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Therapeutic value and price of the new pharmaceuticals commercialized in Argentina: Are they worth what they cost?

Valor terapéutico y precio de los nuevos fármacos comercializados en Argentina: ¿valen lo que cuestan?

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ABSTRACT In Argentina, new drugs can be authorized by presenting the drug's certificate of approval in at least one of 15 countries considered to have rigorous health surveillance, without needing to carry out a local evaluation of the efficacy, safety or added therapeutic value of the new product. In this article, we evaluate the new drugs commercialized in Argentina in 2016 using different approaches: their approval by other regulatory agencies, the demonstration of their efficacy in randomized clinical trials, types of outcomes studied, rating of their added therapeutic value using two widely recognized scales, and their sale price to the public. It is concluded that, as a reflection of what occurs in developed countries, new drugs enter the market at exorbitant prices, but the majority do not represent a significant therapeutic advancements. The result is increased risks to patients and an overburdening of the public and private funding systems.
KEY WORDS Drug Approval; Drug Evaluation; Drug Costs; Argentina.

RESUMEN En Argentina, los nuevos medicamentos pueden ser autorizados presentando el certificado de aprobación en al menos uno de los 15 países considerados de alta vigilancia sanitaria, sin necesidad de realizar una evaluación propia de eficacia, seguridad o valor terapéutico agregado por el nuevo producto. En este artículo, evaluamos los nuevos medicamentos comercializados en Argentina en el año 2016, utilizando diferentes enfoques: su aprobación por otras agencias reguladoras, demostración de eficacia en ensayos clínicos aleatorizados, tipo de desenlaces estudiados, calificación del valor terapéutico agregado por medio de dos escalas reconocidas y el precio de venta al público. Se concluye que, como reflejo de lo que ocurre en los países desarrollados, los nuevos medicamentos ingresan con precios exorbitantes, pero la mayoría no representa un avance terapéutico significativo. El resultado es un aumento de riesgos para los pacientes y una sobrecarga para los sistemas de financiación públicos y privados.
PALABRAS CLAVES Aprobación de Drogas; Evaluación de Medicamentos; Costos de los Medicamentos; Argentina.

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INTRODUCTION

Every year, a huge number of new pharmaceutical products are incorporated into the market, including new formulations, new combinations or new active ingredients. A general belief exists, even among health professionals, that all new drugs offer therapeutic innovation and better results in health, and therefore strategies that accelerate and optimize patient access to these drugs are desirable.

The evaluation process of regulatory agencies generally centers on each individual drug, the efficacy and safety of which must be proven in phase III controlled clinical trials, often in comparison with a placebo. In this way, when a drug enters into the market, we know little about it in comparison with already existing products.

From a public health perspective, the value of a new drug lies in the therapeutic gain and the benefits to health for patients and for society as a whole. Diverse studies that have evaluated the clinical relevance of new drugs that have entered the market all show that the large majority do not offer any additional therapeutic benefit. According to the health authority of Canada, only 6% of the 1,147 new drugs approved between 1990 and 2003 offered substantial therapeutic advantage.[1] Additionally, an evaluation by the National Institute for Health Care Management in the US concluded that just under 15% of the 1,035 drugs approved by the Food and Drug Administration (FDA) between 1989 and 2000 were considered truly innovative.[2] Analyzing the pharmaceuticals introduced in Brazil between 2003 and 2013, it was found that only 17.6% represented an "important therapeutic innovation."[3] The reviews from 2007 to 2016 of the journal *Prescrire* regarding 992 new pharmaceuticals or new uses classified only 23.3% (n = 231) in one of the four categories describing some sort of benefit.[4]Ward *et al*., using a broader take on pharmaceutical innovation, found that of the 290 drugs incorporated in the 2001-2012 period in the British National Formulary, only 26% were very innovative and 19% moderately innovative.[5] In Australia, 32% (n = 19) of the 59 new drugs approved between 2005 and 2007 were evaluated as having added therapeutic value.[6] Analyzing 122 new drugs authorized by the European Medicines Agency (EMA) between 1999 and 2005, van Lujin *et al*. found that only 10% (n = 13) were better than the existing drugs in terms of their effect on clinical endpoints.[7]

A good portion of these presumably new drugs are, in fact, reformulations of others whose patent is about to expire, or molecules similar to others in use that contribute little or nothing in comparison to the existing alternatives, reason for which they have come to be called "me too" drugs.

In Argentina, new drugs – that is, drugs that were never commercialized in the country – can be approved in two ways, according to Decree 150/1992.[8] The first, and most frequent, is if the drugs have already been commercialized in at least one of the 15 countries with high-level health surveillance listed in Annex 1 of the Decree (Germany, Austria, Belgium, Canada, Helvetic Republic, Denmark, Spain, the United States, France, Italy, Israel, Japan, Netherlands, United Kingdom and Sweden), in which case it is only necessary to present the certificate of approval from those countries to the regulatory agency. In the second case, if the drug has not been previously commercialized in Argentina or in the high-level surveillance countries, the maker must offer all relevant efficacy and safety data for a full evaluation by Argentina's National Administration of Drugs, Food and Medical Technology [*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*] (ANMAT).

In practice, this means that for almost the entire drug market in Argentina, the evaluation of efficacy and safety was carried out by another national agency and accepted as valid by the Argentine authorities.

Although no complete agreement or international standard exists, a number of classification systems have been developed

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to categorize the value of new drugs. These systems primarily seek to permit health professionals and the public access to information regarding the therapeutic value added by the new drugs in relation to the previously available options.[9,10,11,12]

A study that evaluated whether or not the drugs commercialized in the USA were registered, commercialized and sold at accessible prices in the Latin American countries where they were tested found great price variation among them, with Argentina being the country where the absolute prices were highest for the drugs evaluated.[13]

The objective of this study is to evaluate the therapeutic value of the new drugs approved by ANMAT during the year 2016 and estimate the monthly cost of treatment.

