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## Access to drugs and vaccines I

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**Generic medicines: old problems and new challenges from a European perspective**

**Dr John Lisman, The Netherlands**

When considering generic medicines, it is important to strike a balance between the public health interest, the interests of the innovative pharmaceutical industry, those of the generic pharmaceutical industry, and ethical values. Public health needs the development of new medicinal products for diseases that cannot be cured at present, as well as the improvement of existing medicinal products and appropriate clinical research. While generic competition can improve the affordability of medicines, quality and comparability have to be safeguarded. For reasons of public health, drug regulatory authorities (DRAs) need harmonized product information that contains all the approved indications for the generic and reference medicinal products.

The innovative pharmaceutical industry is driven by profits, which are most easily made in an exclusive market. Market exclusivity is created by patents, data protection or data exclusivity. Patents are enforced by the industry itself, without the involvement of DRAs. Data protection, in combination with the generally accepted principles of GCP, gives full protection of the product. One of the new types of patent, called a “usage patent”, which gives protection for new indications for an existing product, causes problems for generic competitors. Although market exclusivity is a necessary incentive for companies to develop new medicinal products, sometimes the

protecting system leads to too high a level of protection and too long a period of market exclusivity.

On the other hand, generic competition is an incentive for the innovative industry to develop new medicinal products. The generic pharmaceutical industry is also driven by profits, and generic companies want to market their products as quickly as possible. Moreover, the use of generics has to be promoted by the health care system, and their marketing enabled by a good legal system.

Ethical principles should prohibit the repetition of tests and trials. Test and trial results have to be treated as valuable items, to be used for the benefit of society as a whole and not only for the sponsor.

There should be a fair allocation of market exclusivity to maintain a balance of interests between the innovators and the generic industry, in the interest of public health. Drug regulatory authorities should play a firm role in preventing innovators misusing the courts to stop the introduction of generic medicinal products. Generic competition should be welcomed after the period of market exclusivity; before that innovators should compete on the basis of the quality of new medicinal products. Policies for generic prescription and substitution should be in place, but must make sure that the efficacy, safety and quality criteria for generic medicinal products are as high as for the innovative products.

### **Access to quality pharmaceuticals: the Indian experience Dr Nitya Anand, India**

The key issues for developing countries in relation to drug accessibility are availability, acceptable quality, and affordability. The Indian Government has implemented policies to address these issues, including giving special incentives to the pharmaceutical industry and the research and development bodies, imposing drug price controls, and introducing policies on drug procurement and process patents. Manufacturers in India produce practically all classes of formulations and over 85% of active pharmaceutical ingredients (APIs) at internationally competitive prices. Sizeable amounts of both APIs and formulations are exported to developed and developing countries.

The Drugs and Cosmetics Act 1940 regulates the import, manufacture, sale and distribution of drugs and cosmetics. The Central Drug Standards Control Organization (CDSCO) is responsible for the approval and introduction of new drugs and for the Indian Pharmacopoeia. The State Drug Control Organization looks after the quality of the manufacturing and distribution system. The main objective of quality assurance enforcement is to ensure that all products meet specifications and are manufactured under GMP.

The Indian Pharmacopoeia is managed by the Indian Pharmacopoeia Committee, which updates and publishes the Pharmacopoeia and related publications, procures or prepares and supplies reference substances, takes up laboratory work for the development and validation of test procedures for pharmacopoeial standards, and interacts with international counterparts and with the WHO section on Quality Assurance and Safety: Medicine. The current version of the Indian Pharmacopoeia was published in 1996 but two lists of new drugs were published as addenda in 2000.

In order to achieve effective quality assurance, national pharmacopoeias should incorporate monographs on drugs against diseases of national concern, irrespective of the patent status. More work is needed in collaboration with international agencies to evaluate the biopharmaceutical properties of fixed-dose combinations of drugs. Educational emphasis must be on the storage, trans-shipment, and the other conditions related to the quality of the products taking into account the environment and conditions in the country.

In view of the trend towards global free trade, there is a need for close interaction between countries and harmonization of pharmacopoeial standards. The ambit of the existing pharmacopoeial discussion groups to search for harmonized, but not necessarily identical, standards that can be adopted worldwide should be expanded.

### **Quality of starting materials for drugs and vaccines** **Dr Jose Pena, Chile**

Starting material is defined as any active or inactive substance or compound, used in the manufacture of medicines, that is modified or

disappears during the production process. The quality, safety and efficacy of pharmaceutical products are closely related to the quality of the starting materials. The consequences of using starting materials of inadequate quality can be serious, and this has led WHO to draft recommendations for all parties involved.

Guidelines that are generally accepted by national authorities have been drawn up for the quality control of starting materials for herbal medicinal products, vaccines, and pharmaceutical or biological products prepared by DNA recombinant technology. The uniformity of production depends on the quality of the starting material and therefore the physical, chemical and microbiological properties of such materials should be defined and well documented. The specification of the active substances and of the excipients should be re-evaluated periodically. Wherever possible, pharmacopoeial rules should be followed.

