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Clinical trials in Latin America: implications for the sustainability and safety of pharmaceutical markets and the wellbeing of research subjects

Ensayos clínicos en América Latina: implicancias para la sustentabilidad y seguridad de los mercados farmacéuticos y el bienestar de los sujetos

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ABSTRACT This study sought to verify whether drugs approved by the US Food and Drug Administration (FDA) were registered, commercialized and sold at affordable prices in the Latin American countries where they had been tested, as well as to ascertain their contribution to the quality of the pharmaceutical market. The list of New Molecular Entities (NMEs) approved by the FDA in 2011 and 2012 was consulted to determine the countries where pivotal trials were conducted. Affordability was assessed as a proportion of income and information on safety and efficacy was gathered from independent drug bulletins. In the study years, 33 medications were tested in 12 Latin American countries. Only 60% of the expected registrations had been completed by September 2014. With one exception, all products for which pricing information was obtained (n = 18) cost more than one monthly minimum wage in all countries. Only five drugs were classified as "could be better than available treatments." Just one of the NMEs responds to the health care priorities in low and middle income countries.

KEY WORDS Clinical Trial; Drug Industry; Drug Price; Pharmaceutical Trade; Latin America.

RESUMEN Este estudio buscó verificar si los medicamentos aprobados por la Food and Drug Administration (FDA) de EE.UU. fueron registrados, comercializados y vendidos a precios accesibles en los países latinoamericanos en los que fueron testeados, además de constatar su contribución a la calidad del mercado farmacéutico. Se consultó la lista de nuevas entidades moleculares (NEM) aprobadas por la FDA en 2011 y 2012 para identificar los países en los cuales se realizaron ensayos pivotales. Se analizó la accesibilidad económica como proporción de ingresos y se recolectó información sobre seguridad y eficacia en boletines independientes de medicamentos. En los dos años analizados, se testearon 33 medicamentos en 12 países latinoamericanos. Solo el 60% de los registros esperados se habían completado para septiembre de 2014. A excepción de uno, todos los productos para los cuales se obtuvo información de precio (n = 18) costaron más que un sueldo mínimo mensual en todos los países. Solo cinco medicamentos fueron clasificados como "posiblemente mejores que otros tratamientos disponibles". Solo una de las NEM satisface las prioridades de la atención médica de los países de bajos y medianos ingresos.

PALABRAS CLAVES Ensayo Clínico; Industria Farmacéutica; Precio de Medicamento; Comercialización de Medicamentos; América Latina.

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INTRODUCTION

The phenomenal cost of many novel treatments calls into question whether low- and middle-income countries will be able to access them.[1] The issue becomes more poignant as an increasing number of pivotal[a] trials are carried out in these countries where patients are more easily recruited and retained,[2,3] expediting the completion of clinical trials. Shorter trials allow the pharmaceutical industry to hasten the attainment of marketing approval for the new molecular entities (NMEs) and maximize the benefits they can accumulate during their market-exclusivity period.[4] The inability to recruit enough research participants in high-income countries[5] and the few regulatory hurdles in low- and middle-income countries reinforce this tendency.

There has been little scrutiny of the consequences that conducting clinical trials has on the availability and the appropriate and safe use of new pharmaceuticals, as well as on the private and public health budgets of the host countries. International ethical declarations require that approved NMEs be made available to the populations in which they have been tested.[6] The Latin American regulatory agencies base their marketing decisions on the actions taken by their counterparts in "high sanitary surveillance countries" (United States, Japan, Australia, selected individual countries in Europe and the European Medicines Agency).

Additionally, Latin American patients and patient groups are increasingly using the judiciary system to exercise their constitutional right to health, including access to new and expensive pharmaceuticals. Vargas-Pélaez *et al*.[7] conducted a scoping study of the literature on lawsuits for access to medicines and health services. They identified 65 articles, 80% of which involved a Latin American country (68% Brazil, 9% Colombia and 3% Argentina). The Latin American authors cited in this study mentioned that in some cases the courts decide without taking into consideration the evidence of drug efficacy and safety or the appropriateness of the treatment for a particular patient, possibly putting the plaintiff at risk of adverse effects and drug misuse. Moreover, some authors asserted that the pharmaceutical industry was interested in promoting access to medicines through the courts, because it resulted in the inclusion of medicines in the public formularies that might be useful for only a small group of patients rather than the needs of society.

In other words, current judiciary, ethical and regulatory conditions lead to NMEs being made available in the countries where tested. The final result is that those countries where the NMEs have been tested have to cover the costs of the NMEs, regardless of their safety profile and whether they offer any advantage over cheaper existing treatments. While the magnitude of the financial impact will differ across countries and will in part depend on the sales price of the NMEs in each country, public coverage of these new and expensive NMEs will strain public pharmaceutical budgets.

The health consequences of outsourcing clinical trials have been off the radar of researchers, possibly because it is assumed that the regulatory agencies of "high sanitary surveillance countries" only allow the commercialization of products that are safe and effective, and what is available to the residents of high income countries ideally should also be offered to the residents of less prosperous countries, especially if they have contributed to their development.

Using information on pricing and value of the NMEs approved by the US Food and Drug Administration (FDA) in 2011 and 2012 that were tested in Latin America, this article analyzes some of the health, financial and ethical consequences of outsourcing clinical trials to the region.[b]

This paper explores the following questions: 1) Are new molecular entities approved by the FDA in 2011 and 2012 available in the Latin American countries where the pivotal trials were conducted? 2) If registered, are they marketed at affordable prices? 3) Do these NMEs add therapeutic value to existing treatments, as reported in independent drug bulletins? A discussion on the implications

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of conducting clinical trials in Latin America under current judicial, regulatory and ethical conditions for the national pharmaceutical markets and research participants follows.

METHODS

This is a cross-sectional study. The list of NMEs approved by the Food and Drug Administration (FDA) in 2011 and 2012 was obtained from FDA publications.[11,12] 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 NMEs, included in the FDA's drug approval history, 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. The drug approval histories can be found in Drugs@FDA.[13]

Obtaining the regulatory and marketing status of NMEs

To obtain the regulatory status of the NME in each country, we searched the pharmaceutical registers. 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. Table 1 offers a list of the websites consulted. For the countries without registers or with incomplete registers (Costa Rica, Ecuador, Panama, Peru, Uruguay) we approached the regulatory agencies. All attempts to contact the regulators in Dominican Republic and Venezuela failed. Using the information provided on the websites of the pharmaceutical companies we contacted the USA headquarters to gather information on the marketing status of their products in the selected countries.

Table 1. Databases consulted to obtain registration status of drugs tested and the price of pharmaceuticals, by country and institution.

Country	Institution	Database
Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)	Vademecum Nacional de Medicamentos[14] Listado Oficial de Medicamentos Comercializados[15]
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	Listas de Preços de Medicamentos[16] Medicamentos Analisados[17]
Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	Consulta Datos de Productos[18] Listado de entidades químicas con información no divulgada protegida según el Decreto 2085 de 2002, INVIMA[19]
	Ministerio de Salud y Protección Social (MINSALUD)	Precios de medicamentos – Circular 2, 2012[20]
Chile	Instituto de Salud Pública	Sistema de Consulta de Productos Registrados[21] Precios de remedios[22]
Mexico	Ministerio de Economía	Precios registrados de medicamentos con patente vigente[23] Precios de remedios[24]
Peru	Ministerio de Salud	Catálogo de productos farmacéuticos[25] Módulo de consulta de precios[26]

Source: Own elaboration based on data from Argentina;[14,15] Brazil;[16,17] Colombia;[18,19,20] Chile;[21,22] Mexico[23,24] and Peru.[25,26]

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Determining the price of NMEs

In Latin America, about 78% of the medicines are paid out-of-pocket in retail pharmacies.[27] Since the products of interest were not included in the World Health Organization-Health Action International (WHO/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) (Table 1).

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

Measuring affordability

Wealth was measured using: 1) the monthly minimum wage in 2014, obtained from public announcements in the media; 2) the monthly income per capita, from the 2013 World Bank database of Gross Domestic Product (GDP) per capita;[28] 3) the monthly

Table 2. Monthly minimum wage, monthly income per capita, household net-adjusted disposable income, and household financial wealth (in USD), by country.