METHODS

We identified the drugs approved by ANMAT for commercialization in Argentina during the year 2016, consulting the new medicines approved for use with or without prescription published monthly on ANMAT's website.[14] When a single active ingredient had two dosage forms, they were analyzed separately. The following products were excluded from the study: drugs used for diagnosis, including radiological contrasts; hydroelectrolitic, nutritional and irrigation solutions; products related to hemodialysis; and vaccines and immunoglobulins.

According to the composition, each medicine was classified as a monodrug or a fixed-dose combination drug. The corresponding World Health Organization's Anatomical Therapeutic Chemical (ATC) code was assigned, as indicated in the label authorized by ANMAT or utilizing the WHO Collaborative Centre for Drug Statistics Methodology database, in accordance with the established instructions.[15]

We classified each drug authorized in 2016 as previously commercialized in Argentina if there was at least one product with the same active ingredients and route of administration in the commercial pharmaceutical catalog in January 2016,[16] and as a new drug (ND) in the remaining cases. These NDs correspond to new active ingredients, new combinations of active ingredients, or a new route of administration for an already existing active ingredient. The different packaging of drugs with the same active ingredients and routes of administration were considered to be a single ND in this analysis. We identified the indications for each ND according to the label authorized by ANMAT.

To evaluate the therapeutic value of the NDs four different approaches were used: the approval by other regulatory agencies, the demonstration of their efficacy in randomized clinical trials and types of endpoints studied, the rating provided by the journal *Prescrire* and the application of the therapeutic value scale developed by Ahlqvist-Rastad *et al*.

It was established whether or not the NDs were authorized by the FDA,[17] and the date of approval, the priority assigned to the drug[18] and the state of the drug as treatment for "neglected" or "orphan" diseases were noted. A drug review is "priority" for the FDA when the preliminary review indicates that the drug treats a serious or life-threatening condition and, if approved, would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening condition compared to available therapies; the review is "standard" in all other cases. If was also established whether the drug was approved by the EMA,[19] which regulates the commercialization of new drugs in the European Union. When the ND were not approved by the FDA nor by the EMA, it was established whether they were authorized by the other countries included in the Decree 150/92[8] or whether the ANMAT had performed an independent evaluation. In the latter case, the corresponding ANMAT file was consulted to identify the evaluation criteria utilized.

In the second phase, randomized clinical trials showing the efficacy of the ND were

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identified, based on those described in the labels authorized by the FDA and/or ANMAT; if none were described, a search was carried out in PubMed using the name of the active ingredient and the filter for type of article set to "*randomized controlled trial*." It was considered that a ND has demonstrated efficacy in four situations: 1) when at least one randomized clinical trial shows efficacy for the indication authorized by ANMAT; 2) in the combinations of drugs, if at least one randomized clinical trial shows the efficacy of the coadministered individual components and the bioequivalence of the combination is shown; 3) for new formulations of a drug, when the efficacy of the previous formulation is demonstrated by randomized clinical trials and the bioequivalence of the new formulation is demonstrated; and 4) "drugs with obvious efficacy," defined as those that, even without randomized clinical trials for efficacy, are considered to have high intrinsic value due to their immediate and obvious benefits in uncontrolled studies.[20] It was noted if the efficacy had been demonstrated for clinically relevant variables, validated surrogate variables – those for which there is strong evidence that modification predicts a specific clinical benefit – or only for other surrogate variables.[21,22,23,24,25]

In the third phase, the classification assigned to the new drug by the journal *Prescrire*, an independent French publication that evaluates the new authorized drugs to rate the degree of therapeutic progress, tangible to the patient, that a ND contributes for a concrete indication, positing the benefit/risk balance of the drug in relation to other available therapeutic alternatives.[10] When the drug has a number of indications, the *Prescrire* rating may be different for each of them. In such cases, the best rating among the indications authorized by the ANMAT were used.

Lastly, based on all the information obtained, two of the authors independently applied the therapeutic value evaluation scale developed by Ahlqvist-Rastad *et al.*, that emphasized the degree of novelty of the drug given the previously available options[9] (Table 1). The agreement among the observers was evaluated with Cohen's kappa coefficient and the discrepancies were resolved by consensus.

As none of the classifications utilized up to this point have considered the cost of the drugs, this aspect was incorporated utilizing the sales price to the public published in the commercial drug catalog *Kairos* at the time the drug appeared on the market, and was expressed in US dollars according to the exchange rate for that date. For medications for chronic use, a monthly treatment price was estimated using the daily dose defined by the WHO Collaborative Centre for Drug

Table 1. Classification system of Ahlqvist-Rastad *et al.*

Category		Subcategory	
A	Drugs for conditions with no currently available treatment	A1	Substantial benefit to patients
		A2	Modest therapeutic effect
B	Added therapeutic value: the effect for patients appears to be better than the available alternatives	B1	Greater efficacy
		B2	Greater safety
		B3	More convenient dosage
		B4	More convenient route of administration
C	Similar therapeutic value	C1	First drug in a new class
		C2	New drug in an already existing class
D	Inferior therapeutic value	D1	First drug in a new class
		D2	New drug in an already existing class
E	Uncertain therapeutic value: evaluation limited to surrogate endpoints		

Source: Own elaboration based on Ahlqvist-Rastad *et al.*[9]

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Statistics Methodology.[15] For those cases in which a daily dose was not established, the dosage recommended in the ANMAT-authorized label was utilized, and if this information was lacking, the dosage from the FDA label was utilized. For drugs used sporadically, the sales price of one packaged unit was recorded. For dantrolene, which is only commercialized for hospital use, the average number of vials needed per episode of malignant hyperthermia was calculated, according to the ANMAT-authorized label.

RESULTS

Between 01/01/2016 and 12/31/2016, the ANMAT authorized 825 drugs, of which 10% (n = 82) correspond to a ND. In 79 cases the approval was for a new active ingredient (or a new combination of active ingredients) and in the other three cases, for a new administration route for an active ingredient already in the market.

