consideration of the dose is made in the determination of permeability, although some drugs show saturable uptake in the intestine. Generally, there is a need for the BCS to be more physiologically rigorous, for example, with respect to the use of bio-relevant media instead of simple buffers to determine solubility and the need to define media volumes that can reproduce typical concentrations achieved in the intestinal lumen. There are also issues to be addressed arising from the binary nature of BCS, with respect to the behavior of drugs that show intermediate behavior. For example, for compounds with low permeability but still absorbed to an extent of 50%-85%, should there be an intermediate classification? In addition, some poorly soluble drugs can be classified as "highly soluble" because of a very low dose or solubility ratio, such that dissolution rate rather than solubility is limiting—should they be treated differently from other highly soluble drugs? Initiatives such as the Developability Classification Scheme⁵⁶ are beginning to address these issues.

In Vitro Dissolution or Release

Although *in vitro* dissolution or release testing of solid drug dosage forms is an invaluable tool for evaluating the quality of a product, it often fails to predict its *in vivo* performance. Accordingly, a major challenge is the development of biorelevant dissolution tests that are mechanistically rather than empirically linked to *in vivo* pharmacokinetics, especially with respect to the performance of oral solid dosage forms. Systematic attempts to do this are now in hand (e.g., the European OrBiTo Project^{57,58}) with the goal of acquiring a better understanding of the complexities of luminal fluid composition, hydrodynamics, and transit and the impact of food on these variables and with a view to optimizing physiologically based models for the prediction of the impact of formulation changes on drug exposure and its variability.

Bioequivalence

Traditionally, criteria for bioequivalence have assiduously ignored differences in drug-specific pharmacokinetic-pharmacodynamic relationships by insisting on single limits for all compounds (typically the 80%-125% confidence limit rule for AUC). More consideration is needed of the fundamental fact that for

many drugs dosage is such that exposure (concentration) is logarithmically related to response or, indeed, is at the top of the dose-response relationship where changes in concentration have little impact on effect.⁵⁹ Grasping this nettle with respect to the setting of bioequivalence limits and issues of generic equivalence was never going to be easy but should now be on the agenda for regulators to consider.

International Harmonization of Bridging Studies and the Design of Global Clinical Trials

Because ethnic differences can give rise to differences in pharmacokinetics, drug response, and dosage,^{60–62} bridging studies are often replicated in different ethnic populations to satisfy local regulatory requirements. This is not only expensive but often shoes in delays to regulatory approval and access to medicines. An alternative is to conduct global clinical trials that include sufficient numbers of subjects from different ethnic groups.⁶³ The concept of ethnicity is not precise, and both of these approaches present considerable challenges in trial design, the selection of participants, and data analysis. Heterogeneity among national regulatory agencies, industry, and academia complicates the interpretation of international guidelines. Accordingly, continued attempts are needed to move toward at least regional harmonization.⁶⁴

International Harmonization of Biosimilar Versions of Biologics

As a consequence of variability in raw materials and the manufacturing processes used to produce generic biologic products, it is only possible to establish their biosimilarity rather than their bioequivalence with respect to interchangeability with innovator products. Regulatory assessment of biosimilarity is on a case-by-case basis, dependent on evidence from analytical studies, animal studies (including toxicity studies), and clinical studies (including the evaluation of immunogenicity, pharmacokinetics, and pharmacodynamics). Although evaluations by the EMA and the FDA consider all of these aspects, the regulatory approaches are quite different. The EMA guidelines are divided into 3 sections, namely overarching biosimilar guidelines, product specific guidelines, and other guidelines relevant for biosimilars.⁶⁵ The FDA issued draft guidance regarding a pathway for demonstrating biosimilarity, clearly identifying a stepwise approach.⁶⁶ Accordingly, a challenge for the near future is to reconcile these differences with a view to greater harmonization of regulation.

Epilogue

The challenges identified herein inevitably represent the opinions of a relatively small group of individuals, and not everyone will agree with them as priorities. Nevertheless, we submit that they are key issues for the pharmaceutical sciences to ponder and act on over the next 5 years. Predicting the future longer term is more difficult, especially as the gap between idea and implementation is often underestimated. Although further integration of the pharmaceutical sciences with bioengineering and control engineering and information and behavioral sciences raises the prospects of successful targeted and precision medicine, the scientific advances that flow from this must be affordable, if not cost reducing, for health care systems and available to as many patients as possible. Delinking research and development costs from price to health care systems is a major challenge, particularly with respect to reduction of disease burden in the developing world.⁶⁷

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