Country	Monthly minimum wage[1]	Monthly income per cápita[2]	Monthly household net-adjusted disposable income[3]	Monthly household financial wealth[4]
Argentina	523	1,230	---	---
Brazil	329	929	859	573
Chile	387	1,311	1,147	1,512
Colombia	306	652	---	---
Ecuador	340	477	---	---
Mexico	111	859	1,071	871
Peru	259	550	---	---

Source: Homedes and Ugalde.[8]

--- No data available at the time of the study.

[1]The minimum wage per country was obtained from public announcements in the media. For Argentina, the monthly minimum wage is as of September 2014; for Brazil and Chile, as of July 2014; for Colombia, Ecuador, and Mexico, as of January 2014; for Peru, as of June 2012. Local currencies were exchanged into dollars according to the official exchange rate of September 1, 2014.

[2]Income per capita comes from the 2013 database of the World Bank[28] adjusted by authors to the median value of the year.

[3]Household net-adjusted disposable income from the *Better Life Index* of the Organisation for Economic Co-operation and Development for the year 2014.[29] 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."[30]

[4]Household financial wealth is from the *Better Life Index* of the Organisation for Economic Co-operation and Development for the year 2014.[29] It is defined as "the total value of a household's financial worth, or the sum of their overall financial assets minus liabilities. Financial wealth takes into account: savings, monetary gold, currency and deposits, stocks, securities and loans."[30]

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household net adjusted disposable income;[29] and 4) the monthly household financial wealth as reported by the Organisation of Economic Co-operation and Development (OECD),[30] which was only available for 2011 and for Brazil, Chile and Mexico (Table 2).

These measurements have a number of limitations, due to aspects related to the difficulty of measuring individual and household income and wealth using aggregate data:

1. Income distribution is very unequal in most countries. As can be seen in Table 3 the Gini index of wealth distribution shows a very large concentration of wealth. The table also shows that for practically all countries except Argentina and Venezuela, the wealthiest ten percent of the population receives more than 35% of the GNP.
2. The non-monetized activities, which are highly prevalent in Latin America, and the remittances sent through informal channels – that in some countries such as Mexico and Ecuador are significant – can only be estimated and we do not know the accuracy of the estimates.
3. Income generated from illegal activities such as contraband, drugs or prostitution is not considered when estimating the GNP of a nation.

Table 3. Gini index and income distribution in the lowest and highest deciles, by country.

Country	Percentage of GDP received according to population decile[1]		Gini Index	
	Lowest decile	Highest decile	CIA[2]	WB[3]
Argentina	1.5	32.3	45.8	43.6
Brazil	0.8	42.9	51.9	52.7
Chile	1.8	42.8	52.1	50.8
Colombia	0.9	44.4	55.9	53.5
Costa Rica	1.2	39.5	50.3	48.6
Dominican Republic	1.8	36.4	47.2	45.7
Ecuador	1.4	38.3	48.5	46.6
Mexico	2.0	37.5	48.3	48.1
Panama	1.1	40.1	51.9	51.9
Peru	1.4	36.1	48.1	45.3
Uruguay	1.9	34.4	45.3	41.3
Venezuela	1.7	30.2	39.0	35.6

Source: Homedes and Ugalde.[8]

[1]Data correspond to the following years: Argentina, 2010; Brazil, 2008; Chile, 2009; Colombia, 2010; Costa Rica, 2009; Dominican Republic, 2010; Ecuador, 2010; Mexico, 2010; Panama, 2010; Peru, 2010; Uruguay, 2010; Venezuela, 2006. As clarified in the database, "data come from household surveys, the results adjusted for household size. Nations use different standards and procedures in collecting and adjusting the data. Surveys based on income will normally show a more unequal distribution than surveys based on consumption. The quality of surveys is improving with time, yet caution is still necessary in making inter-country comparisons."[31]

[2]Data from the Central Intelligence Agency (CIA)[31] corresponds to the following years: Argentina, 2009; Brazil, 2012; Chile, 2009; Colombia, 2010; Costa Rica, 2008; Dominican Republic, 2010; Ecuador, 2013; Mexico, 2008; Panama, 2010; Peru, 2010; Uruguay, 2010; Venezuela, 2011.

[3]World Bank (WB) information is for all countries for the year 2012, except for Argentina and Chile, which corresponde to the year 2011. The World Bank data "are based on primary household survey data obtained from government statistical agencies and World Bank country departments.[32] For more information and specificity, see the methodology used by the World Bank.[33]

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4. A relatively large number of breadwinners do not receive a monthly check and have difficulties in determining the yearly income. Frequently, agricultural workers and those in the informal sector do not receive the minimum wage.
5. Databases from international organizations convert local currencies into dollars at a given moment which does not coincide with the time of purchase of the medication, and currency exchanges may vary significantly throughout the year. Some currencies are relatively stable as is the case of Mexico, or Ecuador whose currency is the US dollar, but others for example the Brazilian real fluctuated against the dollar in 2014 almost 9%, and the Argentine peso has also experienced severe depreciations. A second problem is related with the value of the currency. The official and the real value are not always the same, and in some cases the difference can be large. During the years of our analysis the real value (in the black market) of the peso in Argentina was about 40% higher than the official.

Similarly, problems related to household definitions and estimates of number of persons and incomes can also be highlighted. As anthropologists are well aware, the concept of a household/family is not as clearly defined as many may think. Studies of marginal neighborhoods, where very large number of Latin Americans reside, show many varieties of household formations. We can talk about blood and ritual families, and of two or more unrelated persons/families residing under the same roof, sharing some expenditures and having difficulties quantifying the amount that each contributes. We have observed that when household surveys take place, respondents have difficulties answering the questions about the number of persons who live in the household. Migrants can come and go and may have two places of residence but do not always define which the primary one is. Dual nationalities are common, with significant numbers in several countries (Argentina, Bolivia, Ecuador and Mexico) and migrants may or may not be counted in the national censuses. These circumstances are difficult for census workers to handle, and the official figures on number of persons per household may not always be correct. These uncertainties influence the quality of the data on household disposable income presented by national and international agencies. Ritual families are common in Latin America. Godfathers and mothers may not live in the household but the ritual family knows that additional income is available in important cases.

Niëns and Brouwer discuss the challenges in gathering information related to the price of medicines and incomes, and in determining affordability thresholds.[34] Niëns *et al*. decided that a threshold of 5% of total expenditures for the purchase of medicines would classify them as unaffordable in countries such as India and Indonesia.[35] O'Donnell *et al*. considered health care expenditures catastrophic if they surpassed 10% of yearly household income.[36]

In this study, the affordability of each course of treatment of one medicine is presented in relation to the monthly per capita income or household wealth and income, which is equivalent to 8.3% of the yearly income. Whether or not the calculated cost is affordable or results in a catastrophic expenditure depends on the specific socioeconomic status of the individual or the household. Given the high income inequalities of the region (Table 3), the use of average income measures will overestimate the purchasing power of those in the lowest income deciles.

Appraising the therapeutic value of NMEs

Data bases from two reputable independent drug bulletins – *Revue Prescrire* of the French organization Prescrire and *Worst Pills, Best Pills* of the Health Research Group of the US organization Public Citizen – were consulted for evidence of the added value of the NMEs to existing treatments. These reports incorporated safety information and

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Prescrire often included information from other bulletins. In total, we have information from 15 independent pharmacology bulletins from 11 countries. Information from Fojo *et al*.[37] was also used to assess the value of new cancer treatments.

FINDINGS

Registration and availability

The 33 products included in this study are shown in Table 4. Obtaining information on the commercialization status of each product from pharmaceutical companies was difficult. The headquarters of some companies responded quickly (Vertex, Exelixis, GSK, BMS, Sanofi, AstraZeneca), while others referred us to their country subsidiaries or to the companies responsible for commercializing their products outside the USA, and we often had to contact them several times. 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 innovative company 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 USA headquarters. The Vice President of one of the companies 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" (September 5, 2014).

Information on registration status and pricing helped resolve some of the inaccuracies reported by industry. For example, the conclusion was reached 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 price information was not available in either country. Similarly, pricing information indicated the probable availability of pertuzumab in Mexico, rivaroxaban in Colombia and Mexico, and ticagrelor in Argentina. It was impossible to confirm the NME's marketing status in ten cases: pasireotide in Brazil; rilpivirine in Argentina, Chile and Mexico; pertuzumab in Peru; teriflunomide in Chile and Mexico; tofacinitib in Costa Rica and Peru; and vandetanib in Mexico.