We excluded from the analysis products used for diagnosis (n = 2) and an irrigation solution (n = 1). After counting as a single drug the different packaging of new drugs (with the same active ingredients and administration routes), the list was reduced to 45 ND incorporated into the Argentine market in 2016. These are presented, along with the authorized indications, according to the ATC classification order (Table 2). All NDs were authorized as prescription drug products.

Almost a third of the NDs (31%, n = 14) were combinations of more than one active ingredient. The antineoplastic and immunomodulatory drugs were the therapeutic class with the greatest number of new drugs (33%, n = 15, including five monoclonal antibodies and six tyrosine kinase inhibitors), followed by antiinfective drugs (13%, n = 6) (Figure 1).

Table 2. New drugs authorized in Argentina in 2016 and their indications, organized according to the chapters of the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization.

New drug	Indications authorized by ANMAT	ATC code
A) Alimentary tract and metabolism		
Choline salicylate + Benzocaine	Alleviates inflammation and pain caused by ulcerations, wounds or irritation in the lining of the mouth.	A01AD11
Metformin hydrochloride + Dapagliflozin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.	A10BD15
Nitisinone	Hereditary type 1 tyrosinemia	A16AX04
B) Blood and blood-forming organs		
Epoprostenol	Pulmonary arterial hypertension. Anticoagulation in renal dialysis when heparin cannot be used.	B01AC09
Eltrombopag	Thrombocytopenia in adults and children over 6 years of age with chronic idiopathic thrombocytopenic purpura with insufficient response to corticosteroids, immunoglobulin or splenectomy / Thrombocytopenia in patients with chronic hepatitis C to allow treatment using interferon / Severe aplastic anemia that has had an insufficient response to immunosuppressive therapy.	B02BX05
C) Cardiovascular system		
Ambrisentan	Pulmonary hypertension, WHO Functional Class II and III.	C02KX02
Riociguat	Chronic thromboembolic pulmonary hypertension and Pulmonary arterial hypertension, functional class II or III.	C02KX05
Sacubitril + Valsartan	Chronic heart failure with reduced ejection fraction.	C09DX04
Rosuvastatina + Ezetimibe	Primary hypercholesterolemia (heterozygous familial and non-familial).	C10BA06

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ATC= Anatomical Therapeutic Chemical (Classification System); ANMAT= Administración Nacional de Medicamentos, Alimentos y Tecnología Médica.

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Table 2. Continued.

New drug	Indications authorized by ANMAT	ATC code
D) Dermatologicals		
Concentrate of proteolytic enzymes enriched in bromelain	Removal of eschar in adults with deep partial- and full-thickness burns.	D03BA03
Aciclovir + Hydrocortisone	Recurrent oral herpes.	D06BB53
Hydroquinone	Gradual bleaching of hyperpigmented skin.	D11AX11
G) Urologicals		
Hyaluronicacid (intravesical use)	Treatment of symptoms of interstitial cystitis, cystitis caused by recurrent infections, urolithiasis, urinary retention, neoplasia and cystitis induced by radiation.	G04BX
H) Systemic hormonal preparations, excluding sex hormones		
Carbetocin	Restoration of uterine tone and prevention of postpartum hemorrhage after an elective Cesarean section with spinal or epidural anesthesia.	H01BB03
J) General antiinfectives for systemic use		
Posaconazole (tablet, delayed release)	Prevention of invasive fungal infections cause by Aspergillus and Candida in immunocompromised patients. Treatment for infections by Aspergillus that do not improve with amphotericin B or itraconazole, or when these drugs must be suspended.	J02AC04
Posaconazole (parenteral)	Treatment of infections by Aspergillus, Fusarium, chromoblastomycosis, mycetoma, Coccidiodes, that have not responded to other treatments. Also for the prevention of mycosis in high-risk patients (acute myeloid leukemia, myelodysplastic syndrome, autologous bone marrow transplantation).	J02AC04
Emtricitabine +Tenofovir disoproxil fumarate + Rilpivirine	Complete regimen for the treatment of HIV-1 in adult patients without history of antiretroviral treatment and with HIV-1 RNA less than 100,000 copies/ml at the start of treatment and in certain adult patients with viral load suppression defined as RNA less than 50 copies/ml and a stable antiretroviral regimen at the start of treatment, to replace the current antiretroviral treatment.	J05AR08
Abacavir + Lamivudine + Dolutegravir	Adults and children over 12 years of age with HIV who weigh at least 40 kg. Before initiating treatment with drugs that contain abacavir, a detection for the allele HLA-B*5701 in all patients infected with HIV should be carried out, independent of race. Abacavir should not be used in patients with the gene variation HLA-B*5701.	J05AR13
Atazanavir + Cobicistat	HIV-1 in adults.	J05AR15
Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	Hepatitis C genotype 1, including those with compensated cirrhosis	J05AX66
L) Antineoplastic and immunmodulating agents		
Brentuximab vedotin	Relapsed or refractory Hodgkin's lymphoma / Relapsed or refractory systemic anaplastic large cell lymphoma.	L01XC12
Obinutuzumab	In combination with chlorambucil, for the treatment of adult patients with chronic lymphocytic leukemia that has not been previously treated, and with comorbidities for which the treatment with the full dosage of fludarabine is not appropriate.	L01XC15
Nivolumab	Unresectable and metastatic melanoma / Non-small cell lung cancer / Renal cell cancer / Hodgkin's lymphoma.	L01XC17
Pembrolizumab	Unresectable and metastatic melanoma.	L01XC18
Lapatinib	HER2 (ErbB2) overexpressed breast cancer: in combination with capecitabine for advanced or metastatic disease that has progressed after receiving previous treatment that includes anthracyclines and taxanes, and treatment with trastuzumab in metastatic disease / In combination with trastuzumab in patients with metastatic disease and negative hormone receptors that have progressed to previous therapies with trastuzumab in combination with chemotherapy / In combination with an aromatase inhibitor in postmenopausal women with metastatic disease and positive hormone receptors, for whom chemotherapy is not appropriate.	L01XE07
Trametinib	Melanoma with BRAF gene mutation, patients that have not received a BRAF inhibitor.	L01XE25
Ibrutinib	Mantle cell lymphoma / chronic lymphocytic leukemia / chronic lymphocytic leukemia with chromosome 17p deletion.	L01XE27
Nintedanib	Idiopathic pulmonary fibrosis.	L01XE31
Palbociclib	Advanced ER(+)/HER2(-) breast cancer post-menopause, associated with letrozole, as initial endocrine therapy for metastatic disease.	L01XE33
Olaparib	Monotherapy maintenance for relapsed high-grade serous ovarian cancer with BRCA mutation and platinum sensitivity in patients that are responding to platinum-based therapy	L01XX46

