Availability and affordability of new medicines in Latin American countries where pivotal clinical trials were conducted

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Objective To assess whether new pharmaceutical products approved by the United States Food and Drug Administration (FDA) in 2011 and 2012 were registered, commercialized and sold at affordable prices in the Latin American countries where they were tested.

Methods We obtained a list of new molecular entities (new pharmaceutical products) approved by the FDA in 2011 and 2012. FDA medical reviews indicated the countries where pivotal clinical trials had been conducted. The registration status of the products was obtained from pharmaceutical registers; pharmaceutical companies confirmed their availability in national markets and local pricing observatories provided the price of medicines in retail pharmacies. Affordability was assessed as the cost of a course of treatment as a proportion of monthly income. Information on safety and efficacy was gathered from independent drug bulletins.

Findings Of an expected 114 registrations, if the 33 products had been registered in all the countries where tested, only 68 (60%) were registered. Eight products were registered and commercialized in all countries but 10 had not been registered in any of the countries. With one exception, products for which we obtained pricing information (n = 18) cost more than the monthly minimum wage in all countries and 12 products cost at least five times the monthly minimum wage.

Conclusion Many pharmaceutical products tested in Latin America are unavailable and/or unaffordable to most of the population. Ethical review committees should consider the local affordability and therapeutic relevance of new products as additional criteria for the approval of clinical trials. Finally, clinical trials have opportunity costs that need to be assessed.

Abstracts in العربية, 中文, Français, Русский and Español at the end of each article.

Introduction

The high cost of many new medicines calls into question whether people in low- and middle-income countries will have access to them,1 yet an increasing number of pivotal trials are carried out in these countries. Pivotal clinical trials are those included in the applications for market authorization or new drug approval documents submitted to regulatory agencies.

This paper explores two issues: (i) are new molecular entities (hereafter products) approved by the FDA in 2011 and 2012 available in Latin American countries where the pivotal trials were conducted? and (ii) if registered, are they marketed at affordable prices? We also obtained information about the therapeutic relevance of the new products from the databases of two independent drug bulletins.

Methods

This is a cross-sectional study. We obtained the list of new products approved by the United States Food and Drug Administration (FDA) in 2011 and 2012.2,3 One product, Gadobutrol (Gadovist), was approved during the study period but excluded from the study because it is a contrast dye used in radiology, not a pharmaceutical treatment. The FDA’s medical reviews of the new products, included in their drug approval history,4 provided the names of countries where the trials had been conducted. If this information was not available in the medical reviews, we obtained it from the trial sponsors.

Obtaining regulatory status

We searched the pharmaceutical registers for the regulatory status of relevant products in each country. The information included in the registers varies slightly by country. Brazil, Chile and Colombia maintain a register of approved pharmaceuticals; Argentina has a register of marketed products; Mexico publishes a list of the products approved per time period and Peru catalogues products available in pharmacies (See Box 1 for a list of web sites consulted). For the countries without registers (Costa Rica, Ecuador, Panama, Peru, Uruguay) we approached the regulatory agencies. We were unable to reach the regulators in the Dominican Republic or the Bolivarian Republic of Venezuela.

We contacted pharmaceutical companies’ headquarters in the United States of America to gather information on the marketing status of their products in the selected countries.

Cost of medicines

In Latin America, about 78% of all medicines are paid for out-of-pocket in retail pharmacies.5 6 Since the products of interest were not included in the World Health Organization (WHO)/Health Action International (HAI) medicine prices’ database, we obtained the price of the unit dose of each product from the countries’ price observatories, which report the maximum price to consumers (Brazil, Mexico) or the observed consumer prices (Argentina, Chile, Colombia, Ecuador, Peru; Box 1).

The consumer prices for Argentinean products not tracked by its observatory and for products in Costa Rica, where there is no observatory, were provided by pharmacological experts who obtained them from local distributors. The quantities needed to complete a course or a year of treatment were calculated using the FDA-approved product label. The pricing information was gathered between 25 August and 20 September, 2014.