Combining information on registration and availability indicated that ten of the 33 products (30%) were not registered nor commercialized in any of the countries where they had been tested (aclidium bromide, axitinib, bedaquiline, bosutinib, carbozantinib, elvitegravir-cobicistat-emtricitabine-tenofovir disoproxil fumarate, lucinactant, perampanel, tbofilgastrim, ziv-aflibercept); eight (25%) were registered and commercialized in all countries where tested (aflibercept, indacaterol maleate, ipilimumab, linagliptin, regorafenib, roflumilast, taliglucerase alfa, telaprevir); and two products were registered but not marketed in any of the countries where tested (enzalutamide and ezogabine).

Table 5 presents the approval and commercialization status in September 2014 of the products included in the study that were registered and commercialized in some countries but not in others (excluding the ten NMEs that were not registered in any country and the eight that were marketed in all the countries in which they were tested). Of an expected 121 registrations, if the 33 products had been registered in all the countries where tested, only 67 (55%) were completed. Registration did not lead to commercialization on at least eight occasions, and we could not determine the marketing status of seven registered products. In total, we confirmed that 42% of the tested products were marketed where tested. In two cases the pharmaceutical company stated that a product was available when the regulatory agency said it had not been approved.

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Table 4. Products approved by the FDA in 2011 and 2012 that were tested in pivotal trials in Latin America.

International nonproprietary name	Commercial name	Pharmaceutical company	Countries where tested
Aclidinium bromide	Tudorza Pressair®/ Eklaire Genuari®	Forest/ Almirall	Peru
Aflibercept	Eylea®/Eylia®	Bayer	Argentina, Brazil, Chile, Colombia, Mexico
Apixaban	Eliquis®	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, Chile, Peru
Crizotinib	Xalkori®	Pfizer	Brazil
Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Stribild®	Gilead	Mexico
Enzalutamide	Xtandi®	Raffo/Astellas	Argentina, Chile
Ezogabine	Potiga®	GSK	Argentina, Brazil, Mexico
Indacaterol maleate	Arcapta Neohaler/ Onbrize	Novartis	Argentina, Chile, Colombia, Ecuador, Peru
Ipilimumab	Yerboy®	BMS	Argentina, Brazil, Chile, Peru
Linagliptin	Tradjenta	Boehringer	Argentina, Mexico
Lucinactant	Surfaxin	Discovery	Brazil, Chile, Ecuador, Mexico, Panama, Uruguay
Pasireotide	Signifor	Novartis	Argentina, Brazil, Mexico
Perampanel	Fycompa	Eisai	Argentina, Chile, Mexico
Pertuzumab	Perjeta®	Genentech/ Roche	Brazil, Mexico, Peru
Regorafenib	Stivarga®	Bayer	Argentina, Brazil
Rilpivirine	Edurant®	Janssen	Argentina, Brazil, Chile, Costa Rica, Mexico, Panama
Rivaroxaban	Xarelto®	Bayer/Janssen	Argentina, Brazil, Chile, Colombia, Mexico, Peru, Venezuela
Roflumilast	Daliresp®/Daxas®	Forest/Takeda	Brazil
Taliglucerase alfa	Elelyso®/Uplyso®	Pfizer	Chile
Tbofilgastrim	Neutroval®/Granix®	Teva	Brazil, Chile
Telaprevir	Incivek®	Janssen/Vertex	Argentina, Brazil
Teriflunomide	Aubagio®	Genzyme	Chile, Colombia
Ticagrelor	Brilinta®	AstraZeneca	Argentina, Brazil, Mexico
Tofacitinib	Xeljan®	Pfizer	Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Peru, Dominican Republic, Venezuela
Vandetanib	Caprelsa®	AstraZeneca	Argentina, Brazil, Mexico
Ziv-aflibercept	Zaltrap®	Sanofi	Argentina, Brazil, Chile, Colombia, Mexico

Source: Homedes and Ugalde.[8,9]

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Prices of new molecular entities in Latin America

The prices of the 21 NMEs marketed in Latin America, except three that were unavailable, are displayed in Table 6. Prices varied widely by country, both in absolute and in relative terms. Argentina had the highest absolute price for many of the drugs included in this study (aflibercept, apixaban, belatacept, ipilimumab, pasireotide, telaprevir, ticagrelor, tofacitinib, vandetanib), on occasion even doubling the second highest price (aflibercept, belatacept, tofacitinib). Brazil had the lowest prices for apixaban, belatacept, pertuzumab, rivaroxaban and ticagrelor, but the price of

Table 5. Approval and marketing status in September 2014 of selected new molecular entities tested in Latin American countries and approved by the FDA in 2011 and 2012, by country.[1]

New molecular entity	Argentina		Brazil		Chile		Colombia		Costa Rica		Mexico		Panama		Peru		Dominican Republic		Venezuela	
	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized	Registered	Commercialized
Apixaban	R	C	R	C	R	C	R	C	----	----	R	NC[2]	----	----	R	NC	----	----	----	----
Azilsartan medoxonil	R	C	----	----	NR	NC	----	----	----	----	R	C	----	----	NR	NC	----	----	----	----
Belatacept	R	C	R	NC	NR	NC	----	----	----	----	R	NC	----	----	----	----	----	----	----	----
Belimumab	R	C	R	C	R	C	NR	NC	NR	NC	R	C	----	----	NR	C	----	----	----	----
Crizotinib	----	----	R	NC	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Enzalutamide	R	NC	----	----	R	NC	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Ezogabine	R	NC	NR	NC	----	----	----	----	----	----	NR	NC	----	----	----	----	----	----	----	----
Pasireotide	R	C	NR	NOR	----	----	----	----	----	----	R	C	----	----	----	----	----	----	----	----
Pertuzumab	----	----	R	C	----	----	----	----	----	----	R	C	----	----	NR	NOR	----	----	----	----
Rilpivirine	R	NOR	NR	NC	NR	NOR	----	----	NR	NC	R	NOR	R	NC	----	----	----	----	----	----
Rivaroxaban	R	C	R	C	R	C	R	C	----	----	R	C	----	----	R	C	----	----	NOR	NC
Teriflunomide	----	----	----	----	R	NOR	----	----	----	----	R	NOR	----	----	----	----	----	----	----	----
Ticagrelor	R	C	R	NOR	----	----	----	----	----	----	R	C	----	----	----	----	----	----	----	----
Tofacitinib	R	C	NR	NC	R	C	R	C	NR	CI[3]	R	C	----	----	R	CI	NOR	NC	NOR	NC
Vandetanib	R	C	R	C	----	----	----	----	----	----	NR	NOR	----	----	----	----	----	----	----	----

Source: Homedes and Ugalde.[8]

R = Registered; NR = Not registered; C = Commercialized; NC = Not commercialized; NOR = No response; CI = Contradictory information. ---- No clinical trials with the new molecular entity were conducted in the country.

[1]The table does not include the eight NMEs that have been registered and commercialized in all the countries, nor the ten NME that have not been registered nor commercialized in any country.

[2]The company BMS said that apixaban was not marketed in Mexico but we found its price. It could only be available for compassionate use.

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

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Table 6. Price of commercialized medicines by countries where tested and by number of months of income needed to pay for a course or a year of treatment according to the local price (measured in monthly minimum wage and monthly income per capita in USD). Selected countries of Latin America.[1]

