FIP POSITION PAPER THE IMPACT OF GENOMICS ON THE DISCOVERY AND DEVELOPMENT OF GENETIC BASED MEDICINES GENOMICS AND BEYOND

Dramatic changes associated with genomic approaches to drug discovery and development will present substantial challenges to regulatory and standards-setting bodies. Safety and efficacy will remain the pivotal criteria for approval for marketing. Pharmacological responses will be predictable based upon accepted, validated genetic and biochemical models, with small clinical trials serving to confirm predictions. As a consequence of the accelerated pace of development, regulators will require to revise their review and approval processes to accommodate the numbers of applications for marketing authorisations and their complexity.

Approval of applications must be based upon criteria and standards developed and adopted in harmony, by regulators, the industry and organisations representing medicine and pharmacy. Approval requirements will address specific classes of products intended for treating different di-

seases. Applications will demonstrate compliance with such requirements. Post marketing surveillance will serve as a critical adjunct to ensuring safety and efficacy. Regulators should ensure that approval requirements are continually reviewed and revised so that they remain up- odate relative to the state of knowledge of the science. Regulators will rely heavily on advisory bodies and other sources for access to the most current scientific and medical information.

Public standards-setting bodies, including pharmacopoeias, will be challenged to provide standards for product identity, strength, quality, etc. and for analytical and quality control processes, relevant to a wide variety of expected products. This will pose important policy issues relating to the nature and role of standards for a rapidly evolving technology. Standards-setting bodies, while recognising their ethical obligations, should recognise the risks of inhibiting the development of a new technology by establishing standards too early in its evolution. In the face of a rapidly evolving technology and customised approach to medical management, the goal for standards-setting bodies should be to facilitate the evolution of genomic medicine before establishing standards that limit its growth.

Pharmacogenomics will play a pivotal role in decreasing the resources and time invested in discovery and development. Discovery of novel and more clinically relevant targets may reduce the incidence of drug failure. New targets, including multiple possibilities for treatment of a disease, will provide options for selecting candidate medicines for study. This will result in economy of dedicated resources. Analysis of gene expression patterns provides rapid, economical and accurate means of predicting clinical safety and efficacy.

New medicines can be tested ex-vivo on human cells to establish which gene actions or products may be affected by a particular pharmaceutical or biological agent. Further testing can be abandoned promptly in those instances where the candidate agent produces an increase in genes associated with toxic responses or does not affect genes controlling expression pertinent to a particular disease. Ultimately, regulators may require information of this nature for the review and approval of clinical study protocols.

This customised approach to unique health circumstances for genetically discrete populations affords the promise of maximum possible intended outcomes in the management of disease. It will result in the development of novel systems of regulatory review and approval and standards to assure product quality. In light of the pros and cons identified in the paradigm shift from diagnosis and treatment to prediction and prevention, pharmaceutical, medical, scientific, regulatory and standards-setting bodies must be astute and wise in exercising their responsibilities.

Recognising the fluid nature of the present state of knowledge of genomics and pharmacogenomics, the verb "should" is used throughout the text in delineating the issues, listed below, to signify that, in view of the developing scientific, social and regulatory considerations of this nascent, but important, new technology, it is imperative that a flexible perspective be maintained and careful consideration be accorded to distinctions between what is, or should be, obligatory and what should be discretionary.

Realising the Potential of Genomics – Issues for Consideration

1. The profound concept of identifying promising candidates for new medicines based upon the understanding of how a person's genetics determines his or her response to a therapeutic agent should be supported to achieve the best possible therapeutic outcomes. Strategies should be adopted to support pharmacogenetic analysis, availability of genetic materials for study and the development of bioinformatics to integrate and analyse genetic databases. These strategies should be developed following public debate to create appropriate standards, controls and regulations.

2. When possible, a "pre-screening" approach to clinical studies, i.e. targeting a geneticbased therapeutic agent to genotypically defined patients, should be adopted by regulatory authorities as the standard for the design and conduct of clinical trials. Regulatory authorities should facilitate this process by developing appropriate, abbreviated study designs to establish safety and efficacy. Such study designs should be carefully monitored to ensure that the quality and accuracy of the assessments of such trials are not compromised.