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Commercialization status

Obtaining information on the commercialization status of each product from the pharmaceutical companies was difficult. The headquarters of some companies responded quickly with the requested information (Vertex, Exelixis, Glaxo Smith Kline (GSK), Bristol-Myers Squibb (BMS), Sanofi, AstraZeneca), while others referred us to their country subsidiaries or to the companies responsible for commercializing their products outside the United States of America (USA). The accuracy of the information provided depended on the familiarity of the respondent with the company’s practices and databases. Two companies provided contradictory information and one referred us back and forth between the original producer and the licensee. With few exceptions (Pfizer Brazil, Colombia and Mexico; Janssen Argentina; Novartis Argentina and Colombia; Takeda Brazil and Boehringer Mexico), the Latin American offices were less willing to share information than the respondents at headquarters. One company representative wrote: “In response to your question below, we have a policy of restricting the disclosure of proprietary business information/strategies unless we have a formal business relationship protected by a confidential disclosure agreement.”

Information on registration status and pricing helped resolve some of the inaccuracies of information reported by industry. For example, pricing information indicated the probable availability of pertuzumab in Mexico, rivaroxaban in Colombia and Mexico and ticagrelor in Argentina. We decided that bosutinib was not marketed in Argentina or Peru since it was not included on the list of marketed products (Argentina) or in the catalogue of products available in pharmacies (Peru) and because price information was not available in either country.

It was impossible to confirm the marketing status in 10 cases (pasireotide in Brazil; rilpivirine in Argentina, Chile and Mexico; pertuzumab in Peru; teriflunomide in Chile and Mexico; tofacitnib in Costa Rica and Peru; and vandetanib in Mexico).

Measuring affordability

There are challenges in gathering information related to the price of medicines and incomes to determine affordability thresholds. Some argue that a threshold of 5% of total expenditure for the purchase of medicines would classify them as unaffordable in countries such as India and Indonesia. Some authors consider health-care expenditure catastrophic if it exceeds 10% of yearly household income. In this study, the affordability of each course of treatment is presented in relation to the monthly

| Box 1. Databases consulted to obtain registration status of drugs tested and the price of pharmaceuticals |
|---------------------------------|--------------------------------------------------|--------------------------------------------------|---------------------------------|---------------------------------|
| **Argentina**                  | • Vademecum Nacional de Medicamentos, ANMAT\(^1\) | • Listado Oficial de Medicamentos Comercializados LOMAC, ANMAT\(^2\) |
| **Brazil**                     | • Drug price list, Agência Nacional de Vigilância Sanitária\(^a\) | • Medications that have been analysed, Agência Nacional de Vigilância Sanitária\(^b\) |
| **Chile**                      | • Query system of registered products, Instituto de Salud Pública\(^c\) | • Pharmacetical prices, Precio de Remedios\(^d\) |
| **Colombia**                   | • Product data - Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)\(^e\) | • List of chemical entities with unpublished information protected by Decree 2085 of 2002 - Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)\(^f\) | • Drug price – Circular 2, 2012, Ministerio de Salud y Protección Social\(^g\) |
| **Mexico**                     | • Price list, Ministry of Economy\(^h\) | • Pharmacetical prices, Precio de Remedios\(^i\) |
| **Peru**                       | • Catálogo de Productos Farmacéuticos, Ministerio de Salud\(^j\) | Módulo de Consulta de Precios, Ministerio de Salud\(^k\) |

| Table 1. Monthly minimum wage, monthly income per capita, household net-adjusted disposable income and household financial wealth |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Country**                     | **Monthly minimum wage,** |
|                                 | **US$** | **Mean monthly income per capita,** |
|                                 | **US$** | **Average monthly household net-adjusted disposable income,** |
|                                 | **US$** | **Average monthly household financial wealth,** |
| Argentina                       | 523 (since 9/2014) | 1230 | NA | NA |
| Brazil                          | 329 (since 7/2014) | 929 | 859 | 573 |
| Chile                           | 387 (since 7/2014) | 1311 | 1147 | 1512 |
| Colombia                        | 306 (since 1/2014) | 652 | NA | NA |
| Ecuador                         | 340 (since 1/2014) | 477 | NA | NA |
| Mexico                          | 111 (since 1/2014) | 859 | 1071 | 871 |
| Peru                            | 259 (since 6/2012) | 550 | NA | NA |

\(^a\) The minimum wage per country was obtained from public announcements in the media. Local currencies were exchanged into US$ according to the official exchange rate of 1 September 2014.
\(^b\) Household net-adjusted disposable income from the OECD Better Life Index 2014. It is defined as the amount of money that a household earns, or gains, each year after taxes and transfers. It represents the money available to a household for spending on goods or services. The income reported in this publication is for 2011, http://www.oecdbetterlifeindex.org/topics/income/.
\(^c\) Household financial wealth is from the OECD Better Life Index 2014. It is defined as the total value of a household’s financial worth, or the sum of its overall financial assets minus liabilities. Financial wealth takes into account: savings, monetary gold, currency and deposits, stocks, securities and loans. The wealth reported in this publication is for 2011, http://www.oecdbetterlifeindex.org/topics/income/.