New molecular entity and dose	Price (in USD) Months of wages (n) Months of income (n)	Argentina	Brazil[3]	Chile	Colombia	Mexico	Peru
Gross domestic product in purchasing power parity[2]		12,568	15,110	21,980	12,743	16,287	11,438
Aflibercept, 8 injections per year.	Price	30,410	15,259	10,882	10,122	NIO	--
	MMW	58	46	28	33	NIO	--
	MIPC	25	16	8	16	NIO	--
Apixaban, 5 mg (2 pills) per day (730 per year).	Price	1,858	1,259	1,714	1,294	1,536	R, NC
	MMW	3,5	3,8	5	4	14	--
	MIPC	1,5	1,5	0,9	2	2	--
Azilsartan medoxonil, 80 mg once a day (365 pills per year).	Price	R, NC	--	R, NC	--	1,026	R, NC
	MMW	--	--	--	--	10	--
	MIPC	--	--	--	--	1.2	--
Belatacept, 10 mg/kg per treatment. A person weighing up to 50 kg needs 2 vials per treatment, and 16 treatments per year.	Price	42,508	3,293	R, NC	--	R, NC	--
	MMW	81	10	--	--	--	--
	MIPC	35	4	--	--	--	--
Belimumab,10 mg/kg at 2-week interval for the first 3 doses and 4 weeks intervals thereafter. For a total of 15 treatments per year.	Price	NIO	20,995	7,725	R, NC	NIO	NR, C[4]
	MMW	--	64	20	--	--	--
	MIPC	--	23	6	--	--	--
Crizotinib		--	R, NC	--	--	--	--
Indacaterol, (75 µg once a day) 150 µg.	Price	798	--	435	878	--	NIO
	MMW	1.5	--	1.1	3.0	--	--
	MIPC	0.6	--	0.5	1.3	--	--
Indacaterol, (75 µg once a day) 300 µg.	Price	844	--	809	NC	--	NIO
	MMW	1.6	--	2.5	NC	--	--
	MIPC	0.7	--	0.6	NC	--	--
Ipilimumab, 3 mg/kg IV infusion over 90 minutes every 3 weeks for 4 cycles.	Price	175,697	100,189	96,212	--	--	NIO
	MMW	336	305	249	--	--	NIO
	MIPC	143	107	74	--	--	NIO
Linagliptin, 5 mg once a day.	Price	1,012	--	--	--	1,120	NIO
	MMW	1.9	--	--	--	10	NIO
	MIPC	0.8	--	--	--	1.3	NIO
Pasireotide, 600 µg twice a day.	Price	143,309	R, CNC	--	--	88,061	--
	MMW	274	--	--	--	793	--
	MIPC	117	--	--	--	113	--
Pasireotide, 900 µg twice a day.	Price	164,799	--	--	--	99,413	--
	MMW	315	--	--	--	896	--
	MIPC	134	--	--	--	116	--
Pertuzumab, Initial dose 840 mg as a 60-minute IV infusion, followed every 3 weeks thereafter by 420 mg as a 30 to 60 minute IV infusion	Price	--	58,979	--	--	73,713	R, CNC
	MMW	--	179	--	--	644	--
	MIPC	--	75	--	--	85	--

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Table 6. Continued.

New molecular entity and dose	Price (in USD) Months of wages (n) Months of income (n)	Argentina	Brazil[3]	Chile	Colombia	Mexico	Peru
Regorafenib, 4 tablets a day, 21 days of 28-day cycle.	Price	19,584	NIO	--	--	--	--
	MMW	37	--	--	--	--	--
	MIPC	16	--	--	--	--	--
Rilpivirine, for HIV-1 infection in adults who have never taken HIV therapy.		R, CNC	NR, NC	NR, CNC	--	R, CNC	--
Rivaroxaban, 10 mg once a day (Knee=12 days).	Price	162	42,6	55,6	170	59	60
	MMW	0.3	0.1	0.1	0.6	1	0.2
	MIPC	0.1	0.1	0.04	0.3	0.1	0.1
Rivaroxaban, 10 mg once a day (Hip=35 days).	Price	476	124	162	496	171	160
	MMW	0.9	0.4	0.4	1.6	2	1
	MIPC	0.4	0.1	0.1	0.8	0.2	0.3
Roflumilast, one tablet 500 mcg per day.	Price	--	993	--	--	--	--
	MMW	--	3	--	--	--	--
	MIPC	--	1	--	--	--	--
Taliglucerasa alfa, 60 units/kg IV every 2 weeks, 26 treatments per year.	Price	--	--	266,960	--	--	--
	MMW	--	--	584	--	--	--
	MIPC	--	--	203	--	--	--
Telaprevir, 1125 mg twice a day, for 12 weeks.	Price	52,061	44,554	--	--	--	--
	MMW	99	135	--	--	--	--
	MIPC	42	48	--	--	--	--
Teriflunomide		--	--	R, CNC	--	R, CNC	--
Ticagrelor, 90 mg twice a day.	Price	2,681	1,407	--	--	1,879	--
	MMW	5	4	--	--	17	--
	MIPC	2	1.5	--	--	1.8	--
Tofacitinib, 5 mg twice a day.	Price	45,252	NR, NC	NIO	13,504	18,308	R, CNC
	MMW	87	--	--	44	165	--
	MIPC	37	--	--	21	22	--
Vandetanib, 300 mg once a day.	Price	213,618	117,848	--	--	NR, CNC	--
	MMW	408	358	--	--	--	--
	MIPC	174	126	--	--	--	--

Source: Homedes and Ugalde.[9]

MMW = Monthly minimum wage; MIPC = Monthly income per capita; R = Registered: NR = Not registered; C = Commercialized; NC = Not commercialized; CNC = Commercialization not confirmed (it could not be confirmed whether the product was available in the country); NIO = No information obtained.

[1]Prices are for a complete course of treatment, or, in the case of chronic disease, for a year of treatment. All MNW and MIPC figures above 3 months have been rounded. For cells with no information (--), no clinical trials were conducted in the country or the product is not available. In Ecuador there was information only for indacaterol, and to simplify the table we have not included the information, but it is available from corresponding author.

[2]Information from the World Bank for the year 2014. All gross domestic product (GDP) data are reported in purchasing power parity in US dollars based on Atlas methodology used by the International Monetary Fund and the World Bank. The Argentina GDP per capita is based on data officially reported by the National Institute of Statistics and Censuses of Argentina that do not estimate the purchasing power parity. The International Monetary Fund has called on Argentina to adopt measures to address the quality of official GDP and consumer price index data. For more information please refer to the World Bank.[38]

[3]In Brazil, ANVISA publishes a list of maximum prices for the consumer that does not include taxes. The tax rate varies by state from 0-19%. We have included the maximum tax rate to the ANVISA prices.

[4]GlaxoSmithKline says it is available.

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belimumab was more than twice that in Chile. The price of belimumab, indacaterol and ipilimumab was lowest in Chile; Colombia had the lowest price for aflibercept and tofacitinib, and the highest for rivaroxaban.

We could not find any relationship between prices and the GDP per capita or the minimum wages in these countries. In Brazil aflibercept costs US$15,259 per course of treatment; in Argentina, which has a slightly lower GDP per capita than Brazil, the course of treatment of the same medication is US$30,410. Brazilians pay 46 times the monthly minimum wage and Argentines 58, making the treatment unaffordable in both countries but considerably more in Argentina. If we compare aflibercept in Colombia and Chile – the latter has a considerably higher GDP per capita than the former – the drug is slightly cheaper in Colombia, but patients have to pay twice as many monthly minimum wages as Chileans. In the case of indacaterol, in Colombia the cost of the drug is twice that in Chile, and the same is true for rivaroxaban. Many other significant price differences can be found in Table 6.

Table 7 indicates the number of monthly minimum wages (MMW) necessary to purchase one course of treatment or a year of treatment for chronic conditions. In all countries, the cost of all products except one was greater than one MMW. Five medications required more than one and up to four MMW; and six NMEs (39%) cost between 100 and

Table 7. Number of 2014 monthly minimum wages (MMW) needed to purchase one course of treatment or one year of treatment for chronic conditions of the new molecular entities tested in Latin America in 2011 and 2012.

Number of MMW	Argentina	Brazil	Chile	Colombia	Ecuador	Mexico	Peru
<1	Rivaroxaban	Rivaroxaban	Rivaroxaban	Rivaroxaban	--	--	Rivaroxaban
1-4	Apixaban Indacaterol Linagliptin	Apixaban Roflumilast Ticagrelor	Indacaterol	Apixaban Indacaterol	Indacaterol	Rivaroxaban	--
5-9	Ticagrelor	--	Apixaban	--	--	Azilsartan	--
10-19	--	Belatacept	--	--	--	Apixaban Linagliptin Ticagrelor	--
20-39	Regorafenib	--	Aflibercept Belimumab	Aflibercept	--	--	--
40-59	Aflibercept	Aflibercept	--	Tofacitinib	--	--	--
60-99	Belatacept Telaprevir Tofacitinib	Belimumab	--	--	--	--	--
100-149	--	Telaprevir	--	--	--	--	--
150-199	--	Pertuzumab	--	--	--	Tofacinitib	--
200-896	Ipilimumab Pasireotide Vandetanib	Ipilimumab Vandetanib	Ipilimumab Taliglucersa alfa	--	--	Pasireotide Pertuzumab	--

Source: Own elaboration using information from Homedes and Ugalde.[9]

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896 MMW. Using the monthly income per capita (MIPC), Argentineans and Chileans could purchase three products with less than one MIPC, and Brazilians one (see Table 8). One product (rivaroxaban) costs less than one MIPC in all countries, but four products (two for cancer) cost more than 100 MIPC.

