Regulatory pathways for vaccines for developing countries

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Abstract Vaccines that are designed for use only in developing countries face regulatory hurdles that may restrict their use. There are two primary reasons for this: most regulatory authorities are set up to address regulation of products for use only within their jurisdictions and regulatory authorities in developing countries traditionally have been considered weak. Some options for regulatory pathways for such products have been identified: licensing in the country of manufacture, file review by the European Medicines Evaluation Agency on behalf of WHO, export to a country with a competent national regulatory authority (NRA) that could handle all regulatory functions for the developing country market, shared manufacturing and licensing in a developing country with competent manufacturing and regulatory capacity, and use of a contracted independent entity for global regulatory approval. These options have been evaluated on the basis of five criteria: assurance of all regulatory functions for the life of the product, appropriateness of epidemiological assessment, applicability to products no longer used in the domestic market of the manufacturing country, reduction of regulatory risk for the manufacturer, and existing rules and regulations for implementation. No one option satisfies all criteria. For all options, national infrastructures (including the underlying regulatory legislative framework, particularly to formulate and implement local evidence-based vaccine policy) must be developed. WHO has led work to develop this capacity with some success. The paper outlines additional areas of action required by the international community to assure development and use of vaccines needed for the developing world.

Keywords Vaccines/standards; Legislation, Drug/standards; Drug approval/legislation; Clinical trials; Government agencies; Developed countries; Developing countries; Internationality; World Health Organization; Europe; United States (*source: MeSH, NLM*).

Mots clés Vaccins/normes Législation pharmaceutique/normes; Autorisation mise sur marché médicament/législation; Essai clinique; Service ministériel; Pays développé; Pays en développement; Internationalité; Organisation mondiale de la Santé; Europe; Etats-Unis (*source: MeSH, INSERM*).

Palabras clave Vacunas/normas; Legislación de medicamentos/normas; Aprobación de drogas/legislación; Ensayos clínicos; Agencias gubernamentales; Países desarrollados; Países en desarrollo; Internacionalidad; Organización Mundial de la Salud; Europa; Estados Unidos (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: اللقاحات، معايير اللقاحات ؛التشريعات، التشريعات الدوائية، معايير التشريعات؛ اعتماد الأدوية؛ التجارب السريرية؛ الوكالات الحكومية؛ البلدان المتقدمة؛ البلدان النامية؛ العالمية؛ منظمة الصحة العالمية؛ أوروبا؛ الولايات المتحدة.

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Voir page 132 le résumé en français. En la página 133 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة 133.

Background

Vaccine regulation is a complex process, and improvement of national infrastructure in this area has progressed slowly. In 1999, WHO defined six regulatory functions that could be used to assess a NRA, monitor its improvement, and design interventions to impact it (Box 1) (*1*). This definition is useful in that it provides a transparent basis for assessing regulatory functions, while noting potential differences in data analysis because of differing risk–benefit scenarios (*2*). In fact, the differing risk–benefit assessment has led to product divergence (*3, 4*): for example, whole cell versus acellular pertussis vaccine and oral versus inactivated polio vaccine.

Currently, vaccines are developed and used first in the industrialized world in which the regulatory decisions for these products are taken. New vaccines for the developing world targeted at diseases in developing countries may never be used in the industrialized world. These vaccines need to be under appropriate regulatory control from development to use to ensure they are safe, effective, and of high quality.

NRAs differ with respect to the export and import of vaccines. The US Food and Drug Administration was established by its national government with a mandate to function only for the domestic market. The European Medicines Evaluation Agency operates similarly on behalf of the countries of the European Community but has expressed interest in providing additional regulatory functions for vaccines made in Europe but targeted at developing markets. Many competent NRAs in the developing and industrialized worlds could make decisions on new product licensing, but they would need a new regulatory framework to do so on behalf of other countries in the developing world. Finally, some countries import vaccines only from assured sources, counting on the decisions of other regulatory authorities or the recommendations of WHO, or both, because they lack the basic infrastructure to make regulatory decisions on their own. As many

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Box 1. **Six regulatory functions defined by WHO to assess, monitor, and improve national regulatory authorities**

- Published set of requirements for licensing (of products and manufacturers)
- Surveillance of vaccine field performance (safety and efficacy)
- System for batch or lot release
- Use of the laboratory when needed
- Regular inspections of manufacturers for good manufacturing practice compliance
- Evaluation of clinical performance through authorized clinical trials)

manufacturers distribute vaccines beyond their borders, the existing regulatory gaps must be addressed, or vaccine supply will be jeopardized.