NA not available; OECD: Organisation for Economic Co-operation and Development; US$: United States dollars.

\(^1\) The minimum wage per country was obtained from public announcements in the media. Local currencies were exchanged into US$ according to the official exchange rate of 1 September 2014.
\(^2\) Income per capita from the 2013 database of the World Bank adjusted by authors to the mean value.
\(^3\) Household net-adjusted disposable income from the OECD Better Life Index 2014. It is defined as the amount of money that a household earns, or gains, each year after taxes and transfers. It represents the money available to a household for spending on goods or services. The income reported in this publication is for 2011, http://www.oecdbetterlifeindex.org/topics/income/.
\(^4\) Household financial wealth is from the OECD Better Life Index 2014. It is defined as the total value of a household’s financial worth, or the sum of its overall financial assets minus liabilities. Financial wealth takes into account: savings, monetary gold, currency and deposits, stocks, securities and loans. The wealth reported in this publication is for 2011, http://www.oecdbetterlifeindex.org/topics/income/.
household or per capita income. Whether or not this is a catastrophic expenditure depends on the socioeconomic status of the individual or the household. In regions with large income inequalities, such as Latin America, using population averages can be misleading.

Wealth was measured using: (i) monthly minimum wages in 2014, obtained from public announcements in the media; (ii) average monthly per capita income, from a World Bank database; (iii) the monthly household net adjusted disposable income, and (iv) the monthly household financial wealth which was only available for Brazil, Chile and Mexico (Table 1).

Finally, we consulted the databases of two independent drug bulletins (Prescrire, France [http://www.prescrire.org/fr/Search.aspx], and the Health Research Group – Public Citizen, USA [http://www.worstpills.org/search/]) for assessments of the clinical relevance of the new products compared with existing treatments.

Findings

The 33 products included in this study are shown in Table 2. Of an expected 114 registrations, if the 33 products had been registered in all the countries where tested, 60% (68/114) were completed. Three cases were excluded as the regulatory status of the product

### Table 2. Products approved by the United States Food and Drug Administration in 2011 and 2012 that were tested in pivotal trials in Latin America