The results using monthly household net adjusted disposable income and monthly household financial wealth were very similar to MIPC findings. Comparisons between MMW and MIPC measurements in the seven Latin American countries housing over 85% of all clinical trials conducted in the region are shown in Table 6. The hypothesis that the large majority of the population cannot afford the drugs tested in their countries is categorically confirmed.

Therapeutic advantage of NMEs

Prescrire and Health Research Group evaluated 26 of the 33 NMEs included in this study, and determined that 21 of the 26 (80%) offered no therapeutic advantage over existing treatments and had significant side effects, advising against the use of ten of them (Table 9). According to these sources and the independent bulletins cited by Prescrire, the remaining five products (crizotinib, enzalutamide, ipilimumab, pasireotide, and telaprevir) could offer some advantage to a subset of patients, but the risk-benefit ratio remained uncertain. Only three of these five products were available in the countries where tested.

Table 8. Number of 2013 monthly income per capita (MIPC) needed to purchase new molecular entities that were tested in Latin American countries in 2011 and 2012.

Number of MIPC	Argentina	Brazil	Chile	Colombia	Ecuador	Mexico	Peru
<1	Indacaterol Linagliptin Rivaroxaban	Rivaroxaban	Apixaban Indacaterol Rivaroxaban	Rivaroxaban	--	Rivaroxaban	Rivaroxaban
1-4	Apixaban Ticagrelor	Apixaban Belatacept Roflumilast Ticagrelor	--	Apixaban Indacaterol	Indacaterol	Apixaban Azilsartan Linagliptin Ticagrelor	--
5-9	--	--	Aflibercept Belimumab	--	--	--	--
10-19	Regorafenib	Aflibercept	--	Aflibercept	--	--	--
20-39	Aflibercept Belatacept Tofacitinib	Belimumab	--	Tofacitinib	--	Tofacitinib	--
40-59	Telaprevir	Telaprevir	--	--	--	--	--
60-99	--	Pertuzumab	Ipilimumab	--	--	Pertuzumab	--
100-149	Ipilimumab Pasireotide	Ipilimumab	--	--	--	Pasireotide	--
150-199	Vandetanib	Vandetanib	--	--	--	--	--
200-203	--	--	Taliglucerasa alfa	--	--	--	--

Source: Own elaboration using information from Homedes and Ugalde.[9]

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Eight of the 33 products included in our study (25%) were included in Fojo *et al*.'s evaluation.[37] Only one of them (enzalutamide) increased overall survival significantly (by 4.8 months) in patients with castration-refractory prostate cancer; four increased the progression-free survival period (vandetanib, pertuzumab, carbozantinib, crizotinib), two did not fulfill the American Society of Clinical Oncology (ASCO) criteria to determine clinical relevance (ziv-aflibercept, regorafenib), and the authors were uncertain about ipilimumab (Table 10).

In contrast with the methodology used by the independent drug bulletins mentioned above, Fojo *et al*.[37] assessed the value of each NME without comparing it with other treatment options. Two NMEs that qualified as useful in their publication (vandetanib and pertuzumab) were questioned by the independent drug bulletins. Vandetanib was considered more dangerous than beneficial, and the benefit-risk ratio of pertuzumab was judged to be insufficiently known. While *Australian Prescriber* and *Medical Letter* thought that it appeared to increase survival without worsening the condition of human epidermal growth factor receptor 2 (HER-2) positive women with metastasis of breast cancer, *Medical Letter* thought that the effect on overall survival had not been determined and others considered that it increased the side-effects, the benefits were uncertain, and there was insufficient information to recommend its commercialization. At a price of more than US$50,000 (pertuzumab) and

Table 9. Summary of the assessments carried out by independent drug bulletins regarding new molecular entities tested in Latin American countries and approved by the US Food and Drug Administration in 2011 and 2012.

New molecular entity and indication	Assessment by independent drug bulletins
Aclidinium bromide[39] Chronic obstructive pulmonary disease.	***Revue Prescrire***. Nothing new. Not better than existing treatments. Same cardiovascular adverse effects than others in its class. ***Arznei-Telegramm*** (Germany). Do not recommend it. There is a need for more studies comparing it to other long-term bronchodilators. Long-term efficacy data and side-effects need to be better understood. ***Drugs and Therapeutics Bulletin*** (United Kingdom). Need to compare to other bronchodilators in phase III studies. Similar effects as placebo in terms of episodes that required the use of antibiotics, corticosteroids, hospitalization. ***Gebu*** (Netherlands). There is no information proving that it improves prognosis or limits exacerbations. No therapeutic advance. Do not use.
Aflibercept[40] Wet age-related macular degeneration (AMD).	***Revue Prescrire***. Does not add value to existing treatment with ranibizumab – measured in terms of efficacy, side-effects or ease of administration. ***Medical Letter*** (USA). Same efficacy as ranibizumab, and has not been tested against bevacizumab, cheaper and same efficacy. ***Australian Prescriber*** (Australia). Adverse events are similar to those of ranibizumab.
Apixaban[41] To reduce the risk of stroke and dangerous blood clots in patients with atrial fibrillation that is not caused by a heart valve problem.	***Revue Prescrire***. Not demonstrated to be better than warfarin (severe cases) or warfarine or aspirin (mild cases). Has not been compared to dabigatran. Poor evidence and there is no antidote. ***Worst Pills, Best Pills***. We recommend that patients not use this drug for seven years after its approval date, because it does not represent a clear therapeutic breakthrough over the existing drug, warfarin.[42]

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Table 9. Continued.

New molecular entity and indication	Assessment by independent drug bulletins
Axitinib[43] Previously treated kidney cancer.	***Prescrire International***. In patients with metastatic kidney cancer in whom interferon alfa has failed, the only available comparative trial showed that axitinib did not prolong overall survival compared to sorafenib. Axitinib has a burdensome adverse effect profile and carries a risk of numerous drug-drug interactions. The only trial results available in early 2013 suggest that, compared to sorafenib, axitinib does not prolong survival in patients with kidney cancer who have previously received interferon alfa. After sunitinib treatment failure, there is no evidence that axitinib is more clinically beneficial than appropriate supportive care. Its adverse effect profile is just as burdensome as that of sorafenib. It also carries a risk of numerous drug interactions. ***Medical Letter*** (USA). In previously treated patients with advanced renal cell carcinoma, axitinib appears to be modestly more effective tan sorafenib in increasing progression-free survival and similarly effective in improving overall survival. How it compares to other kinase inhibitors remains to be determined. ***Australian Prescriber*** (Australia). Axitinib provides another option for those who have relapsed despite previous treatment. Although it may temporarily reduce disease progression, it does not seem to prolong overall survival any more than sorafenib.
Bedaquiline[44] Multidrug resistant tuberculosis.	***Worst Pills, Best Pills.*** Do not use. Those receiving the drug were five times more likely to die than those receiving a placebo. Instead of looking into this more carefully, the FDA approved the drug with the warning: "In one clinical trial, more deaths were seen in people who were treated with Sirturo® compared to people who did not receive Sirturo®."
Belatacept[45] To prevent acute rejection in adult patients who have had a kidney transplant (10 mg per kg per treatment).	***Revue Prescrire***. Nothing new. Not more effective and it is not less nephrotoxic in the long run. Adverse effects (lymphoma and infections) appear to be more frequent with belatacept. It is better to use cyclosporine. ***Medical Letter*** (USA). Same efficacy as cyclosporine after one year. It has not been compared to tracolimus. Has side effects – like lymphoma and serious infections. Need more long-term data. ***Arzneimittelkommission der deutschen Ärzteschaft*** (Germany). Even though there are more kidney rejections, overall survival is similar to that of patients treated with cyclosporine. Was not evaluated against standard treatment. More comparative and long-term data are needed.
Belimumab[46] Patients with active, autoantibody-positive lupus who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs.	***Revue Prescrire***. Nothing new. When added to standard treatment, there is a small increase in the number of patients who respond to the treatment but it exposes the users to allergic reactions that can be severe, as well as to risks of cancer and infections that are not well defined. Do not complicate the treatment adding belimumab. ***Medical Letter*** (USA). Small reduction in the activity of lupus, appears to decrease the consumption of corticosteroids. Has not been studied in patients with renal problems linked to lupus or with severe problems in the central nervous system. ***Info från Läkemedelsverket*** (Sweden). Severe adverse drug reactions. The long term consequences are unknown.
Bosutinib[47] Adults with Philadelphia chromosome–positive chronic myelogenous leukemia who no longer benefit from or tolerate other treatment.	***Revue Prescrire***. Could offer some benefits but in exchange for serious adverse events. Uncertain risk-benefit ratio. Best to use it only for research until side effects are better known.
Crizotinib[48] To treat lung cancer, non-small cell carcinoma, after other chemotherapies have failed.	***Revue Prescrire***. The benefit-risk ratio is uncertain. Probably an extra 8 months of life. However, the claim is made on radiology findings and there is no information on global survival. Need to have more studies. ***Medical Letter*** (USA). Has prolonged life in 4-5% of lung cancer patients. The effect on overall survival is unknown. ***Arzneimittelkommission der deutschen Ärzteschaft*** (Germany). Side effects are poorly evaluated. Need information on patients with liver or renal failure and older patients. Efficacy and safety evaluations are incomplete. Current information is encouraging, but comparative trials with palliative and other treatments have not been completed.

