HOW MANY HEALTHY LIFE YEARS COULD COUNTRIES IN LATIN AMERICA AND THE CARIBBEAN GAIN WITH A BETTER ALLOCATION OF PHARMACEUTICAL SPENDING?

Case Studies for Chile, Colombia, and the Dominican Republic

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IDB

INTRODUCTION

- **Health spending is increasing across the world due to epidemiologic and demographic changes, the emergence of costlier new health technologies and the increased demand for services due to higher incomes and ageing populations.** During the last two decades, health spending in Latin America and the Caribbean has risen from 6.6 to 7.9 percent of GDP. By 2030, health spending is expected to increase by an additional 2 percentage points, not accounting for the new challenges countries face post-pandemic, such as the investment required to prepare for similar future events [1], While it is neither realistic nor desirable to completely halt this spending growth, sustaining it exclusively through higher budgetary allocations is not viable. This is especially true considering the fiscal restrictions resulting from the pandemic's economic impact, increasing indebtedness and an uncertain macroeconomic situation. Achieving better health outcomes will crucially depend on investing available resources intelligently, securing better prices for products, avoiding waste and prioritizing investments that provide more healthy life years for the same amount of money. Better-invested resources translate into improved population health.

- **This brief will focus on two potential sources of spending inefficiency that have not been previously analyzed for the region.** One is the funding of branded, generally higher-priced drugs when unbranded generics are available. The other is the procurement of certain pharmaceutical products with reduced or uncertain effectiveness and a high price relative to their clinical benefits when other resource allocation options that could generate more population health are available.

- **The IADB's Social Protection and Health Division has conducted a series of studies analyzing these two aspects of pharmaceutical spending in three countries within the region:** the Dominican Republic, Chile and Colombia. Our findings reveal the costs of these decisions for health systems in terms of lost health and out-of-pocket household expenses [2-5]. This policy brief summarizes the main findings of these studies and offers related policy recommendations.

JEL codes: H10, H11, H21, H30, H51, H61, I1

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1. THE OPPORTUNITY COST: HEALTH AND GAINS NOT OBTAINED

WHAT IS OPPORTUNITY COST AND HOW DO WE MEASURE IT

Opportunity cost refers to the returns or other forms of benefits we could have obtained had we made a different decision. In simpler terms, it is what we give up by choosing a specific course of action [6]. Regardless of who makes the decisions for health, be it households or health authorities, any resource allocation decision has an opportunity cost. If we could invest in either "a" or "b", the opportunity cost of investing in "a" is the benefits we could have obtained by investing in "b", and vice versa.

The Opportunity Cost for Health Systems

Policymakers in all health systems face difficult decisions regarding which interventions, programs or activities should be funded with public resources. Given that resources are finite, funding one intervention inevitably means not funding others. These decisions have implications in terms of population health gains or losses because of the investments not made or interventions left unfunded.

In health, benefits are usually measured in clinical outcomes that are ideally of relevance to individuals. Examples include life years gained, improved quality of life or other criteria that indirectly suggest better health status, such as better glucose control or fewer asthma episodes per month. A common concept used to measure health benefits is Quality-Adjusted Life Years (QALY). This measure accounts for the fact that a year lived with a disease is not equivalent to a year in perfect health, adjusting the life years by the quality lost due to the condition. One QALY equals a year lived in perfect health.

Economic evaluations provide tools to make the opportunity costs of decisions visible and quantifiable, allowing us to compare the health outcomes that could be obtained by allocating resources to different alternatives. For example, an economic evaluation might show that a new, costlier drug for advanced lung cancer extends the period without disease progression by an average of three weeks. However, the resources used to fund the new drug could instead be allocated to another drug or intervention that provides much greater health gains for a larger number of people. In this case, investing in the first rather than the second alternative would imply a loss of population health.

> **For a given health system, the opportunity cost is the population health it forgoes by investing in one health technology instead of another.**

To calculate the opportunity cost, we can use the Net Health Benefit (NHB) calculation. Broadly speaking, the NHB is calculated as the amount of health obtained with one intervention minus the health that could have been gained by spending those resources on alternative interventions. These alternatives could be the best available therapeutic option for the same condition or interventions to treat or prevent other conditions. NHB is generally expressed in QALYs. When NHB is positive, an intervention is considered desirable; conversely, it is not considered worthwhile when NHB is negative.

It is also possible to compare the health benefits of one technology with the health gains that could be achieved if the same resources were invested in the health system as a whole, such as by improving the timeliness or quality of existing services. For this purpose, we use the cost-effectiveness threshold (CET) as a measure of how much it costs a health system, on average, to produce one QALY. In other words, it is the average price of a QALY in the health system. If a health system's CET is $10, investing $1,000 in that system would, on average, produce 100 QALYs ($1,000/$10).

This brief's annex presents related mathematical expressions for interested readers.

The Opportunity Cost for Households

When households cover a significant proportion of health spending out-of-pocket, the consequences of inefficient allocations fall directly on families rather than on the health system. For example, buying higher-cost branded drugs (either generics or innovators) instead of unbranded generic substitutes of equal effectiveness and lower prices leads to added costs for households, with no additional clinical benefits. If households were to substitute branded drugs for their generic equivalents, they could use the resources saved to consume other goods and improve their well-being. In this case, the opportunity cost is the additional consumption these households could fund with the savings from the substitution.