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Source: Own elaboration based on the indications approved by ANMAT.
ATC= Anatomical Therapeutic Chemical (Classification System); ANMAT= Administración Nacional de Medicamentos, Alimentos y Tecnología Médica.

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Table 2. Continued.

New drug	Indications authorized by ANMAT	ATC code
Venetoclax	Chronic lymphocytic leukemia with chromosome 17p deletion, patients that have received at least one prior therapy.	L01XX52
Mifamurtide	High-grade resectable non-metastatic osteosarcoma after a macroscopic complete surgical resection in children, adolescents and young adults.	L03AX15
Teriflunomide	Relapsing-remitting multiple sclerosis.	L04AA31
Ustekinumab	Moderate to severe plaque psoriasis / Active psoriatic arthritis.	L04AC05
Pomalidomide	Associated with dexamethasone, in adults with resistant or recurrent multiple myeloma, that have received at least two previous treatments, including lenalinomide and bortezomib, and that have experienced a progression in the disease in the last treatment.	L04AX06
M) Musculo-skeletal system		
Dantrolene sodium 3-1/2 hydrate	Malignant hyperthermia	M03CA01
Hyaluronic acid sodium salt + lidocaine hydrochloride	Symptomatic treatment of pain and articular function in knee arthrosis, shoulder periarthritis and other synovial joints.	M09AX01
N) Nervous system		
Doxepin	Primary insomnia, short-term treatment.	N06AA12
R) Respiratory system		
Olodaterol	Long-term maintenance treatment with daily administration in patients with Chronic Obstructive Pulmonary Disease (COPD).	R03AC19
Umeclidinium + Vilanterol	Bronchodilator maintenance treatment to alleviate COPD symptoms in adult patients.	R03AL03
Olodaterol + Tiotropium bromide	Long-term maintenance treatment with daily administration in patients with COPD.	R03AL06
Umeclidinium bromide	Bronchodilator maintenance treatment to alleviate COPD symptoms in adult patients.	R03BB07
S) Sensory organs		
Brimonidine + Brinzolamide	Open angle glaucoma or ocular hypertension in patients for which monotherapy produces an insufficient reduction in intraocular pressure.	S01EC54
V) Various		
Citrulline malate	Asthenia, once it has been ruled out as a secondary effect of an underlying disease, of any origin (physical or psychiatric).	V06DD
Radium 223 dichloride	Alpha particle-emitting radioactive therapeutic agent indicated for treatment of patients with prostate cancer that is resistant to castration with symptomatic metastasis to the bone and without known visceral metastatic disease.	V10XX03

Source: Own elaboration based on the indications approved by ANMAT.
ATC= Anatomical Therapeutic Chemical (Classification System); ANMAT= Administración Nacional de Medicamentos, Alimentos y Tecnología Médica.

Approval by other regulatory agencies

The majority of the NDs approved by ANMAT in 2016 had been previously authorized by the FDA (80%, n = 36) and the EMA (78%, n = 35). Of the six ND that were not authorized by either of these two agencies, four had approval in countries listed in the Annex I of Decree 150/92 (carbetocin, hydroquinone, rosuvastatin + ezetimibe, and citrulline malate) and the remaining two were evaluated directly by ANMAT (hyaluronic acid + lidocaine for intra-joint use and choline salicylate + benzocaine as a topical oral treatment). Of the 36 NDs approved by the FDA, 53% (n = 19)

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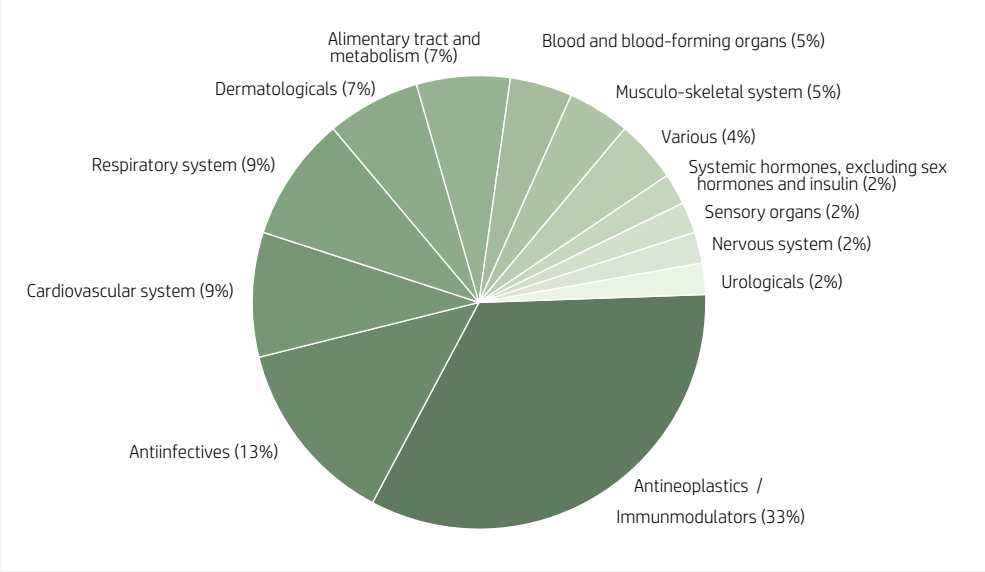

Figure 1. New drugs (n=45) approved in Argentina in 2016, according to the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization.