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Table 9. Continued.

New molecular entity and indication	Assessment by independent drug bulletins
Elvitegravir, cobicistat, emtricitabine, tenofovir, (Stribild)[49] Treatment of HIV in adults who have never taken HIV medicines before.	***Revue Prescrire***. In the adult population, not better than other available combined-treatments in terms of convenience of administration, effectiveness or adverse events. ***Medical Letter*** (USA). Can be useful in people who are HIV positive but have never received treatment. Cannot be used in patients with renal failure, has multiple drug interactions. ***Der Arzneimittelbrief*** (Germany). Can be an alternative. Need to know more about adverse events.
Enzalutamide[50] Treatment of patients with castration-refractory prostate cancer.	***Revue Prescrire***. Similar to abitaterone. Can be useful if the patient cannot be treated with abiraterone (patients with cardiac or liver problems). Be mindful of drug interactions and seizures. ***Medical Letter*** (USA). Second hormonal treatment that can increase survival on patients treated with docetaxel. No head-to-head studies comparing with abiraterone. ***Der Arzneimittelbrief*** (Germany). Proven to increase survival by 4.8 months when compared with placebo. Need to pay attention to adverse effects and drug interactions.
Indacaterol maleate 75 µg[51] Long term maintenance of airflow obstruction in chronic obstructive pulmonary disease.	***Worst Pills, Best Pills***. Do not use. The FDA should have not approved the 75 µg dosage form, lower dosage had same effects. No advantages over other bronchodilators, does not deserve approval.
Ipilimumab[52] Treatment of patients with late-stage (metastatic) melanoma.	***Revue Prescrire***. Need more studies to evaluate benefit-risk ratio. A clinical trial with a questionable design showed an increase in overall survival, but there are serious adverse reactions which can compromise the quality of life. ***Medical Letter*** (USA). Capable of increasing life expectancy in patients with melanoma that cannot be surgically removed or has metastasized. Serious side effects. ***Australian Prescriber*** (Australia). More studies need to be done because patients with brain metastasis have been excluded from the studies. ***Arznei-Telegramm*** (Germany). In comparison with an experimental vaccine, ipilimumab increases life expectancy by a few months. The benefits are uncertain. Twenty percent of the patients suffer serious adverse events, and 3.1% of the patients die. Too expensive, more than €100.000. We do not recommend its use.
Linagliptin[53] An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	***Revue Prescrire***. No evidence of proven efficacy on diabetes complications. Not more effective than other gliptines. Adverse effects are severe, not worth using it. ***Medical Letter*** (USA). The long term effects are unknown. ***Australian Prescriber*** (Australia). Adverse events: muscle-skeletal problems, high blood pressure, headaches, high level of triglycerides and uric acid, allergies and pancreatitis. ***Pharma Selecta*** (Netherlands). More studies are needed. ***Institut for rationel farmakoterapi*** (Denmark). None of the clinical trials has compared linagliptin with other treatments of the same group. Few patients 75 years of age and over. ***Worst Pills, Best Pills***. Do not use.[54]
Pasireotide[55] Treatment of Cushing's disease patients who cannot be helped through surgery.	***Revue Prescrire***. Possibly effective in 25% of the patients, but has many adverse effects, some of which are severe (hyperglycemia, gallbladder stones, diarrhea, nausea, prolongation of QT, bradycardia, hypothyroidism, low levels of cortisone etc.). Only when there is no other treatment and the surgery has failed. ***Info från Läkemedelsverket*** (Sweden). Only for those who cannot or do not want to have surgery, or when surgery has been insufficient. Good responders are easy to identify (during the second month of treatment) and for the non-respondents the treatment should be interrupted.
Perampanel[56] Adjunctive treatment of partial-onset seizures in epileptics aged >11 years.	***Revue Prescrire***. No demonstrated added value. Adverse effects need to be better documented (cardiac toxicity, impact on growth).

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Table 9. Continued.

New molecular entity and indication	Assessment by independent drug bulletins
Pertuzumab[57] Treatment of patients with human epidermal growth factor receptor 2-positive late-stage (metastatic) breast cancer.	***Revue Prescrire***. The benefit-risk ratio is not well-known. Increases global survival of women with metastasis of breast cancer or with local recidivated cancer. Pertuzumab is added to trastuzumab+docetaxel; and it increases side effects. It should only be used in clinical trials. ***Australian Prescriber*** (Australia). Appears to increase survival without worsening (progression) the condition of HER-2 positive women with metastasis of breast cancer. ***Medical Letter*** (USA). Same as *Australian Prescriber* but adds that the effect on overall survival has not been determined. ***Der Arzneimittelbrief*** (Germany). Adds 6.1 months of progression-free survival compared to placebo. Women participating in the trial were not representative of patients with this health problem. Considers that there is insufficient information to recommend its commercialization. ***Arzneimittelkommission der deutschen Ärzteschaft*** (Germany). Serious adverse effects more frequent in women treated (35.6%) than in placebo group (28%). The women studied are different than the typical patient population. Therefore the benefits are uncertain, especially in older women, with a more serious disease or previously treated. ***Info från Läkemedelsverket*** (Sweden). More adverse events, women with cardiac risks not included in the study.
Regorafenib[58] Treatment of patients with colorectal cancer that has progressed after treatment and spread to other parts of the body.	***Revue Prescrire***. Appears to increase overall survival by several weeks (6.4 months with regorafenib, 5 months with placebo) in certain types of patients with metastatic colon cancer, in good condition, after several treatments. Many adverse events (40% of the patients), some of them serious, even deadly. Need more studies. Until then symptomatic treatment. ***Medical Letter*** (USA). Can improve free-progression survival in patients with metastasis of colon cancer or of local cancer that has already been treated. Adverse events in 50% of the patients.
Rilpivirine[59] Treatment of HIV-1 infection in adults who have never taken HIV therapy.	***Revue Prescrire***. Not more effective than efarivenz. Rilpivirine causes more crossed resistances and it does not have less adverse events. Stay with efavirenz. ***Medical Letter*** (USA). Appears to be as effective as efarivenz in HIV positives not treated with antirretrovirals and could have less adverse effects. But the development of resistance and virus failures is more frequent with rilpivirine. The development of resistance to rilpivirine could lead to crossed resistances with other products. ***Der Arzneimittelbrief*** (Germany). An option with less side effects, but need to know more about resistance. ***Info från Läkemedelsverket*** (Sweden). The development of resistance occurs more frequently with rilvipirine than with other antiretrovirals. The development of resistance to rilpivirine could lead to crossed resistances with other products.
Rivaroxaban[60] To reduce the risk of blood clots, deep vein thrombosis, and pulmonary embolism after knee or hip replacement.	***Revue Prescrire***. Not better than enoxaparine. ***Worst Pills, Best Pills***. We recommended that patients do not use rivaroxaban for seven years after its approval date. It does not represent a clear therapeutic breakthrough over the existing drug, warfarin (Coumadin, Jantoven, Athrombin).[42]

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Table 9. Continued.