| Non-proprietary name | Commercial name | Pharmaceutical company | Countries where pivotal clinical trials were conducted |
|----------------------|-----------------|-------------------------|--------------------------------------------------------|
| Aclidium bromide     | Tudorza Pressair®/Eklare Genuair® | Forest/Almirall | Peru |
| Afiblercept          | Eylea*/Eylia*   | Bayer                   | Argentina, Brazil, Chile, Colombia, Mexico |
| Apixaban             | Eliquis*/Elicus* | BMS                     | Argentina, Brazil, Chile, Colombia, Mexico, Peru |
| Axitinib             | Inlyta*         | Pfizer                  | Brazil |
| Azilsartan, medoxomil | Edarbi*       | Takeda                  | Argentina, Chile, Mexico, Peru |
| Bedaquiline          | Sirturo*        | Janssen                 | Brazil |
| Belatacept           | Nulojix*        | BMS                     | Argentina, Brazil, Chile, Mexico |
| Belimumab            | Benlysta*       | GSK                     | Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Peru |
| Bosutinib            | Bosulif*        | Pfizer                  | Argentina, Brazil, Chile, Colombia, Mexico, Peru |
| Cabozantinib         | CometrIQ®       | Exelixis/Sobi           | Brazil, Peru |
| Crizotinib           | Xalkor*         | Pfizer                  | Brazil |
| Evtiggrav/obicistat/ emtricitabine/tenofovir disoproxil fumarate | Stribild* | Gilead                   | Mexico |
| Enzalutamide         | Xtandi*         | Raffo/Astellas          | Argentina, Chile |
| Ezogabine            | Potiga*         | GSK                     | Argentina, Brazil, Mexico |
| Indacaterol maleate  | Arcapa Neohaler*/Onbrize* | Novartis               | Argentina, Chile, Colombia, Ecuador, Peru |
| Iplimumum            | Yerboy*/Yervoy* | BMS                     | Argentina, Brazil, Chile, Peru |
| Linagiptin           | Tradjenta*      | Boehringer              | Argentina, Mexico |
| Lucinactant          | Surfaxin*       | Discovery               | Brazil, Chile, Ecuador, Mexico, Panama, Uruguay |
| Pasireotide          | Signifor*       | Novartis                | Argentina, Brazil, Mexico |
| Perampanel           | Fycopma*        | Eisai                   | Argentina, Chile, Mexico |
| Pertuzumab           | Perjeta*        | Genentech/Roche         | Brazil, Mexico, Peru |
| Regorafenib          | Stivarga*       | Bayer                   | Argentina, Brazil |
| Ripivirine           | Edurarant*      | Janssen                 | Argentina, Brazil, Chile, Costa Rica, Mexico, Panama |
| Rivaroxaban          | Xarelto*        | Bayer/Janssen           | Argentina, Brazil, Chile, Colombia, Mexico, Peru, Venezuela (Bolivarian Republic of) |
| Rofumilast           | Daliresp*/Daxas* | Forest/Takeda           | Brazil |
| Taliglucerase alfa   | Elelyso*/Ulypo*  | Pfizer                  | Chile |
| Tbo-filgastrin       | Neutroval*/Granix* | Teva                  | Brazil, Chile |
| Telaprevir           | Incivek*        | Janssen/Vertex          | Argentina, Brazil |
| Teriflunomide        | Aubago*         | Genzyme                 | Chile, Colombia |
| Ticagrelor           | Brilinta*       | AstraZeneca             | Argentina, Brazil, Mexico, Dominican Republic, Mexico, Peru, Venezuela (Bolivarian Republic of) |
| Tofacitinib          | Xeljan*         | Pfizer                  | Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico |
| Vandetanib           | Caprelsa*       | AstraZeneca             | Argentina, Brazil, Mexico |
| Ziv-afiblercept      | Zaltrap*        | Sanofi                   | Argentina, Brazil, Chile, Colombia, Mexico |
### Table 3. Approval and marketing status in September 2014 of products tested in Latin American countries and approved by the FDA in 2011 and 2012

| Non-proprietor name | Argentina | Brazil | Chile | Colombia | Costa Rica | Mexico | Panama | Peru |
|---------------------|-----------|--------|-------|----------|-----------|--------|--------|------|
|                      | R   | M   | R   | M   | R   | M   | R   | M   | R   | M |
| Apixaban             | Yes | A   | Yes | A   | Yes | A   | –   | –   | Yes | NA |
| Azilsartan medoxomil | Yes | A   | –   | –   | No  | NA  | –   | –   | Yes | A  |
| Belatacept           | Yes | A   | Yes | NA  | No  | NA  | –   | –   | Yes | NA |
| Belimumab            | Yes | A   | Yes | A   | Yes | A   | No  | NA  | No  | NA |
| Crizotinib           | –   | –   | Yes | NA  | –   | –   | –   | –   | –   | – |
| Enalaprilamide       | Yes | NA  | –   | –   | Yes | NA  | –   | –   | –   | – |
| Ezogabine            | Yes | NA  | No  | NA  | –   | –   | –   | –   | –   | – |
| Fasitroide           | Yes | A   | No  | FA  | –   | –   | –   | –   | Yes | A  |
| Pertuzumab           | –   | FA  | No  | NA  | –   | –   | No  | NA  | Yes | NA |
| Rivaroxaban          | Yes | A   | Yes | A   | Yes | A   | Yes | A   | Yes | A  |
| Teriflunomide        | –   | –   | –   | –   | Yes | FA  | –   | –   | Yes | FA |
| Tofacitinib          | Yes | A   | Yes | FA  | –   | –   | Yes | A   | –   | – |
| Vandetanib           | Yes | A   | Yes | A   | –   | –   | –   | –   | No  | FA |

A: available; C: received contradictory information; FA: failed to get an answer; FDA: (United States) Food and Drug Administration; M: marketing status; NA: not available; R: registered.

1. The table does not include the eight new products that have been registered and commercialized in all the countries, neither does it include the ten new products that have not been registered or commercialized in any country.

