Testimony
of

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Rare Diseases: Expediting Treatment for Patients
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Mr Chairman, Ranking Member and Distinguished Members of the Subcommittee, my name is Lincoln Tsang.

Thank you for the opportunity to discuss certain technical and regulatory issues that are viewed as relevant to facilitating research development and approval of new methods of treatment to ensure their timely access by patients with rare diseases. My statement is drawn upon my experience as a medical research scientist, a regulator and now a private legal practitioner.

I am a partner in the international law firm of Arnold & Porter. I am based in its London office. My practice is focused on regulatory, compliance, enforcement, market access and public policy concerning the life sciences sector. Much of my practice involves cross-border related matters. Prior to joining the law firm in November 2002, I was a senior official of the UK regulatory agency, the Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency) where I worked for nearly 13 years and latterly as its head of biologicals and biotechnology. During my tenure in the UK regulatory agency, I served as the UK representative on various advisory committees within the European Medicines Agency, and as an advisor to the European Commission, the Council of Europe, and the World Health Organisation. I also liaised on behalf of the UK regulatory agency with other regulatory authorities including Food and Drug Administration (FDA) in the United States, HealthCanada, Australia Therapeutic Goods Administration on certain matters of common interest. I was previously appointed by the

European Commission to represent the European Union on the International Conference on Harmonisation on the technical requirements for pharmaceuticals, an international cooperative effort which was initially founded by the United States, the European Union and Japan. This cooperative initiative has been expanded considerably in terms of its geographical reach and the adopted regulatory technical guidelines are accepted world-wide.

I have also been appointed by UK Ministers to serve on various advisory committees in such capacity as a non-executive director of the National Institute for Biological Standards and Control, a Commissioner of the British Pharmacopoeia Commission where I have served as Chair of its Sub-committee on Biologicals and Biotechnology and Vice Chair of its Sub-Committee on Nomenclature, and a non-executive member of the Regulatory Oversight Committee of the Health Protection Agency. Most recently, I was appointed by the Council of Europe to serve as its special advisor to assist in developing its Convention on combatting counterfeit medical products.

Before I joined the UK government services, I was a medical research scientist of a research team funded by Cancer Research Campaign (now Cancer Research UK) that involved in the development of anti-cancer drugs, one of which has now been approved for clinical use world-wide for treating brain tumours, namely glioblastoma in adults, and gliomas in children and adults. I started my career working in the National Health Service in the UK.

I have lectured on life sciences regulatory law and public policy at various universities including Yale University, University College London, King's College London.

My brief curriculum vitae is attached.

Challenges in developing new treatments for rare diseases

Innovative medical technologies and medicines are critical to improving health and well-being.

Medical advances in science and technology, including genomics, will open up avenues to develop new therapeutic approaches in advanced therapies based on gene, cell and tissue engineering, and to re-purpose already approved drugs for new therapeutic

indications with a view to addressing diseases and conditions where there is an unmet medical need.

However, the potential for these new therapeutic approaches can only be realised if they are approved for clinical application to optimise care and management of patients.

Healthcare delivery is now increasingly focused on planning the patient journey, to improve the quality or efficiency of clinical management and to alter the focus of care towards the activities most valued by the patient. There is a greater need now for new methods of diagnosis and treatment for rare diseases. There may be as many as 7,000 rare (commonly known as "orphan") diseases[1], many of which are life-threatening or debilitating, where there exists no authorised or satisfactory method of treatment. They affect most critically the very young who often do not survive beyond adolescence. Without treatment, their quality of life will be seriously affected and their lives may be shortened. This represents the grim reality that many of these patients and their families are facing.

Orphan legislation varies amongst the developed countries and was introduced at different times. The United States led the way by enacting the Orphan Drug Act of 1983 which introduced an incentive system for the development of orphan products in the US. Following the introduction of the US Orphan Drug Act, a number of developed countries and regions built a regulatory framework designed to provide incentives for companies to develop products for orphan diseases, which would not normally justify investment in research development or marketing, owing to their poor financial return. Apart from the EU, countries such as Japan, Australia and Singapore have developed their own regulatory frameworks to encourage the development of products for orphan diseases.

The clinical development of new technologies intended to treat rare diseases is fraught with practical challenges. There may be disease-specific complexities, such as poor understanding of the natural history of the therapeutic indication due to there being little information available about disease progression, variable phenotypic characteristics of the

[1] The US defines an orphan condition based on disease incidence of less than 200,000 patients which would represent approximately 61 cases per 100,000 based on the current estimate of US population of 326 million. In the EU, an orphan condition is defined as a life-threatening or debilitating disease or condition affects less than 5 in 10,000 persons in the EU. In Japan, a disease or condition is considered rare if it affects fewer than 50,000 patients or less than 40 in 100,000 based on the population in Japan.

patient populations and clinical courses, geographical dispersion of a small number of patients and the relative paucity of published clinical trials to inform study execution.