Source: Own elaboration based on the Anatomical Therapeutic Chemical (ATC) classification system.[15]

qualified for priority review and 42% (n = 15) were for orphan diseases.

Drugs evaluated directly by ANMAT

The criteria identified in the two original evaluations carried out by ANMAT were diverse. In the case of choline salicylate and benzocaine for topical oral treatment, the approval was based on the efficacy and safety of the individual components, without reference to studies that evaluated the fixed-dose combination.[26] Regarding hyaluronic acid and lidocaine for intra-joint use, it was framed as a new use of the previously approved hyaluronic acid, and not as a new drug.[27]

Proven efficacy in randomized controlled trials

For 62% of the ND (n = 28), randomized controlled trials were found that demonstrated efficacy; another 20% (n = 9) were new combinations or formulations of drugs that already had randomized clinical trials showing efficacy, in which case the bioequivalency was all that was demonstrated in order for the new preparation to be approved (Table 3).

Of the 18% of ND (n = 8) without randomized clinical trials for efficacy, 4% (n = 2) can be categorized as drugs "with obvious efficacy," that is, dantrolene for malignant hyperthermia and nitisinone in hereditary tyrosinemia. The remaining 13% (n = 6) did not have randomized clinical trials for efficacy; two of these, antineoplastic drugs, were evaluated in uncontrolled trials.

The second aspect to be evaluated was whether there was proven efficacy for clinically relevant endpoints or for surrogate endpoints (validated or not validated). Of the NDs, 44% (n = 20) showed efficacy in relevant endpoints; another 22% (n = 10) were effective in validated surrogate variables: forced expiratory volume in the first second (FEV1) for Chronic Obstructive Pulmonary Disease (EPOC), [28,29] undetectable viral load in HIV drugs,[22] sustained virologic response for hepatitis C, [30,31] reduction in low-density lipoproteins (LDL)

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Table 3. Evaluation of new drugs authorized in Argentina in 2016, according to existence of randomized clinical trials for efficacy, type of endpoint with demonstrated benefit, rating assigned by the journal *Prescrire* and the scale created by Ahlqvist-Rastad *et al.*

ATC code	New drug	Randomized controlled clinical trials for efficacy	Type of endpoint with demonstrated benefit	*Prescrire* Rating	Scale of Ahlqvist-Rastad *et al.*
A) Alimentary tract and metabolism					
A01AD11	Choline salicylate + Benzocaine	No	None	Not acceptable	E
A10BD15	Metformin hydrochloride + Dapagliflozin	Yes-FDC	Surrogate-NV	Not acceptable	D2
A16AX04	Nitisinone	Obvious efficacy	Relevant	Bravo	A1
B) Blood and blood-forming organs					
B01AC09	Epoprostenol	Yes	Relevant	Offers an advantage	C1
B02BX05	Eltrombopag	Yes	Relevant	Nothing new	C1
C) Cardiovascular system					
C02KX02	Ambrisentan	Yes	Surrogate-NV	Nothing new	C2
C02KX05	Riociguat	Yes	Surrogate-NV	Possibly helpful	C2
C09DX04	Sacubitril + Valsartan	Yes	Relevant	Possibly helpful	B1
C10BA06	Rosuvastatin + Ezetimibe	Yes-FDC	Surrogate-V	Not evaluated	C2
D) Dermatologicals					
D03BA03	Concentrate of proteolytic enzymes enriched in bromelain	Yes	Relevant	Not evaluated	B1
D06BB53	Aciclovir + Hydrocortisone	Yes	Relevant	Not acceptable	C2
D11AX11	Hydroquinone	Yes	Relevant	Not acceptable	D2
G) Urologicals					
G04BX	Hyaluronic acid (intravesical use)	No	No	Not evaluated	E
H) Systemic hormonal preparations, excluding sex hormones					
H01BB03	Carbetocin	Yes	Relevant	Nothing new	C2
J) Antiinfectives for systemic use					
J02AC04	Posaconazole (tablet, delayed release)	Yes-NF	Relevant	Possibly helpful	C2
J02AC04	Posaconazole (parenteral)	Yes-NF	Relevant	Possibly helpful	B4
J05AR08	Emtricitabine +Tenofovir disoproxil fumarate + Rilpivirine	Yes-FDC	Surrogate-V	Nothing new	C2
J05AR13	Abacavir + Lamivudine + Dolutegravir	Yes-FDC	Surrogate-V	Nothing new	C2
J05AR15	Atazanavir + Cobicistat	Yes-FDC	Surrogate-V	Nothing new	C2
J05AX66	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	Yes-FDC	Surrogate-V	Nothing new	C2
L) Antineoplastic and immunmodulating agents					
L01XC12	Brentuximab vedotin	Yes	Relevant	Judgment reserved	C1
L01XC15	Obinutuzumab	Yes	Relevant	Nothing new	C2
L01XC17	Nivolumab	Yes	Relevant	A real advance	B1
L01XC18	Pembrolizumab	Yes	Relevant	Nothing new	C2
L01XE07	Lapatinib	Yes	Surrogate-NV	Possibly helpful	C1

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Source: Own elaboration based on information from the evaluations of the journal *Prescrire*.[10]
ATC= Anatomical Therapeutic Chemical (Classification System); FDC= fixed-dose combination; NF= new formulation; NV= not validated; V= validated.
Note: See Methods section for details regarding the categories utilized and the assignment criteria.

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Table 3. Continued.