2. BMS said that apixaban was not marketed in Mexico but we found its price. It may only be available for compassionate use.

3. The Caja Costarricense de Seguridad Social, the social security agency that provides health care including free medications to 90% of the Costa Rica's population, has not bought tofacitinib and it is not available in major pharmacies.

Note: For cells with no information, no clinical trials with this product were conducted in the country.
Research

Clinical trials in Latin America

Núria Homedes & Antonio Ugalde

The bulletins of Prescrire and/or the Health Research Group evaluated 25 of the 32 products and determined that 20 (80%) had no advantage over existing treatments and had significant side-effects. According to these sources, and other bulletins reviewed by Prescrire, the remaining five products (crizotinib, enzalutamide, ipilimumab, pasireotide, telaprevir) may provide some therapeutic benefit to a subset of patients, but the risk–benefit ratio was uncertain (details available from the corresponding author).

Table 4. Cost of a course of treatment (or a year of treatment for chronic conditions) for new products tested in Latin America in relation to the monthly minimum wage, 2014

| Cost* | Argentina | Brazil | Chile | Colombia | Ecuador | Mexico | Peru |
|-------|-----------|--------|-------|----------|---------|--------|------|
| < 1   | Rivaroxavan | Rivaroxavan | Rivaroxavan | Rivaroxavan | Rivaroxavan | Rivaroxavan | Rivaroxavan |
| 1–4   | Apixaban, Indacaterol, Linagliptin, Ticagrelor | Apixaban, Apixaban, Roflumilast, Ticagrelor | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan |
| 5–9   | Belatacept | – | – | – | – | – | – |
| 10–19 | – | – | Belimumab | – | – | – | – |
| 20–39 | Aflibercept, Regorafenib | Aflibercept | Aflibercept | Aflibercept | Aflibercept | Aflibercept | Aflibercept |
| 40–59 | Belatacept, Tofacitinib | Belimumab | – | Tofacitinib | – | – | – |
| 60–99 | Telaprevir | – | – | – | – | – | – |
| 100–149 | – | – | – | – | – | – | – |
| 150–200 | Pasireotide | – | – | – | – | – | – |
| 201–896 | Ipilimumab, Vandetanib | Ipilimumab, Vandetanib | Ipilimumab, Taliglucerase alfa | – | – | – | – |

* Multiple of average monthly per capita income. Note: Information about income is available in Table 1.

Table 5. Cost of a course of treatment (or a year of treatment for chronic conditions) for new products tested in Latin America in relation to average monthly per capita income, 2014

| Cost* | Argentina | Brazil | Chile | Colombia | Ecuador | Mexico | Peru |
|-------|-----------|--------|-------|----------|---------|--------|------|
| < 1   | Indacaterol, Linagliptin, Rivaroxavan, Roflumilast | Rivaroxavan, Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Azilsartan, Linagliptin, Ticagrelor | Apixaban, Indacaterol, Rivaroxavan | Rivaroxavan |
| 1–4   | Apixaban, Ticagrelor | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Indacaterol, Rivaroxavan | Apixaban, Azilsartan, Linagliptin, Ticagrelor | Apixaban, Indacaterol, Rivaroxavan | Rivaroxavan |
| 5–9   | Belatacept | – | Belatacept | Aflibercept, Belimumab | – | – | – |
| 10–19 | Regorafenib | Aflibercept, Belimumab | – | Aflibercept | – | – | – |
| 20–39 | Aflibercept, Belatacept, Tofacitinib | – | – | Tofacitinib | – | – | – |
| 40–59 | Telaprevir | – | – | – | – | – | – |
| 60–99 | Ipilimumab, Pertuzumab, Telaprevir | Ipilimumab | – | – | – | – | – |
| 100–149 | Ipilimumab, Pasireotide, Vandetanib | – | – | – | – | – | – |
| 150–200 | – | – | – | – | – | – | – |
| 201–203 | – | – | Taliglucerase alfa | – | – | – | – |

* Multiple of average monthly per capita income. Note: Information about income is available in Table 1.
Discussion

According to our data, 20 months after the FDA had approved the commercialization of 33 products in the USA, only eight (25%) had been registered and commercialized in all the Latin American countries where they had been tested. Thirty percent (10/33) had been neither registered nor commercialized in any of the countries; 45% (15/33) were registered and some of these were commercialized in several countries.