This paper addresses three types of situations for which regulatory pathways must be assured, given the different national regulatory activities defined above:

1. To ensure that vaccines developed, produced, and licensed in an industrialized country for intended global use are evaluated for their safety and efficacy, not only for the target population in the country of manufacture but also in the target populations of the developing world. This would be the case for an 11-valent pneumococcal conjugate vaccine that could be used in many countries with different disease burdens.
2. To maintain a licence for a product developed, produced, and licensed in an industrialized country when there is no longer a product market in that country. This is the expected situation for combination vaccines based on diphtheria–tetanus–whole cell pertussis (vaccines manufactured and licensed in Europe).
3. To find a pathway to licensure for a product when the market is only in the developing world, regardless of where the product is developed. This could be the case for vaccines against many tropical diseases, such as malaria and leishmaniasis. Lack of a pathway represents "regulatory risk" for potential product developers.

We have considered five possible approaches to ensure that regulatory functions are assured for developing market vaccines. These approaches vary in their applicability to the situations above (Table 1).

Possible approaches

Licensing in the country of manufacture

In most countries, licensing data are considered only in support of products for domestic use, but many countries with incipient regulatory authorities depend on a marketing authorization in the United States or Europe, regardless of the product. Actions by American and European regulatory agencies to expand their mandate thus could be helpful. In this context, efforts to encourage manufacturers to license their products in the United States or Europe, even if the domestic market is only small, might be useful (such as the situation with so-called orphan vaccines) (*5*).

Proposal to the European Commission

The European Commission has determined that products may be considered for licensing by the European regulatory structure only if they have a market in Europe. Under new legislation being considered by the European Parliament, the loss of such a market would mean that currently licensed products would eventually have their authorization withdrawn. An innovative compromise is described, however, in proposed new article 52 of Council Regulation (EEC) No 2309/93: a scientific assessment of a product file on request of WHO by European Medicines Evaluation Agency, with continuing regulatory oversight in the country of manufacture (*6*). A marketing authorization would not be granted, but a scientific opinion of the file could be given for products for which the applicant was located in Europe, was registered as a manufacturer in a European Member State, and was responsible for final batch release. The member state in which the applicant is located would be responsible for regular good manufacturing practice inspections of the manufacturing site after assessment of the vaccine. WHO could suggest representation at the appropriate level to provide disease-specific information for the target market. Further clarification is needed on how reports of adverse events are incorporated into the regulatory process and on batch release provisions. The amendment is expected to be approved and put in force in 2004.

Export provisions

The country that would receive the vaccine would perform regulatory functions under export provisions for products manufactured but not licensed in the country of manufacture (for example, as described in the US Federal Food, Drug and Cosmetic Act and defined in the Code of Federal Regulations (*7*)). The burden would be on the exporter to determine compliance with regulatory requirements and ensure that the recipient country is acceptable (that is, listed — Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, European Union, or European Economic Area — or determined by the US Food and Drug Administration to meet statutory or regulatory requirements); however, the product must be manufactured, processed, and packaged "in substantial conformity" with current good manufacturing practice (*5*). Use of export provisions shifts responsibility for regulatory oversight to the receiving country, so NRAs in potential receiving countries would need to be strengthened. For vaccines destined for a wider developing country market, an arrangement in one receiving country to ensure regulatory oversight on behalf of other recipient countries might be explored. This would in most cases require enabling regulatory legislation.

Shared manufacturing with licensing in the country of final manufacture

In shared manufacturing, licensing and regulatory oversight is performed in the country in which the finished product is released. Until recently, the feasibility of this approach was limited by the credibility of quality of manufacturing and regulatory institutions in developing countries. The NRAs of developing countries have steadily improved, and, today, 11 countries classed as developing countries or economies in transition have vaccine production and a NRA assessed by WHO as fully functional. Manufacturers in eight of these countries already produce certain products that are prequalified for sale to United Nations agencies.