ATC code	New drug	Randomized controlled clinical trials for efficacy	Type of endpoint with demonstrated benefit	*Prescrire* Rating	Scale of Ahlqvist-Rastad *et al.*
L01XE25	Trametinib	Yes	Relevant	Offers an advantage	B1
L01XE27	Ibrutinib	Yes	Relevant	Judgment reserved	B1
L01XE31	Nintedanib	Yes	Surrogate-NV	Not acceptable	E
L01XE33	Palbociclib	Yes	Surrogate-NV	Not acceptable	E
L01XX46	Olaparib	No-Last line	Surrogate-NV	Not acceptable	E
L01XX52	Venetoclax	No-Last line	Surrogate-NV	Not evaluated	C1
L03AX15	Mifamurtide	Yes	Surrogate-NV	Inaceptable	E
L04AA31	Teriflunomide	Yes	Surrogate-NV	Inaceptable	D2
L04AC05	Ustekinumab	Yes	Relevant	Nothing new	C2
L04AX06	Pomalidomide	Yes	Relevant	Possibly helpful	B1
M) Musculo-skeletal system					
M03CA01	Dantrolene sodium 3-1/2 hydrate	Obvious efficacy	Relevant	Drug of choice*	A1
M09AX01	Hyaluronic acid sodium salt + lidocaine hydrochloride	No	No	Not acceptable	E
N) Nervous system					
N06AA12	Doxepin	Yes	Surrogate-NV	Not evaluated	D2
R) Respiratory system					
R03AC19	Olodaterol	Yes	Surrogate-V	Nothing new	C2
R03AL03	Umeclidinium + Vilanterol	Yes	Surrogate-V	Nothing new	C2
R03AL06	Olodaterol + Tiotropium bromide	Yes	Surrogate-V	Nothing new	C2
R03BB07	Umeclidinium bromide	Yes	Surrogate-V	Nothing new	C2
S) Sensory organs					
S01EC54	Brimonidine + Brinzolamide	Yes-FDC	Surrogate-V	Nothing new	C2
V) Various					
V06DD	Citrulline malate	No	No	Nothing new	E
V10XX03	Radium 223 dichloride	Yes	Relevant	Nothing new	B1

Source: Own elaboration based on information from the evaluations of the journal *Prescrire*.[10]
ATC= Anatomical Therapeutic Chemical (Classification System); FDC= fixed-dose combination; NF= new formulation; NV= not validated; V= validated.
Note: See Methods section for details regarding the categories utilized and the assignment criteria.
*Although not classified in *Prescrire*'s progressive therapeutic scale, the journal considers it to be a drug of choice for malignant hyperthermia.

in hyperlipidemia,[22] and intraocular pressure in glaucoma treatment.[23] Among the authorized NDs, 24% (n = 11) showed efficacy only in non-validated surrogate variables and 9% (n = 4) had no proof of efficacy. These results are described in Table 3 and summarized in Table 4.

Classification assigned by the journal Prescrire

Of the 45 ND authorized in 2016, 39 were evaluated in the journal *Prescrire*. More than 70% of these did not offer advantages: the category encompassing the greatest number of drugs was "nothing new" (41%, n = 16), with another 26% (n = 10) classified as "not

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Table 4. Existence of randomized clinical trials and types of endpoints evaluated for the new drugs approved in Argentina in 2016.

Are there RCT showing efficacy?	Proof of efficacy			No proof of efficacy	Total
	In relevant endpoints	In surrogate endpoints			
		Validated	Not validated		
Yes	16	4	8	-	28
Yes – Fixed-dose combination	-	6	1	-	7
Yes – New formulation	2	-	-	-	2
Drugs with obvious efficacy	2	-	-	-	2
No – Last-line oncological drugs	-	-	2	-	2
No	-	-	-	4	4
Total	20	10	11	4	45

Source: Own elaboration.
RCT=Randomized clinical trials.
Note: See detailed description of the categories in the Methods section.

acceptable" and 5% (n = 2) as "judgment reserved." Only 28% of the ND evaluated by *Prescrire* (n = 11) were classified in categories that represent a minimum advance with respect to the previous therapeutic options (Table 5).

Evaluation of therapeutic value

There was good interobserver agreement in assigning therapeutic value to the NDs (κ = 0,90). The evaluation, according to the scale of Ahlqvist-Rastad*et al*., shows that the majority of the ND (51%, n = 23) do not have added therapeutic value (category C), another 9% (n = 4) are considered inferior to the existing alternatives (category D) and 18% (n = 8) have uncertain therapeutic value (E). Only 22% (n = 10) of the ND represent some degree of added therapeutic value (categories A and B) (Figure 2 and Table 3).

Table 5. Evaluation of the journal *Prescrire* regarding the new drugs (n=39) approved in Argentina in 2016.

Category	Concept	Quantity	%
Bravo	A major therapeutic advance in an area where previously no treatment was available	1	2.6
Of choice[a]		1	2.6
A real advance	An important therapeutic advance but has certain limitations	1	2.6
Offers an advantage	The product has some value but does not fundamentally change the present therapeutic practice	2	5.1
Possibly helpful	The product has minimal additional value, and should not change prescribing habits except in rare circumstances	6	15.4
Nothing new	The product is a new substance but with no evidence that it has more clinical value that other substances of the same group	16	41.0
Not acceptable	Product without evident benefit but with potential or real disadvantages	10	25.6
Judgment reserved	Rating is postponed until better data and a more thorough evaluation of the drug are available	2	5.1

Source: Own elaboration using the categories assigned by the journal *Prescrire* to the new drugs, according to the journal's evaluation system.[10]
[a]This category was used for dantrolene in the treatment of malignant hyperthermia, which was not classified in the progressive therapeutic scale of the journal *Prescrire*, but the journal considers it a drug of choice for this indication.

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Sale price to the public of the new drugs

Of the 45 NDs authorized, there were five for sporadic use and 40 for chronic use. In 20 of the chronic use drugs, the monthly price of the defined daily dose was calculated; in another 17 the dose from the ANMAT label was used, and in one the dose from the FDA label was used. There were two products (hydroquinone and nitisinone) for which it was not possible to obtain the sales price.