The suboptimal implementation of differential or tiered pricing for pharmaceuticals, a strategy recommended by WHO to enhance access to pharmaceuticals, has led to arbitrary decisions. For example, the antiretroviral drug atazanavir is supplied for free to people living with human immunodeficiency virus in Peru. The country pays about 6.34 United States dollars (US$) per tablet while Argentina pays US$ 3.04, Brazil US$ 1.00 and the Plurinational State of Bolivia US$ 0.48 (personal communication), prices that with the exception of the Plurinational State of Bolivia do not correspond to the wealth of the countries. It is conceivable that the establishment of national or public health sector affordability thresholds would render new pharmaceuticals accessible.

Within pharmaceutical companies, there seems to be little communication between the research and development units and those responsible for marketing the final products. Clinical trials are outsourced when the countries meet the conditions of the sponsor or of the contract research organizations managing the trial, such as having large urban centres with researchers willing to enrol patients, expedited approval of protocols and sufficient patients who can be readily recruited. The registration and marketing of new products are business decisions based on a country’s regulatory conditions, the presence of a business affiliate or partner, the willingness of the health system to include a product in its formulary, the number of patients who can afford the treatment and estimates of drug profitability for the company.

Latin American agencies responsible for the approval of clinical trials, including the research ethics committees, do not consider if the tested products will be available and affordable. Only Brazil requires that all drugs tested in the country be registered when found to be safe and effective. Resolution 446 of its regulatory agency (Anvisa) reads: “When developing new drugs, if safety and effectiveness is proven, its registration is obligatory in Brazil.” However, as our findings demonstrate, it appears that the regulation is not being enforced.

In sum, neither the sponsors of the clinical trials, nor the regulatory agencies, nor any of the bodies that approved ethical declarations regarding clinical trials have suggested pre-trial mechanisms to ensure that new products will be available and affordable in those countries where testing has taken place. Without such mechanisms, declarations such as those of the Council for International Organizations of Medical Sciences (CIOMS), the Universal Declaration on Bioethics and Human Rights, or the Declaration of Helsinki are difficult to fulfil (Box 2).

International Ethical Guidelines Asserting That Post Trial Access to Treatment Should Be Ensured

Council for International Organizations of Medical Sciences

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

Commentary on Guideline 10

This is applicable especially to research conducted in countries where governments lack the resources to make such products or benefits widely available. Even when a product to be tested in a particular country is much cheaper than the standard treatment in some other countries, the government or individuals in that country may still be unable to afford it. If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical.

The negotiation should cover the health-care infrastructure required for safe and rational use of the intervention, the likelihood of authorization for distribution and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when this economic information is not proprietary.

In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community.

Universal Declaration on Bioethics and Human Rights. Article 15 – Sharing of benefits

Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries.

Declaration of Helsinki (2013)

Item 22. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

“In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community.” (Commentary on Guideline 10).

Latin American regulatory agencies have very limited resources for assessing the safety and efficacy of new products, some of which are very complex. For this reason, they depend on the FDA or the European Medicines Agency’s decisions to grant approval. The pharmaceutical industry claims that conducting trials in Latin America strengthens research capacity in biomedical science, but it could also be suggested that high payments to principal investigators lure some of them away from developing other products needed in the region, such as treatments for dengue, malaria...
and leishmaniasis or from the development of generic biopharmaceuticals, a move that could save lives and money.29 Industry prices are not related to product development costs30,31 and some new products are unaffordable even in high-income countries. In both the USA and the United Kingdom of Great Britain and Northern Ireland,32–35 physicians and health authorities are increasingly reluctant to accept expensive medications offering little improvement over existing cheaper alternatives with demonstrated safety and efficacy.

In January 2014, a new consensus framework for ethical collaboration between patients’ organizations, healthcare professionals and the pharmaceutical industry was published.36 The framework states that:

“Continuing to advocate and support the principle that all human subject research must have legitimate scientific purpose, aims to improve health outcomes and be ethically conducted…”36

To comply with this consensus and with universally-accepted ethical principles,37,39,40 the pharmaceutical industry should: (i) reconsider research and commercial strategies to ensure that new products add therapeutic value to the existing therapeutic arsenal at an affordable price; (ii) include the estimated local prices for potential new products in clinical trial protocols so that the regulatory agencies and research ethics committees can consider the affordability of the product when authorizing the research; (iii) work with regulatory agencies in the countries where products are tested to ensure registration and availability of new products that prove to be safe and effective.