One of the challenges faced by many developing countries in the short term is to have therapeutic equivalence. In order to achieve this, we need to work on the basis of pharmaceutical equivalence, bioequivalence and GMP. A proposal, to be considered for adoption in February 2003 by the WHO Expert Committee on Pharmaceutical Specifications for a Certification Scheme for Starting Materials Circulating in International Trade, includes two possible schemes. The first one is a Model Certificate for the Production of the Pharmaceutical Raw Materials, to be issued by the national regulatory authority. If there is no such body, WHO proposes a Model Certificate for the Production of Pharmaceutical Starting Materials, to be issued by the producer. A Certificate for Pharmaceutical Starting Material can be requested within the framework of the Scheme by the exporter, the importer or the regulatory authority of the importing country.

The Certificate is intended to be a confidential document issued by the competent authority in the exporting country. If there are any doubts concerning the status or validity of the certificate, the competent authority in the importing country might require a copy to be sent directly from the certifying authority. If there is no specific

approval, each certificate will be drawn up in the language of the certifying authority and it will be the applicant's responsibility to provide any translations required. Since the issuing of these certificates means a heavier workload for the certifying authorities, this should probably be funded by the applicant; the certificate will be valid until a given date. However, the certificate would no longer be valid if the manufacturing process changes, or if the manufacturer does not comply with GMP. The certifying authority will be responsible for ensuring the authenticity of the data certified.

In parallel with implementation of the guideline on Good Trade and Distribution Practices, each certificate should identify the importing country so as to prevent misuse of the system and counterfeiting. Moreover, it can avoid the issuing of unnecessary complementary certificates by independent authorities. The certifying authority could have a comprehensive register of the countries to which starting materials have been exported.

### **Fixed-combination medicines: an Australian perspective**

#### **Dr Leonie Hunt, Australia**

Australia has an independent regulatory system, which covers premarket assessment, pharmacovigilance programmes, the use of standards, enforcement of GMP requirements, a register of approved goods, and clinical trials. Independent expert advisory committees have been used extensively to provide guidance for decisions. For medicine regulations, there are the Australian Guidelines for Registration of Drugs. International guidelines are adopted whenever appropriate.

Fixed-combination products are important tools in therapeutic regimes. They may have a number of potential advantages over single therapies, including greater effectiveness, improved safety profile and simpler therapy. However, there are also potential disadvantages. As the formulation is fixed, doses cannot be easily adjusted to meet the needs of individual patients. For patients who are well controlled by single therapies, fixed combinations may give unnecessary exposure to a second medicine. Furthermore, there are additional adverse events. Therefore, justification is needed for each

particular fixed-combination product, and the development of such a product should address the issues of the benefit and risk of the combination. Justification should take into account effectiveness, safety and improved compliance.

Fixed combinations must be of acceptable quality and logical combination. Moreover, the effect of interactions, within or outside the combination, on the pharmacodynamics and pharmacokinetics, should be investigated. In Australia, it is generally recommended that new combinations should be used as an add-on to single therapy, unless it can be demonstrated that use of the combination drug as first-line treatment is optimal. The minimum effective dose and maximal dose response should be established for the drugs used alone and in combination. The efficacy of the combination should be compared with the effective doses of the medicines alone, other reference therapies, and placebo. Finally, animal studies should have been performed and human data are required, for the medicines administered singly and in combination, to ensure safety.

In summary, fixed-dose combinations offer potential advantages to patients but are not always appropriate or rational. Careful selection of the medicines to be used, and assessment of use of the combination, are required to maximize the benefit.

### **Drugs for neglected diseases: challenges for regulators** **Dr Krisantha Weerasuriya, WHO, South-East Asia Region**

Neglected diseases are generally tropical diseases, for which there is a lack of effective drugs. There is often a high disease burden in particular areas and sometimes a fatal outcome. The most neglected diseases include visceral leishmaniasis, African trypanosomiasis and Chagas disease.

In the past 25 years, 1393 new chemical entities have been granted market authorization. Among these, there were only 16 drugs for neglected diseases, all of which were included in the WHO Model List of Essential Drugs. Of the other 1377, only 21 were considered important enough to be included in the WHO List.

At present, there are no significant projects to develop drugs for the neglected diseases initiated by the pharmaceutical industry. A few products are in the pipeline but the industry is involved as partners with non-industry institutions; this situation is unlikely to change in the future. Therefore, a major challenge for regulators is to play a role in encouraging the development of these drugs. This is most pertinent for regulators in the developing world, who might consider fast-track registration, limited-release schemes for specific products, and joint evaluation of new products of public health importance.

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## Recommendations

1. WHO should continue its efforts in strengthening international guidelines for registration of generic drugs.
2. In collaboration with Member States, WHO should continue to focus on activities related to good trade and distribution practices of starting materials to assure the use of high quality materials.
3. WHO should work with other technical partners, within the concept of a global alliance, to improve the quality of products moving in international commerce.
4. WHO should establish a pre-qualification quality assurance system for essential medicines.
5. WHO should continue its prequalification project for procurement of medicines for priority diseases.
6. In collaboration with Member States, WHO should develop additional international guidance on important elements of combination medicines focusing on rational use to maximize the benefit in specific disease treatment.

7. Governments and drug regulatory authorities should encourage the development of therapies for neglected diseases through incentives, co-operative efforts and public/private initiatives.

8. Progress should be reported back to the ICDRA.