New molecular entity and indication	Assessment by independent drug bulletins
Roflumilast[61] To decrease the frequency of flare-ups (exacerbations) or worsening of symptoms from severe chronic obstructive pulmonary disease (COPD).	***Revue Prescrire***. Better not to use it. Serious adverse events. ***Medical Letter*** (USA). Offers some advantages, but due to side effects it is best to limit its use for people who do not respond to other treatments. ***Agence canadienne des medicaments et des technologies de la santé*** (Canada). Minimum clinical improvements and too many side effects. Clinical trial data invalidated due to deviations of protocol and lack of data on important aspects of how patients evaluate the treatment. ***Arznei-Telegramm*** (Germany). Too many side effects. Recommend not to use it. ***Arzneimittelkommission der deutschen Ärzteschaft*** (Germany). Efficacy has not been evaluated against reference treatments. ***Pharma Selecta*** (Netherlands). No information on long-term effects. Too many adverse events. Limited role on patients with severe COPD. ***Navarra Salud*** (Spain). Doubtful efficacy. Adverse events worrisome. Do not use. ***Dialogo Sui Farmaci*** (Italy). Moderate efficacy, insufficient information about safety profile. Do not use. ***Gebu*** (Netherlands). Efficacy and safety insufficiently documented. Do not use. ***Institut for rationel farmakoterapi*** (Denmark). It has not been studied in comparison to standard treatment.
Telaprevir[62] Certain adults with chronic hepatitis C.	***Revue Prescrire***. Might be indicated in certain patients, after they have tried boceprevir, longer studies are necessary with close monitoring of adverse events.
Teriflunomide[63,64] Multiple sclerosis.	***Revue Prescrire***. Leflunomide was authorized in 1999. Teriflunomide is the main metabolite of leflunomide and its adverse effects should be the same. No demonstrated effect in improving or delaying the evolution of the problems. Better not to use it, and use interferon-beta. ***Arznei-Telegramm*** (Germany). No advantage. ***Pharma Selecta*** (Netherlands). Easy administration (oral). Adverse events. Little experience in multiple sclerosis (good experience in rheumatoid arthritis). ***Info från Läkemedelsverket*** (Sweden). Do not use in multiple sclerosis. ***Drugs and Therapeutics Bulletin*** (United Kingdom). Not better than other treatments. ***Australian Prescriber*** (Australia). Not all patients benefit and the majority suffer adverse events. Benefits are modest and need to be balanced with side-effects.
Ticagrelor[65] To reduce cardiovascular death and heart attack in patients with acute coronary syndromes (ACS).	***Revue Prescrire.*** Has not decreased mortality compared to clopidrogel. Has more adverse events. It is better to use clopidrogel associated with aspirin or just copidrogel. ***Arznei-Telegramm*** (Germany). Could be better than clopidrogel but seven times more expensive. ***Arzneimittelkommission der deutschen Ärzteschaft*** (Germany). Better for some patients, worse for others. In general not better than clopidrogel. ***Der Arzneimittelbrief*** (Germany). Risk-benefit ratio insufficiently evaluated. ***Info från Läkemedelsverket*** (Sweden). Do not use for more than one year because the therapeutic experience is so far limited. ***Institut for rationel farmakoterapi*** (Denmark). May have better outcomes, serious side effects.
Vandetanib[66] Late-stage medullary thyroid cancer in adults, ineligible for surgery whose disease is growing or causing symptoms.	***Revue Prescrire***. No proven impact on survival in patients with metastatic or inoperable medullary thyroid cancer. Serious adverse events. More dangerous than beneficial.

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Table 9. Continued.

New molecular entity and indication	Assessment by independent drug bulletins
Ziv-aflibercept[67] Colon cancer with metastasis.	***Revue Prescrire***. Aflibercept does not offer advantages over bevacizumab. Both products might add a few weeks and have very serious side effects (including death). Better not to use it.
	Medical Letter (USA). Serious adverse events, but most of them are also present in patients treated with bevacizumab.
	Arzneimittelkommission der deutschen Ärzteschaft (Germany). Combined with FOLFIRI it has been associated with a moderate increase in survival than placebo, but it has shown more side effects. Risk-benefit ration unclear.
	Info från Läkemedelsverket (Sweden). Severe adverse events.

Source: Homedes and Ugalde;[9] Prescrire;[39,40,41] Public Citizen;[42] Prescrire;[43,44,45,46,47,48,49,50] Public Citizen;[51] Prescrire;[52,53] Public Citizen;[54] Prescrire.[55,56,57,58,59,60,61,62,63,64,65,66,67]

Note: Neither Prescrire nor the Health Research Group of Public Citizen had evaluated azilsartan medoxonil, taliglucerasa alfa, tofacitinib, cabozantinib, ezogabine, lucinactant or tbo-filgastrim.

Table 10. Efficacy of oncological treatments approved by the US Food and Drug Administration in 2011 and 2012 and tested in countries of Latin America.

NME	Indication	Gain in months		Would have met ASCO criteria
		Progression-free survival (months)	Overall survival (months)	
Ipilimumab	First line treatment of melanoma.	0	2.1	Uncertain
Vandetanib	Advanced medullary thyroid carcinoma.	11.1*	NIO	Yes
Pertuzumab	Human epidermal growth factor receptor 2-positive breast cancer.	6.1	NIO	Yes
Ziv-aflibercept	Second line metastatic colorrectal cancer with FOLFIRI.	2.2	1.4	No
Enzalutamide	Second line treatment, castration-refractory prostate cancer.	NIO	4.8	Yes
Regorafenib	Metastatic colorectal cancer.	0.3	1.4	No
Carbozantinib	Advanced medullary thyroid carcinoma.	7.2	NIO	Yes
Crizotinib	Non-small cell lung cancer expressing *anaplastic lymphoma kinase* (ALK) gene	4.7	NIO	Yes

Source: Own elaboration using information from Fojo *et al*.[37]

*Estimated. NIO = No information obtained. ASCO = American Society of Clinical Oncology.

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US$100,000 (vandetanib) per treatment in Brazil and US$200,000 in Argentina (vandetanib), these NMEs are not affordable.

DISCUSSION

The pharmaceutical industry claims that the implementation of clinical trials in Latin America strengthens research capacity in biomedical science and transfers highly desirable foreign exchange to the region.[68] However, there are also negative consequences for the financial sustainability and safety of the pharmaceutical market and for the wellbeing of research participants.

Financial sustainability and safety of pharmaceutical market

There seems to be little communication between the research and development units of the pharmaceutical companies 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 expedited approval of protocols, large urban centers with quality hospitals, and an abundance of easy-to-recruit patients.[4] On the other hand, 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 public health care 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 regulatory agencies do not deny market authorizations when the product has already been commercialized in high surveillance countries. The fact that the FDA and the European Medicines Agency [69,70,71,72,73,74,75,76,77] tend to approve NMEs without ensuring that they are more effective and/or safer than existing treatments[78] results in the presence of the same products in Latin America, regardless of how they affect the financial sustainability and safety of the corresponding markets. Moreover, Brazil's ethical guidelines require that all drugs tested in the country be registered when found to be safe and effective. Resolution 446 of 2012 of the regulatory agency (ANVISA) reads: "When developing new drugs, if safety and effectiveness is proven, its registration is obligatory in Brazil."[79] However, it appears that ANVISA is not enforcing the regulation.

As shown, the price of marketed products was unaffordable for the large majority of the Latin American population. By definition, unaffordability implies that a person or household cannot redistribute resources to obtain the product. This is also becoming a problem for high-income countries. Physicians and health authorities in the United States and the United Kingdom are reluctant to prescribe and pay expensive medications offering little advantage over existing cheaper alternatives with better-known safety and efficacy profiles.[80,81,82,83]

Medicine prices are unrelated to product development costs[84,85] and our data indicate that pharmaceutical manufacturers are not abiding by WHO's recommendations to set prices according to countries' wealth or tiered pricing.[86] We have not identified any articles discussing the large price differentials among neighboring Latin American countries. Why the same drug represents a higher financial burden for Argentines than Brazilians, Mexicans or other Latin Americans needs to be better understood. Exploring these differences will require a detailed analysis of all the drug pricing components in each country, including the manufacturer's sale price, transportation costs, importation tariffs, the margin of benefits for distributors and dispensers, sales taxes and others. This analysis might demonstrate that governments can adopt policies to increase the affordability of NMEs, but it is also likely to show large differences in the manufacturer's sale price, which tends to be based on the industries' assessment of what each country is willing to pay. More collaboration among pharmaceutical policy makers and

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procurement experts across Latin American countries could lead to improved pricing structures for the region.