**Study limitations**

The information on registration and commercialization status of new products may contain inaccuracies. We identified and corrected some errors through triangulation, but others may not have been detected. Some FDA reviews did not specify which of the clinical trials were pivotal. Even though we also gathered information from trial sponsors, we may have included trials that technically might not be considered pivotal. There are unavoidable limitations in estimating thresholds of affordability, since financial sacrifices and risks cannot be easily defined by others. These are personal decisions that are influenced by personal values and culture.

Evaluating the price of drugs continues to be complex and currently there is no standard method. Despite their shortcomings, country observatories, which tend to be based on the WHO/HAI methods, are probably the best and most reliable sources of information. Currency variations add to the complexity of reporting pricing information across countries. We priced the drugs in September 2014, but the data used to determine monthly income is from 2013. Moreover, in the Latin American countries included in this study, income is very poorly distributed. If we were to remove the highest two income deciles, the income per capita for the rest of the population would be drastically reduced, and therefore the affordability threshold would have to be lowered.

**Conclusion**

Many pharmaceutical products tested in Latin America are unavailable and/or unaffordable to most of the population and add little therapeutic value compared to existing treatments. There is an urgent need to determine the public-sector affordability thresholds for new pharmaceutical products, and efforts should be made to ensure that ethics committees can take into consideration the affordability and clinical relevance of the new products in their assessment of the clinical trial protocols. The products included in this study did not respond to the most pressing medical needs of people in the region and may have diverted scientific resources from addressing issues of higher relevance. While governments welcome the investments that accompany foreign trials, it is important to document their opportunity costs.

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Évaluer si les nouveaux produits pharmaceutiques approuvés par la Food and Drug Administration (FDA) en 2011 et 2012 ont déjà été homologués, mis sur le marché et vendus à des prix abordables dans les pays d'Amérique latine où ils ont été testés.

Méthodes Nous nous sommes procuré la liste des nouvelles entités moléculaires (nouveaux produits pharmaceutiques) approuvées par la FDA en 2011 et 2012. Les comptes-rendus médicaux de la FDA indiquaient les pays dans lesquels ces essais cliniques pivots avaient été menés. Le statut des produits en matière d'homologation nous a été révélé par les registres pharmaceutiques; les sociétés pharmaceutiques ont confirmé la disponibilité des produits sur les marchés nationaux et les observatoires locaux des prix nous ont communiqué le prix des médicaments dans les pharmacies de détail. Leur accessibilité financière a été évaluée au regard du revenu mensuel. Des informations sur leur innocuité et leur efficacité ont été recueillies dans des bulletins pharmaceutiques indépendants.

Résultats Sur les 114 homologations escomptées si les 33 produits avaient été homologués dans tous les pays où ils ont été testés, seules 68 (60%) étaient accordées. Huit produits étaient homologués et commercialisés dans tous les pays, mais 10 n'avaient été homologués dans aucun des pays. À une exception près, les produits pour lesquels nous avons obtenu des informations tarifaires (n=18) ont un prix supérieur au salaire minimum mensuel dans tous les pays et 12 produits coûtent au moins cinq fois plus que le salaire minimum mensuel.

Conclusion De nombreux produits pharmaceutiques testés en Amérique latine sont indisponibles et/ou inaccessibles financièrement pour la majeure partie de la population. Les comités d'éthique devraient envisager de prendre en compte l'accessibilité financière et l'intérêt thérapeutique des nouveaux produits au niveau local comme critères supplémentaires d'approbation des essais cliniques. Enfin, les essais cliniques ont des coûts d'opportunité qui doivent être évalués.

Résumé
Disponibilité et accessibilité financière des nouveaux médicaments dans les pays d'Amérique latine où ont été menés des essais cliniques pivots

Recherche
Clinical trials in Latin America

Núria Homedes & Antonio Ugalde

Summary
Evaluation of New Medicines in Latin America during the Clinical Trial Period

Objectives To evaluate whether new pharmaceutical products approved by the Food and Drug Administration (FDA) in 2011 and 2012 were already registered, marketed and available at affordable prices in Latin American countries where they had been tested.