The treatment price of the new drugs for chronic use shows great dispersion, from $13 to $56,516 per month (in US dollars). The price of most drugs was elevated, with an average price of $7,974 and a median of $5,849 (interquartile range: Q1 = $172; Q3 = $14,284). For the NDs with added therapeutic value, the price was even more elevated, with an average price of $13,800 (median = $13,821; interquartile range: Q1 = $5,021; Q3 = $13,325).

When grouping the drugs by primary indication, their concentration into different price ranges according to the pathology treated can be observed (Figure 3). It can also be observed that the monthly price of treatment for the 14 drugs for oncological use goes from $3,000 to $56,000, with an average of $17,700. To contrast this information, only five of these drugs had added therapeutic value, five had similar therapeutic value to existing drugs, three had unknown therapeutic value and one was considered inferior to existing alternatives.

DISCUSSION

This study found that, in the year 2016, 45 NDs were incorporated into the Argentine market, the majority of which were previously approved by the FDA and the EMA. Of these NDs, 13% did not have randomized clinical trials demonstrating efficacy and 24% had demonstrated efficacy only for non-validated surrogate variables. In terms of therapeutic value, 72% of the NDs did not represent significant advances according to the evaluation of the journal *Prescrire* and 78% did not add therapeutic value according to the classification of Ahlqvist-Rastad *et al*. For the two drugs

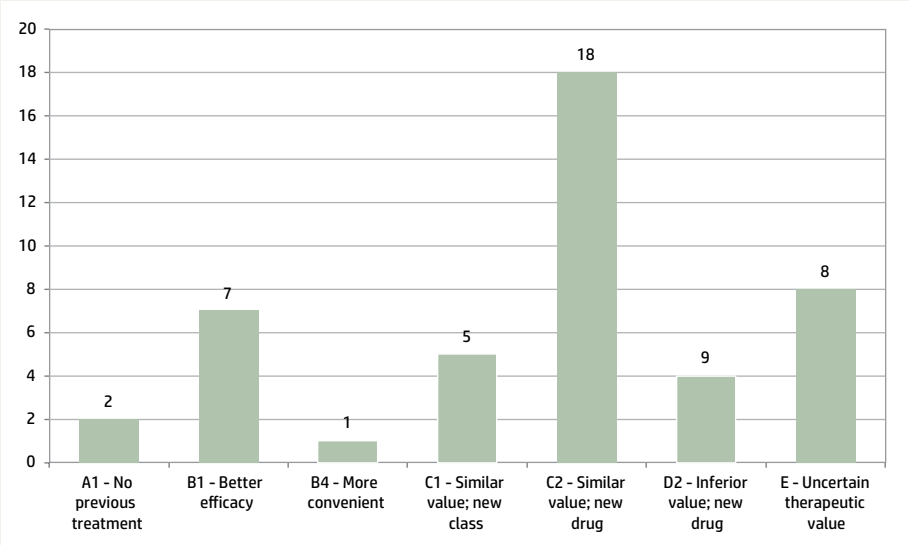

Figure 2. Therapeutic value of the new drugs(n=45) approved in Argentina in 2016, according to the classification of Ahlqvist-Rastad *et al.*

Source: Own elaboration based on the classification of therapeutic value by Ahlqvist-Rastad *et al.*[9]

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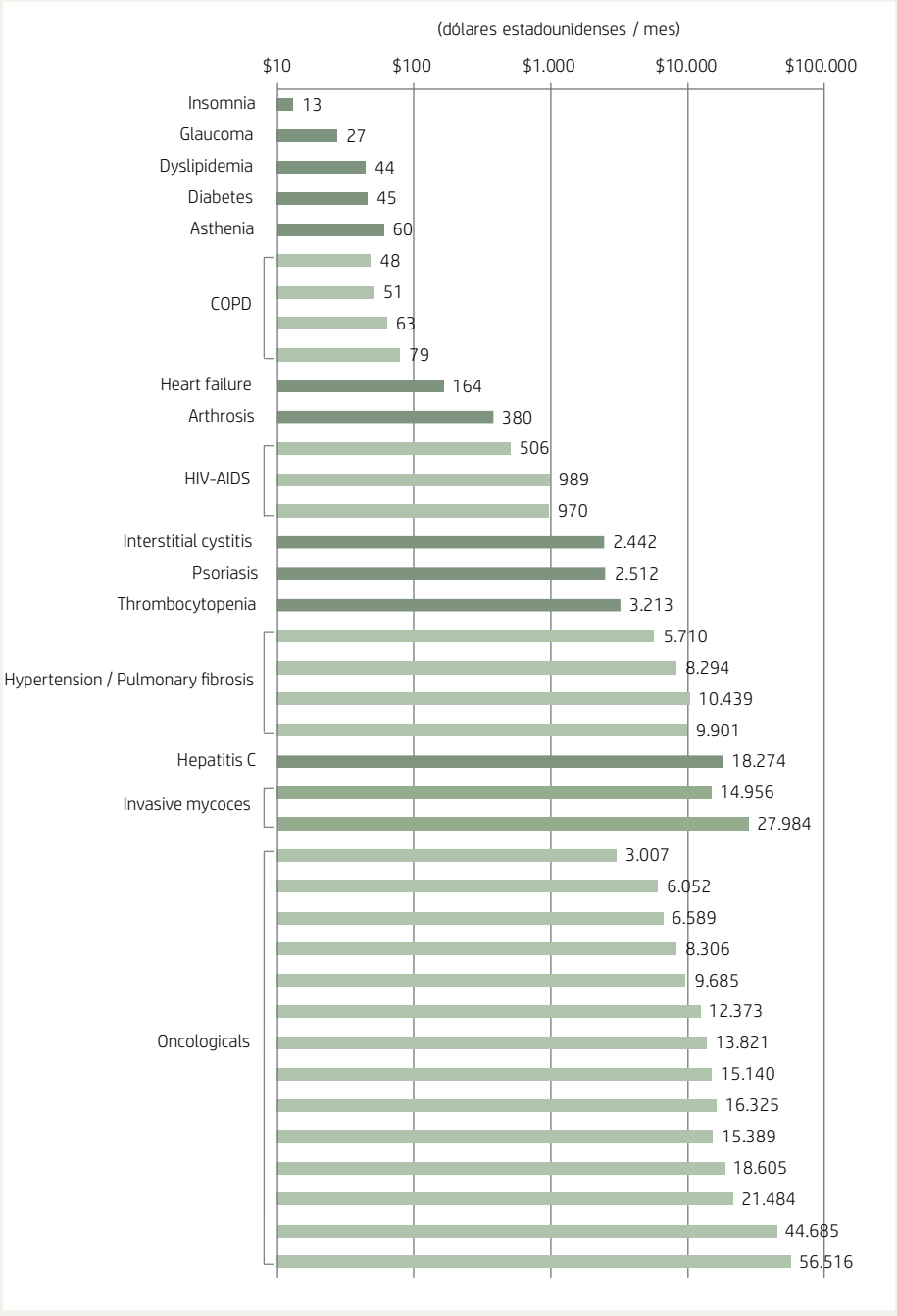