3. Developers of genetic-based therapeutic agents should be encouraged to select patient populations for study irrespective of gender, age, race, ethnicity or economic status.

4. Developers of genetic-based therapeutic agents should examine the opportunity to salvage agents that may have failed in earlier clinical trials because of limited efficacy or presence of a particular adverse response. The objective should be to determine if tailoring such agents to, or from, persons with specific genetic characteristics may provide an opportunity for specific people or population sub-groups to benefit from their use.

5. Regulatory authorities should recognise that where genetic-based pharmaceutical agents are approved for use in very limited populations, the numbers and size of clinical trials required for approval should be determined by a more streamlined review process. Such a policy will result in increased numbers of genetic-based medicines moving through the approval process. To encourage the development of new medicines for very limited populations with special needs, legislative bodies should consider providing incentives such as offering added intellectual property protection similar to that provided by the Orphan Drug Act in the United States.

6. Investigations should be undertaken to determine variables that may affect study results. These variables may be genetic or environmental and may be helpful in determining whether single or multiple genes are involved and whether a common set of genetic variants affects agents in a particular chemical or pharmacological class. Such studies will be helpful in establishing the role of environmental factors in therapeutic response.

7. The accelerated pace of development of new medicines will inevitably result in a considerable increase in new applications for marketing approval. The industry involved in

the development of genomic-based medicines should have discussions with regulatory authorities to make the process more efficient, commensurate with and responsive to these expectations, while remaining mindful of the need to ensure the quality and thoroughness of assessments. The joint aim should be to specify criteria for approval related to specific product classes. Post-marketing surveillance should be strengthened to confirm its role as a critical component in ensuring safety and efficacy. Advisory bodies and health professional organisations, including pharmaceutical bodies, should be included in decision-making processes. Regulatory authorities should ensure that any changes do not compromise the quality and thoroughness of review.

8. Important points to be considered by public standard setting bodies include determining what kinds of standards are appropriate for this new technology and when they should be imposed. Public standards should address the processes to be employed and the products to be produced. Public standards-setting bodies should also consider their responsibilities to facilitate the evolution of genomic-based agents as well as standards that define genomic products and processes. Where feasible, standard setting bodies should consider new concepts for quality assurance related to product classes instead of individual products. These bodies should work in cooperation with regulatory agencies, the industry and professional organisations engaged in pharmacogenomics, to define and establish appropriate standards.

9. Safeguards, including legislation when necessary, should be developed to ensure that employers and insurance providers are prohibited from denying employment or insurance coverage to persons with particular genetic profiles, e.g. persons who may be predisposed to a particular malady, persons for whom an existing medicine is either too costly, or persons for whom alternative treatments do not exist. Organisations incorporating genetics into development of new therapeutic agents should be thoroughly familiar with concerns expressed by bioethics bodies and should exercise continuing vigilance to ensure that such information is appropriately safeguarded. An individual must have the right to protect the confidentiality of personal genetic information.

10. Pharmacists should be adequately prepared for their role in understanding genomics and in preparing and dispensing genomic-based medicines. They should be prepared to counsel their patients on the appropriate use of such agents and be mindful of their role in post marketing surveillance by monitoring patients to ensure appropriate compliance with medication regimens and to detect the presence of potential untoward effects. Pharmacy curricula must evolve to embrace the sciences of genetics, genomics and pharmacogenomics. Continuing pharmacy education (lifelong learning) curricula should be designed to maintain up-to-date knowledge, on the part of practitioners, of the sciences as they continue to evolve.

11. Standards for bioethical considerations in research, testing and treatment of humans should be established. Relevant international and national bodies have an obligation to determine the impact of research and treatment with genomic-based therapies on health care systems and

society. Institutional Review Boards and equivalent local bioethics bodies should establish requirements for review of proposals for conducting clinical investigations of genomic-based medicines in human subjects. They should also ensure that such investigations, when authorised, are monitored so that requirements for ethical conduct for research are met.