Contract non-profit organization

A contract agency or organization could be used to make regulatory decisions on a regional or global basis for products for use in the developing world. The major hurdle to this type of procedure is the development of a mandate for such a group to make decisions of this nature on behalf of countries. A secondary hurdle would be finding financing for such an initiative. Some decisions,

Table 1. **Summary of regulatory options**

Option	Characteristics					Remaining issues
	Covers all six functions	Appropriate epidemiological assessment (situation 1)	Can be applied when local market disappears (situation 2)	Reduces regulatory risk for manufacturers (situation 3)	Enabling rules and regulations exist	
Licensing in country of manufacture (industrialized or developing country)	Yes	No	Unlikely	No	Case by case basis, but generally no	Implies enlarging current regulatory mandate in industrialized countries or enhancing research and development and regulatory capacity in developing countries, or both.
European Medicines Evaluation Agency's dossier review	Possibly	Possibly	Possibly	Possibly	Proposed to European Medicines Evaluation Agency for 2004 but not in countries of potential recipients	Explore interim solutions and how ongoing regulatory oversight will be done. May be useful backup to shared manufacture.
Export provision	Yes	Possibly	Possibly	Yes	Only in exporting country	Possibilities of using this method for countries in specific regional groupings. Need new regulatory framework in receiving country to make regulatory decisions on behalf of other countries.
Shared manufacture	Yes	Possibly	Yes	Yes	Yes	Being implemented or planned for some developing market vaccines, depends on implementation by vaccine manufacturers.
Non-profit contract licensing organization	Possibly	Possibly	Yes	Yes	No	Difficulty of mandate for such an organization, as well as funding. However, appropriately constituted advisory committees on global or regional basis could contribute to this approach.

however, already could be considered on behalf of countries on a global or regional basis. For example, scientific and technical review of clinical trial protocols could be made at the global or regional level through experts with epidemiological experience of the product and target populations. The data generated by such trials could also be assessed by the same group, provided that it had the confidence of the countries on whose behalf it was acting. In addition, decisions on eventual use, schedule, dose, and concomitant vaccinations could be taken on behalf of countries at a regional or multinational level by immunization advisory committees. Such committees, while recommended at the national level, thus could act for regional groupings with similar epidemiology.

Summary

Table 1 summarizes the attributes and characteristics of each of the proposed approaches. Clearly, no single approach satisfies all of the needs, and a number of interventions must be put in place if regulatory hurdles for vaccines for the developing world are to be overcome.

Intervention points for strengthening regulatory capacity for vaccines for the developing world

The options outlined above and summarized in Table 1 clearly show a number of interventions that will be needed on the part

Table 2. **Countries in which assessments of national regulatory authorities (NRAs) had been conducted and regulatory authority experts were identified and selected to conduct NRA assessment and follow-up visits, at October 2002**

WHO regions	NRA assessed against indicators	Countries with NRA experts identified for NRA assessments and follow-up visits
African	Algeria Côte d'Ivoire Nigeria Senegal South Africa Uganda Zimbabwe	Algeria Nigeria Senegal South Africa Zimbabwe
Americas	Argentina Brazil Chile Cuba	Brazil Canada (not yet assessed) Cuba USA (not yet assessed) Venezuela (not yet assessed)
Eastern Mediterranean	Egypt Islamic Republic of Iran Iraq Morocco Oman Pakistan Saudi Arabia Syrian Arab Republic Tunisia	Egypt Islamic Republic of Iran Tunisia Morocco
European	Armenia Belgium Bulgaria France Hungary Kazakhstan Republic of Moldova Poland Romania Russian Federation Sweden Switzerland Turkey Turkmenistan Ukraine Uzbekistan	Belgium Bulgaria France Germany (not yet assessed) Hungary Italy (not yet assessed) Netherlands (not yet assessed) Poland Russian Federation Switzerland Ukraine United Kingdom (not yet assessed)
South-East Asia	Bangladesh Bhutan India Indonesia DPR Korea Myanmar Nepal Sri Lanka Thailand	India Indonesia Sri Lanka Thailand
Western Pacific	Australia China Japan Republic of Korea Philippines Viet Nam	Australia China Japan Republic of Korea

of the international community. Some of these, along with an update on progress on their implementation, are defined below.

Enlarging the current mandate of regulatory authorities

An extremely useful result would be the expansion of the mandate of regulatory authorities in developed countries — for example, the United States and Europe, in which many vaccines for the developing world are being developed — to cover licensing of products that would not be used in their domestic markets. Already WHO, along with others dedicated to accessibility of such products, is working with the US Food and Drug Administration and European Medicines Evaluation Agency to look at options. The file review process of the European Medicines Evaluation Agency is only one of the innovative solutions proposed. Unless, and until, regulatory authorities in most countries are at a level at which they confidently can take decisions on licensing of innovative products, the input of these industrialized countries' regulatory authorities will be needed and encouraged.