Methods We obtained the list of new molecular entities (new pharmaceutical products) approved by the FDA in 2011 and 2012. The FDA's medical reports indicated the countries in which the pivotal clinical trials had been conducted. The status of the products in terms of registration was confirmed by pharmaceutical companies; the companies confirmed the availability of the products on the national markets and local observatories provided information on the price of the medicines in retail pharmacies. Their financial accessibility was evaluated in terms of the monthly income. Information on the safety and efficacy of the medicines was collected in independent drug bulletins.

Results Out of the 114 expected registrations if the 33 products had been registered in all the countries where they were tested, only 68 (60%) were actually registered. Eight products had been registered and marketed in all the countries, but 10 had not been registered in any country. With one exception, the prices for which information was obtained (n=18) were higher than the monthly minimum wage in all the countries and 12 products cost at least five times more than the minimum wage.

Conclusion Most of the medicines tested in Latin America are unavailable and/or unaffordable financially for a large part of the population. Ethics committees should consider the financial accessibility and therapeutic interest of new products at the country level as additional criteria for approval of clinical trials. Finally, clinical trials have opportunity costs which should be evaluated.

Conclusions
Non availability and financial accessibility of new medicines in Latin American countries

Purpose To assess whether new pharmaceutical products approved by the US Food and Drug Administration (FDA) in 2011 and 2012 were already registered, marketed and available at affordable prices in the Latin American countries where they had been tested.

Methods We obtained the list of new active medicinal substances (new medicinal products) approved by the FDA in 2011 and 2012. The FDA's medical reports indicated the countries in which the pivotal clinical trials had been conducted. The status of the products in terms of registration was confirmed by pharmaceutical companies; the companies confirmed the availability of the products on the national markets and local observatories provided information on the price of the medicines in retail pharmacies. Their financial accessibility was evaluated in terms of the local minimum wage. Information on the safety and efficacy of the medicines was collected in independent drug bulletins.

Results Out of the 114 expected registrations if the 33 products had been registered in all the countries where they were tested, only 68 (60%) were actually registered. Eight products had been registered and marketed in all the countries, but 10 had not been registered in any country. With one exception, the prices for which information was obtained (n=18) were higher than the monthly minimum wage in all the countries and 12 products cost at least five times more than the minimum wage.

Conclusion Most of the medicines tested in Latin America are unavailable and/or unaffordable financially for a large part of the population. Ethics committees should consider the financial accessibility and therapeutic interest of new products at the country level as additional criteria for approval of clinical trials. Finally, clinical trials have opportunity costs which should be evaluated.
Objetivo
Evaluar si los nuevos productos farmacéuticos aprobados por la Administración de Alimentos y Medicamentos (FDA) de los Estados Unidos en 2011 y 2012 fueron registrados, comercializados y vendidos a precios asequibles en los países de América Latina en los que se probaron.

Métodos
Se obtuvo una lista de las nuevas entidades moleculares (los nuevos productos farmacéuticos) aprobados por la FDA en 2011 y 2012. Los análisis médicos de la FDA indicaron los países en los que se habían llevado a cabo los ensayos clínicos decisivos. El estado del registro de los productos se obtuvo de los registros farmacéuticos; las empresas farmacéuticas confirmaron su disponibilidad en los mercados nacionales y los observatorios de precios proporcionaron el precio de los medicamentos en farmacias minoristas. La asequibilidad se evaluó como el costo de un ciclo de tratamiento en proporción a los ingresos mensuales. La información sobre seguridad y eficacia se obtuvo de boletines independientes de medicamentos.

Resultados
De los 114 registros esperados si los 33 productos se hubieran registrado en todos los países en los que se habían probado, solo se completaron 68 (el 60%). Se registraron y comercializaron ocho productos en todos los países, pero 10 no habían sido registrados en ninguno de los países. Con una excepción, los productos sobre los que obtuvimos información sobre precios (n = 18) costaban más que el sueldo mínimo mensual en todos los países y 12 productos costaban al menos cinco veces el sueldo mínimo mensual.

Conclusión
Varios productos farmacéuticos probados en América Latina no se encuentran disponibles o no son asequibles para la mayor parte de la población. Los comités de revisión ética deberían considerar la asequibilidad local y la relevancia terapéutica de los nuevos productos como un criterio adicional a la hora de aprobar ensayos clínicos. Finalmente, los ensayos clínicos tienen costes de oportunidad que necesitan ser evaluados.
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