In order to establish the clinical efficacy and safety of new methods of treatment, the randomised controlled trial has been accepted by regulatory authorities around the world as the gold standard. This trial design minimises selection bias in order to elicit the true treatment effect of the new therapy.

Whilst this classic study design is commonly used in studies of new therapies designed to treat common diseases as it may involve a large number of more readily available clinical trial subjects, this may not be feasible in a small population. By necessity, clinical trials in rare diseases enrol fewer trial subjects who may not necessarily be concentrated in a particular geographical region. In combination with significant clinical differences between trial subjects (commonly known as inter-subject variability) observed in many rare diseases, this diminishes the 'power' of the study to detect a therapeutic difference. Statistical power is the likelihood that a study will detect an effect when there is an effect there to be detected.

Given the rarity of orphan diseases, the timely and adequate recruitment of eligible trial participants is recognised as a challenge to initiate and complete a study. For new treatments intended for a larger patient population, regulatory authorities may often demand two or more pivotal confirmatory studies sufficiently powered to be carried out, and this may necessarily involve a relatively large patient population. As has been recognised by the US and EU regulatory authorities, such a requirement is more challenging to satisfy for treatments intended for orphan conditions.

Because of the low incidence of the disease in each country given its rarity, there is often a need to enrol patients from a number of countries to obtain a large enough sample size of trial subjects to establish the clinical efficacy. Since trial subjects are geographically dispersed, multi-centre studies must be initiated in various international centres of excellence. Technically speaking, the problem (from a resource perspective) is the need to set up multiple trials to meet different regulations and requirements. The solution would be a common trial design but this may not be possible, given varying regulatory approaches. The demand to satisfy various regulatory requirements is obviously more critical for small and medium sized enterprises with very limited resources.

Whilst certain authorities have established parallel scientific advice, such as FDA and EMA, the respective agencies do not have to arrive at the same view on the study design, such as the parameter(s) used to measure the clinical outcome following administration with the new therapy (commonly known as an endpoint or variable). This may become a practical issue in the final analysis of the data derived from studies with disparate trial designs.

In a rare disease setting, there is clearly a tension between the need for transformative innovation to treat such devastating conditions which require a considerable time, financial investment in research and development, and the need for timely patient access to such innovation. Innovation will not serve the public health imperatives, and most importantly patients, if it is not approved, adopted and diffused in the healthcare system for the benefit of society at large.

In this highly regulated sector, the need for timely approval of innovative treatments to be accessed by patients with orphan conditions has attracted a great deal of debate and attention in recent years.

Approval of treatments for orphan conditions

Given their statutory mandate as guardians of public health, regulatory authorities understandably require a dataset submitted for product approval to be sufficiently robust in the sense of its scientific certainty. On the other hand, patients and those involved in the care and management of such patients with rare, life-threatening and debilitating conditions, not unreasonably, expect expedited product approval to ensure timely access to such life-saving methods of treatment, whilst accepting the scientific uncertainty of the pre-approval dataset.

Regulatory authorities are mandated by their respective legislature to supervise product approval and post-approval processes to ensure that the marketed products are clinically safe and effective and of an acceptable quality standard. Timely access by patients to innovative methods of treatment in therapeutic areas with unmet medical need serves an important public health purpose, especially for those patient populations with a high disease burden, that represents the impact of a health problem as measured by financial cost, mortality, morbidity, or other health-related indicators.

In an evolving regulatory framework, striking the right balance of these competing interests relating to (a) regulatory control of innovation based on robust evidence and (b) timely patient access to transformative innovation, has been a continuing debate amongst the regulatory authorities, legislature, payers, healthcare professionals and most importantly the patients.

That said, although more flexibility could be introduced, regulatory authorities generally have the authority and some regulatory latitude to determine the level of evidence that is required to inform a benefit/risk assessment that underpins product approval.

Contrary to the general belief, being designated as an orphan product does not automatically permit a regulatory authority to approve it more quickly or with less evidence than drugs intended for non-orphan populations.

As a general matter, it is my understanding that the standard of approval for orphan product is legally the same as the standard of approval for all other drugs in the US. The FDA requires 'substantial evidence' of effectiveness derived from 'adequate and well controlled investigations'. Whilst FDA has the power to apply the regulations flexibly[2], and have often done so in the orphan drug context, it is under no obligation to do so[3].