The judicialization process described in the introduction may encourage the pharmaceutical industry to maintain high prices with the aggravated consequence of exposing patients to NMEs that, according to independent drug bulletins, should not be used. Latin American patients and patients' groups—often financially supported by the innovative pharmaceutical companies—sue the governments[87,88,89,90,91] to gain access to the newest treatments, including those that have not been included in national formularies.[92,93,94] Judges tend to base their decisions on individual needs instead of societal priorities; if this trend continues, health care systems will be severely strained and many could go bankrupt.[95,96,97,98,99,100] Without denying the difficulties, it would be useful to assess the NME affordability threshold for the public health sector. Our hypothesis is that most of the NMEs discussed in this paper are not affordable for the ministries of health or the central governments.

The wellbeing of research participants

If the 26 products included in our study for which we obtained efficacy and safety information from independent sources are a sample representative of the NMEs tested in Latin America, we need to conclude that the current research and development models of NMEs are faulty. Two questions need to be pondered: 1) Did ethics committees appropriately protect human research participants, considering that to consciously expose research participants to unnecessary risks would translate into a violation of the ethical principle of beneficence?; and 2) Did the clinical trials have to be conducted in the vulnerable populations of Latin America who, given current prices, are unlikely to benefit from the discoveries?

The fact that a large number of NMEs failed to add therapeutic value to existing treatments leads us to conclude that the patients enrolled in the experimental arm of the clinical trial were in fact worst off than if they had not participated in the study and received the standard treatment. Similarly, the patients included in the control arm, except those who received the best available treatment, were also incurring unnecessary risks, especially if they were enrolled in a placebo-controlled or non-inferiority trial. Some of these risks could potentially have been avoided if research sponsors, regulatory agencies and ethics committees had conducted a more in-depth analysis of the results of pre-clinical studies and of earlier phases of the clinical trials[101,102] and if the NMEs were always tested against the best available treatment.

According to article 20 of the Helsinki Declaration, vulnerable populations should not be enrolled in clinical trials when the products can be tested in non-vulnerable populations.[103] Latin American trial subjects tend to be of low socioeconomic status, are often medically illiterate, and according to some authors should be considered vulnerable.[104,105,106] All products included in this study, except bedaquiline, which is used in the treatment of multidrug-resistant tuberculosis, could have been tested in non-vulnerable populations.

Another ill consequence of conducting clinical trials sponsored by industry that needs to be further explored is how they displace research that would be more relevant for the region. The rewards offered to principal investigators, including but not limited to payments, lure some of them away from developing other products needed in the region, such as treatments for dengue, malaria and leishmaniasis or from the increasingly urgent need of developing biological generics that could save lives and dollars.[107,108]

Complying with ethical and regulatory premises

In a broken research and development system with many unnecessary clinical trials that do not result in better therapies and

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render the NMEs unaffordable for the private and public sectors, some ethical, judicial and regulatory conditions designed to protect the population have ironically had the opposite effect. Allowing the exploitation of vulnerable populations also has negative consequences for the sustainability and safety of the pharmaceutical markets.

Most ethical guidelines such as those of Council for International Organizations of Medical Sciences (CIOMS),[6] the Universal Declaration on Bioethics and Human Rights,[109] or the Declaration of Helsinki[103] assert that post trial access to treatment should be ensured. According to Guideline 10 of the CIOMS, which refers to "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.[6]

The document also includes commentaries regarding the guidelines. Some of the most crucial aspects of the contents of the commentary on Guideline 10 are as follows:

> [...] 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.*[6] [italics added]

Similarly, article 15 of the Universal Declaration on Bioethics and Human Rights, regarding the "Sharing of benefits" of clinical trials, states that the "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."[109] Principle 22 of the Declaration of Helsinki highlights that "in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."[103]

Nevertheless, in contrast with the commentary of Guideline 10 of the CIOMS, neither the sponsors of the clinical trials, or the regulatory agencies, or any of the bodies that approved ethical declarations regarding clinical trials have suggested pre-trial mechanisms to ensure that NMEs will be made available at affordable prices. Without such mechanisms, Latin American Research Ethics Committees and regulatory agencies approve the implementation of many clinical trials that should not be authorized, facilitating the violation of the justice principle and the exploitation of trial participants.

In January 2014, a new Consensus Framework for Ethical Collaboration between Patients' Organizations, Health Care

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Professionals and the Pharmaceutical Industry was published, the third point of which states:

> Clinical Research. 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...[110]

If the industry wants to be congruent with its own consensus framework, and with universally accepted ethical principles[6,103,109] it will have to:

- Include in clinical trial protocols the projected price of the potential NME so that the regulatory agencies and research ethics committees can take into consideration the affordability of the NME before authorizing the research.
- Establish a mechanism to guarantee the registration and availability of the new NMEs that prove to be safe and effective, in coordination with the regulatory agencies of the countries where the NMEs are tested.
- Reconsider their research and commercial strategies to ensure that NMEs add therapeutic value to the existing therapeutic arsenal at an affordable price.
- Discontinue sponsorship non-inferiority clinical trials, unless they are strictly necessary.

Until these conditions are met, it might be better to forego compliance with the requirement that NMEs be made available in the countries where tested. Similarly, given the proclivity of reputable regulatory agencies to approve NMEs that according to independent pharmacology experts should not be approved, Latin American regulatory agencies might want to consider delinking their market authorization decisions from those made by the regulatory agencies of high sanitary surveillance countries and instead use the information provided independent drug bulletins. Given the dearth of true innovation, delaying the approval of NMEs until independent assessments are available will not be detrimental for the Latin American residents. Exceptions could be made for true breakthrough NMEs.

Limitations

Some FDA reviews of NMEs 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. We were unable to avoid the limitations for determining the affordability thresholds that other researchers had previously encountered. What humans are willing to sacrifice and the risks they are ready to confront cannot be easily defined by others; it is a personal decision that is heavily influenced by personal values and culture.

To determine the price of drugs continues to be complex, and currently there is no gold-standard methodology. At this point, despite their shortcomings, the country observatories are probably the best and most reliable source of information, which tends to be based on variations of the WHO-HAI methodology. Currency variations add to the complexity of reporting pricing information across countries. We priced the drugs in September of 2014, but the data used to determine the MIPC is from 2013. During this time differential, some currencies depreciated while others appreciated.

Moreover, in the Latin American countries included in this study, income is very poorly distributed (Table 3). If we were to remove the highest two income deciles, the income per capita for the rest of the population would be drastically reduced, in most countries halved, and therefore the affordability threshold would have to be lowered.

The information on registration and commercialization status of NMEs may contain inaccuracies. Using triangulation methods we identified and corrected some errors, but others may not have been detected.

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CONCLUSIONS

This is the first study that questions the health benefits of the clinical trials implemented in Latin America not only for trial subjects but for the health systems and residents of those countries.

Many of the products tested are unavailable and/or unaffordable to the large majority of Latin Americans, and only a few proved to be more efficacious for a select group of patients but with significant side effects. The balance between the benefits and the negative economic and health consequences of conducting clinical trials in Latin America lead us to suggest that the number of trials should be drastically reduced.

The current drug research and development model is very questionable, and perhaps until the model is improved clinical trials should only be carried out in the countries where the corporations are headquartered. We conclude that:

1. There is an urgent need to determine the public sector affordability of NMEs. Since the pricing of NMEs is unrelated to research and development and production costs, the industry has wide pricing margins.
2. The risk of having to register and commercialize very expensive products, endangering the budget of the ministries of health without improving the health of the patients is a reason to reduce the implementation of clinical trials in Latin America.
3. There is a need to strengthen ethics committees so that in their evaluation of clinical trials they can pay significant attention to the affordability and pertinence of the NME.
4. The products included in this study did not respond to the most pressing therapeutic needs of the region, and they may divert scientific resources from addressing issues of higher relevance. While governments more than welcome the investments that accompany foreign trials, it is important to document their opportunity costs.
5. The Latin American regulatory agencies should use the information provided by independent pharmaceutical experts and bulletins when they evaluate the request to market NMEs. Exceptions could be made for the few true breakthrough NMEs.
6. It is important to uncover the reasons for drug price differentials across the different countries of the region.

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ENDNOTES

[a] Pivotal clinical trials are those included in the applications for market authorization or New Drug Approval (NDA) documents that are submitted to the regulatory agencies.

[b] This article is based on the original version of an article that was divided in two and published by the same authors in the *Bulletin of the World Health Organization*[8] and in *PLoS One*.[9] The reasons for the division of the original article are explained in *Accountability in Research. Policies and Quality Assurance*.[10]

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