Figure 3. Approved new drugs, according to pathology treated and monthly price of treatment in US dollars. Argentina, 2016.

Source: Own elaboration using prices published in the catalog *Kairos*.[16]
Note: The price scale is logarithmic for ease of representation.

evaluated only by ANMAT, the approval criteria used were not robust. In addition, the price of the drugs was substantial, with a median of $5,849 per month for chronic use drugs. Only one out of every 4 NDs represented a therapeutic advance and almost all are sold at practically inaccessible prices.

These results are in agreement with those obtained in the previously cited studies. The studies carried out in different parts of Latin America and the world all show an absence of added therapeutic value of the majority of the new drugs that are commercialized. In synthesis, in the best case scenario, only a

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quarter of these drugs represents some type of improvement in the existing therapeutic options.

The value of these drugs can be analyzed using two different but complementary approaches. The first contemplates the pharmaceutical innovation and evaluates, for example, the novelty of the chemical structure, the molecular target, the action mechanism, the drug class, the synthesis method or the drug formulation.[11,12] The second focus privileges the degree to which the new drug represents an added therapeutic value with respect to the previously available options, that is, its concrete additional benefit for patients.[9,10] With the first focus, applied by regulatory agencies, a drug that is more effective than a placebo can be considered innovative, however with the second criteria, which is stricter and has greater public health relevance, it is necessary to demonstrate benefit in clinical trials as compared to the best available alternative.

A number of studies have compared the new therapeutic agents registered by the FDA, the EMA and other regulatory agencies. Although no significant differences were found for the marketed new drugs, a recent study observed that the indications approved by the FDA, the EMA and the Swiss agency Swissmedic (SMC) for the same drugs differed in content in 76.9% of cases.[33] It is clear that discrepancies among regulatory agencies are not only based on the evidence, but also cultural, political and economic factors as well as the characteristics of each health care system.[34]

Although the FDA's designation of different categories such as "priority review" or "orphan drug" appears to promote stricter innovation criteria, in practice there are so many drugs classified as priority that the term loses specificity and becomes indiscriminate. Regarding the orphan diseases investigated, these are usually genetic syndromes or oncological variants with a very low prevalence in the USA, and not infectious diseases of high prevalence in developing countries, for which there are no effective therapeutic alternatives.

The therapeutic value of a ND is even less certain when, using the "accelerated approval" route established by regulatory agencies, the drug appears on the market with demonstrated efficacy only for non-validated surrogate variables or even without controlled trials. Examples of these questioned surrogate variables include the six-minute walk test for pulmonary arterial hypertension[32] and many of the habitual endpoints of oncological drug studies.[35] The post-commercialization studies required by regulatory agencies to complete this information exceed the stipulated time frame and often do not contribute the expected information regarding clinically relevant endpoints.[24,25,36,37,38,39,40]

The result of this lax form of drug approval is the incorporation of products with unproven efficacy and safety in clinically relevant variables, with preliminary safety information and, in general, a price that stresses the viability of funding mechanisms.

The legal framework in Argentina, which permits the inscription of any drug approved by the regulatory agencies in developed countries,[8] reproduces locally the same problems. Bills exist to create an agency for the evaluation of health technologies that could intervene in the incorporation of new drugs into the social security system. It is crucial that in these types of decisions, standards be used that consider the added therapeutic value of a new drug, in addition to the analysis of cost-effectiveness in comparison with the alternatives.

However, the results of the analyzed studies suggest that to respond to the local health priorities larger changes are necessary in the legal framework, abandoning the automatic inscription of drugs approved by the regulatory agencies of other countries. The new form of inscription should include an independent evaluation of the new drugs and approve the entry into the local market of those drugs that represent true advances.

As an example of interventions of this type in other Latin American countries, a recent decree in Colombia establishes that the inscription of new drugs is dependent on an evaluation of their therapeutic value in relation to a selected comparison, along with an economic evaluation, that could include an

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analysis of cost-effectiveness as well as the budget impact.[41] In this way, the evaluation of the therapeutic value and the establishment of the price occur prior to the drug entering the local market.

CONCLUSIONS

As a mirror of what occurs in developed countries, only a minor fraction of the new drugs approved in Argentina in 2016 represented a significant therapeutic advance. Nevertheless, the majority had a very elevated price. The result is an increase in risks to patients who are exposed to drugs without proven clinical efficacy and an overburdening of public and private funding systems. To improve these results, an evaluation of the therapeutic value and the price of the drug should be incorporated as a requirement for the authorization of the inscription of new drugs in Argentina, or at least be a step to authorize their inclusion in the social security system.

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