Strengthening developing countries' NRAs

Led by WHO, much progress has been made in strengthening regulatory authorities in developing countries. WHO's work is based on the use of a five-step process: benchmarking; assessment; developing an institutional plan to address gaps; implementation of the plan, including technical inputs; and monitoring and evaluation. Benchmarking has used the defined characteristics of a well-functioning regulatory authority mentioned above (*1*). This resulted in an assessment tool that was used to assess at least 48 NRAs between October 1998 and October 2002. Such assessments provide a systematic way to address identified critical gaps through institutional development plans elaborated jointly by the national staff of NRAs and assessment teams. Technical input that is needed is provided through WHO's Global Training Network (*8*). The final step is impact monitoring, which takes the form of follow-up assessments and various proficiency tests.

More than 80 experts have been trained in the assessment methods and have become resources for their local regulatory agencies as well as other countries. Table 2 shows the countries that have been assessed so far and the location of trained experts. Already 91% of the 192 countries that report to WHO, which represents 74% of the annual birth cohort, use vaccines overseen by a competent NRA. In addition, a collaboration of the nine strongest NRAs in developing countries has been put in place to develop the special expertise needed to make licensing decisions on innovative products.

Enhance the ability to authorize and evaluate clinical trials

Key to solid licensing decisions for new products will be the ability to authorize clinical trials and evaluate the data that arise from them. WHO has addressed this, to some extent, by providing a new curriculum on authorization and evaluation of clinical trials as part of its Global Training Network initiative. More work is needed though. The use of expert committees at the regional or international level to assist in protocol and data review would be an extremely useful adjunct to expanding the ability of NRAs in this area in a way that would reflect the needs of the specific epidemiological situation of these countries.

Discussion

Bringing the fruit of new vaccine development initiatives to the developing world, especially in cases in which developing countries are the sole or major user of the product, could be significantly delayed if regulatory pathways are not in place to ensure that these products are under comprehensive regulatory oversight for their production, trials, and use. This paper, which builds on the regulatory functions defined by WHO as essential to ensuring quality, safety, and efficacy of a product, has assessed five possible approaches to achieve this goal and has analyzed some of the remaining activities that must be put in place to achieve it. Clearly, none of the five approaches is ideal, so efforts must be made to ensure that facilitating actions are put in place for each. A number of actions that will require input from the international community are needed to build on the work already started by WHO to strengthen NRAs. These include actions on the part of countries with well-functioning regulatory systems, such as the United States and Europe, to share decisions and provide input into training, the development of experts capable of acting at the regional and global level to assist with the evaluation of clinical trial information, and necessary legislative framework changes in countries to ensure that these regulatory functions can be implemented. ■

Conflicts of interest: none declared.

Résumé

Mécanismes de réglementation concernant les vaccins dans les pays en développement

La réglementation dresse souvent des obstacles qui limitent l'usage des vaccins conçus exclusivement pour les pays en développement. Il y a à cela deux raisons principales : le rôle de la plupart des autorités de réglementation est de réglementer les produits utilisés seulement dans leur juridiction et ces autorités n'ont habituellement qu'un pouvoir limité dans les pays en développement. Il existe toutefois certaines options : homologation dans le pays de fabrication, examen des dossiers par l'Agence européenne pour l'évaluation des médicaments au nom de l'OMS, exportation vers un pays doté d'une autorité de réglementation nationale compétente pour assumer toutes les fonctions de réglementation sur le marché du pays en développement, partage de la fabrication et de l'homologation dans les pays en développement ayant des compétences en matière de fabrication et de réglementation, et recours à un organisme contractuel indépendant en vue d'une homologation réglementaire mondiale. Toutes ces options ont été examinées à la lumière de cinq critères : assurance de l'ensemble des fonctions de réglementation pendant toute la durée de vie du produit, évaluation épidémiologique suffisante, possibilités d'application aux produits retirés du marché du pays producteur, diminution pour le fabricant des risques liés à la réglementation, existence de textes réglementaires à appliquer. Aucune de ces options ne satisfait tous les critères. Dans tous les cas, il faudra mettre en place des infrastructures nationales (y compris un cadre législatif et réglementaire afin notamment de formuler et mettre en œuvre

une politique locale factuelle en matière de vaccination). L'OMS a mené avec un certain succès des travaux en vue de mettre en place ce type de capacités. Le présent article décrit d'autres domaines d'action auxquels la communauté internationale devra s'intéresser pour assurer le développement et l'utilisation des vaccins dont les pays en développement ont besoin.