In the EU, the adopted regulatory standard for approval[4] is that clinical data should be based on 'controlled clinical trials' if possible, randomised and (as appropriate) versus placebo and versus an established medicinal product of proven therapeutic value. Any other design must be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

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[2] While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy. (Code of Federal Rules Section 314.105)

[3] Saskinowski F et al. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs DIA Therapeutic Innovation & Regulatory Science (2015) Volume: 49 issue: 5, page(s): 680-697

[4] Part I Section 5.2.5.1 of Annex I to Directive 2001/83/EC

The EU legislature has recognised that in certain exceptional circumstances, a marketing authorisation may be granted on the basis of less comprehensive data[5] either where because the disease is rare that comprehensive clinical data cannot reasonably be generated under normal conditions of use, or where in the present state of scientific knowledge, comprehensive information cannot be provided, or where because it would be contrary to generally accepted principles of medical ethics to collect such information it would not be possible for a manufacturer to provide comprehensive data. These are all circumstances in which it may be justified to grant a marketing authorisation in order to address an unmet medical need under exceptional circumstances to advance patient interests.

In addition, for certain rare, life-threatening and debilitating conditions, the EU legislature has created a regulatory pathway for a conditional marketing authorisation to be granted, subject to annual renewal, based on a re-assessment of the benefit/risk[6]. The grant of such an essentially "temporary" marketing authorisation is based on certain specific conditions being satisfied. Whilst accepting that there is uncertainty as to whether the submitted clinical data can comprehensively elucidate the benefit/risk balance of a medicinal product, the immediate access to the product in view of an unmet medical need is sufficient to justify its authorisation, provided that the manufacturer is able to provide the comprehensive data post-authorisation to confirm the benefit/risk balance.

A specific Delegated Regulation has been adopted by the European Commission in order to provide the EMA and the EU national regulatory authorities with greater clarity of the situations in which post-authorisation efficacy may be required, such as (a) where concerns relating to some aspects of efficacy of the product are identified and can be resolved only after the product has been marketed; (b) where the understanding of the disease, the clinical methodology or the use of the product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly.

[5] Part 3 Section 5 of Annex I to Directive 2001/83/EC

[6] Article 14(7) of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency; Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

The requirement for post-authorisation efficacy studies may arise, for example: if the initial efficacy assessment is based on surrogate (i.e. not clinical) endpoints which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions; or uncertainties with respect to the efficacy of a product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence.

Regulatory latitude

Many established regulatory authorities including the FDA in the US and EMA in the EU have declared in their respective mission statements that in addition to their role to safeguard public health and patient safety, they are responsible for advancing public health by helping to facilitate or otherwise expedite the approval of medical innovations to maintain and improve the health of patients.

In this case, it is my understanding that the US Congress has legislative power to provide clearer directions to FDA to fully embrace less conventional and/or less commonly seen methodological approaches to elucidate benefit/risk balance in exceptional circumstances so that a new method of treatment is not unjustifiably delayed or denied subject to certain specific post-authorisation safeguards to monitor the ongoing benefit/risk balance of the approved product[7].. Such an explicitly flexible and pragmatic approach may serve the public health imperative of improving patient care in a clinical setting where there is a demonstrable unmet medical need.

It has been said when a method of treatment fails, researchers must be clear that there is a true lack of biological effect, rather than failure due to inadequate study design[8]. Therefore, approval process ought to take full account of the detailed knowledge of the pathophysiology (meaning the disordered physiological processes associated with disease or injury) of the orphan disease and the pharmacology (meaning uses, effects, and modes of action) of the new method of treatment to facilitate the design of efficient clinical development which will in turn help determine the amount of clinical data required to inform an assessment of clinical efficacy and safety

[7] This may be similar to the approach taken by the EU as explained above (see paragraphs 27-29)

[8] Dickson PI et al. Research challenges in central nervous system manifestations of inborn errors of metabolism. Mol Genet Metab (2011); 102: 325-338

In the context of product approval in a rare disease setting where there is an unmet medical need, consideration should be given to the following points:

- What constitutes an adequate level of scientific evidence to presume strongly a favourable benefit/risk balance to support product approval?

- Is it feasible or practical to generate comprehensive data within a reasonable timeframe following product approval?

- Can the scientific uncertainty of the submitted dataset can only be resolved by specific and enforceable post-authorisation studies, including real-world evidence?

As indicated above, patients to be enrolled in clinical trials for rare disease are geographically dispersed and many clinical studies are conducted in various centres of excellence. Therefore, greater cooperation amongst various national and regional regulatory authorities to agree on the design of the multi-centre clinical trials will greatly facilitate the efficient execution of product development to serve the patients with rare diseases and to optimise their care and management. With strong international cooperation, it will often be possible to rely upon only one well-designed clinical study to elucidate the true treatment effects of a transformative method of treatment for all global regulatory authorities.

However, note also that even though the trial data demonstrate a favourable benefit/risk, in many countries, patient access may not be realised if the new therapies are not accepted on grounds relating to cost-effectiveness and affordability, given the increasingly cost conscious healthcare delivery systems.

Mr Chairman, Ranking Member and Members of the Subcommittee, thank you once again for the opportunity to provide this testimony. I am happy to answer any question.

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