Resumen

Sistemas de regulación de las vacunas para los países en desarrollo

Las vacunas diseñadas para ser usadas sólo en los países en desarrollo tropiezan con trabas reguladoras que pueden restringir su uso. Ello se debe fundamentalmente a dos razones: la mayoría de los organismos se han establecido para ocuparse de regular los productos exclusivamente dentro de su jurisdicción, y por lo general se considera que en los países en desarrollo esos organismos de reglamentación funcionan de manera deficiente. Se han delimitado algunas opciones para la regulación de tales productos: autorización en el país de fabricación, examen del dosier por la Agencia Europea para la Evaluación de Medicamentos en nombre de la OMS, exportación a un país dotado de un organismo nacional de reglamentación competente que pueda asumir todas las funciones de regulación para el mercado del país en desarrollo, fabricación y autorización compartidas en un país en desarrollo que posea medios competentes de fabricación y regulación, y recurso a una entidad independiente contratada para la aprobación reglamentaria global. Estas distintas opciones se han evaluado con arreglo a cinco criterios: el aseguramiento de todas las funciones de regulación para la vida del producto, la idoneidad de la evaluación epidemiológica, su aplicabilidad a los productos ya no empleados en el mercado nacional del país fabricante, la reducción del riesgo de regulación para el fabricante, y la normativa para la ejecución. Ninguna de las opciones satisface todos los criterios. En todos los casos es necesario desarrollar infraestructuras nacionales (incluido el marco legislativo regulador de base, en particular para formular e implantar políticas locales basadas en la evidencia en materia de vacunas). La OMS ha guiado con cierto éxito algunas actividades orientadas a desarrollar esa capacidad. En el artículo se esbozan otras esferas en las que la comunidad internacional necesita que se actúe para asegurar el desarrollo y utilización de las vacunas que precisa el mundo en desarrollo.

ملخص

السبل التنظيمية للقاحات المستخدمة في البلدان النامية

تواجه اللقاحات المصممة للاستخدام فقط في البلدان النامية العديد من المعوقات التنظيمية التي قد تحد من الاستفادة من هذه اللقاحات. ويرجع هذا الأمر إلى سببين أساسيين : أولهما أن معظم السلطات التنظيمية منوط بها تنظيم المنتجات التي يقتصر استخدامها على مناطق سلطتها، أما السبب الثاني فيتمثل في النظرة التقليدية إلى السلطات التنظيمية في البلدان النامية على أنها ضعيفة. وقد تم استعراف بعض خيارات السبل التنظيمية لهذه المنتجات: مثل الترخيص في بلد المنشأ، ومراجعة الملف من قبل وكالة تقييم الأدوية الأوربية بالنيابة عن منظمة الصحة العالمية، والتصدير لبلد يحظى بسلطة تنظيمية وطنية ذات كفاءة يمكنها التعامل مع كافة الوظائف التنظيمية لسوق البلدان النامية، والتصنيع والترخيص المشترك في بلد نام يتمتع بإمكانيات تنظيمية وتصنيعية ذات كفاءة، وكذا التعاقد مع جهة مستقلة للحصول على الموافقات التنظيمية العالمية. وقد تم تقييم هذه الخيارات على أساس خمسة معايير هي: ضمان كل الوظائف التنظيمية طوال فترة عمر المنتج، ومدى ملائمة التقييم الوبائي، ومدى القابلية للتطبيق على المنتجات التي لم تعد تستخدم في السوق المحلي للبلد المصنع، والحد من المخاطر التنظيمية للمصنّع ، والقوانين واللوائح الحالية المتعلقة بالتنفيذ. ومما لا شك فيه أنه لا يوجد خيار واحد يلبي كل المعايير. كما أنه لابد من إعداد بنية أساسية وطنية لكل الخيارات (تشمل الإطار التشريعي التنظيمي اللازم لصياغة وتنفيذ السياسات المرتكزة على بينات، التي تنظم استخدام هذه اللقاحات). وقد قادت منظمة الصحة العالمية الجهود الرامية إلى تنمية هذه القدرات وحققت قدرا لا بأس به من النجاح. كما تحدد هذه الورقة مجالات العمل التي يتطلبها المجتمع الدولي من أجل ضمان إنتاج واستخدام اللقاحات اللازمة للعالم النامي.

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