Buying branded drugs causes an added expense for households, with no additional clinical benefit.

When households cover health costs out-of-pocket, the most common way to measure the opportunity cost is to compare the benefits households would obtain by spending a given amount of resources on one good or another. There are several methods to estimate this, including utility functions and willingness to pay studies. The case studies discussed here estimated the opportunity cost as the additional consumption households could achieve with the savings from substituting branded drugs with unbranded generic drugs[1].

2. THE OPPORTUNITY COST OF FUNDING BRANDED DRUGS WHEN UNBRANDED GENERIC ALTERNATIVES ARE AVAILABLE: THE CASES OF CHILE AND THE DOMINICAN REPUBLIC

To illustrate the opportunity cost of using branded drugs instead of unbranded generics for households and health systems in the region, the project conducted two case studies: one in Chile and the other in the Dominican Republic.

The first analyzed the opportunity cost for Chilean households, while the second focused on the opportunity cost for the Dominican social security system.

In Chile, households directly pay for 32 percent of national health spending, representing 40 percent of their consumption. This out-of-pocket spending is one of the highest among OECD countries [7]; reducing it has long been a priority for health authorities. A third of household spending goes to drug spending [8].

40 percent of outpatient drugs acquired by the Chilean population are purchased privately in the retail market in private pharmacies, and only 4 percent of households have insurance coverage or reimbursement for these drugs [2]. Substituting branded innovator and generic drugs with lower-priced unbranded generics, therefore, has the potential to decrease household out-of-pocket spending and allow them to consume more of other goods and services.

In the Dominican Republic, the Sistema de Seguridad Social en Salud (SDSS, Health Social Security System) provides health benefits through the Seguro Familiar de Salud (SFS, Family Health Insurance) through both the contributive and the subsidized regimes. Members of the contributive regime buy their outpatient drugs in private retail pharmacies, with the health system covering around 70 percent of the cost through the SFS [9]. This brief analyzes the contributive regime's opportunity cost of funding branded innovator and generic drugs instead of unbranded generic alternatives, focusing on the active ingredients included in the SFS formulary for outpatient contexts and purchased through retail pharmacies.

Table 1 presents definitions of the terms we will use going forward.

POTENTIAL SAVINGS FROM GENERIC SUBSTITUTION

Both case studies focused on outpatient prescription drugs purchased in private pharmacies. In Chile, households pay for all these purchases, while in the Dominican Republic, the contributive social security system covers 70 percent of drugs included in the SFS. According to the case studies, sales in these markets totaled US$1.2 billion in the Dominican Republic in 2019 and US$2.7 billion in Chile in 2017.

To estimate potential savings, the authors divided the markets into the following segments.

1. Segments where *no* substitution is possible:
   - Because only innovator drugs are available;
   - Because only unbranded generics are available; or
   - Because no unbranded generics are available, although there is at least one branded generic.
2. Segments where substitution is possible (both branded and unbranded alternatives are available).

TABLE 1 Definitions

	Definition
Active ingredient	Chemical substance contained in the pharmaceutical product that achieves the desired effect in the target tissue.
Innovative product	First brand of the active ingredient to be approved and enter the market. Its patent can be current (*on-patent*) or it may be expired (*off-patent*). For the purposes of this brief, the first me-too product to enter the market is considered an innovative.
***Me-too* products**	Drugs similar to an existing drug in the same class, generally obtained by introducing minor changes to the original compound. *Me-too* drugs frequently have identical or nearly identical effects as the original and can be used to treat the same conditions. The first of these to enter the market is generally granted patent protection.
Patent	Exclusive right given by a state to use and exploit an invention, forbidding others from using it without consent. When a company is the first to develop an active ingredient, it can apply for a patent, granting it exclusive use of the invention for a period of time (usually 20 years).
Unbranded generic	Generic drug composed of the same active ingredient as its innovative counterpart and marketed using the international nonproprietary name. The pharmacological effect of a generic drug should be exactly the same as that of its innovative counterpart, this is ensured through the evaluation and approval process by a specialized agency before entering the market. When the innovative product's patent expires, other companies can market generic drugs.
Branded generic	Drug containing the same active ingredient as an innovative product but marketed under a proprietary brand name.

Source: The authors.

Starting with the segment where substitution is possible (group 2 in the above classification), the authors estimated the potential savings from a shift toward unbranded generics. Figures 1 and 2 present the results.

The first interesting result is the significant price difference between branded products and unbranded generics: in Chile, branded products are, on average, six times more expensive; while in the Dominican Republic, they are, on average, three and a half times costliers.

Second, the fraction of the market where unbranded generics are available and substitution is possible is relatively small: 29 percent of total sales in Chile (US$491 million) and 41 percent in the Dominican Republic (US$663 million). Moreover, in segments where substitution is possible, branded products (innovators and branded generics) have a high market share, representing 74 percent of sales value in Chile and 84 percent in the Dominican Republic.

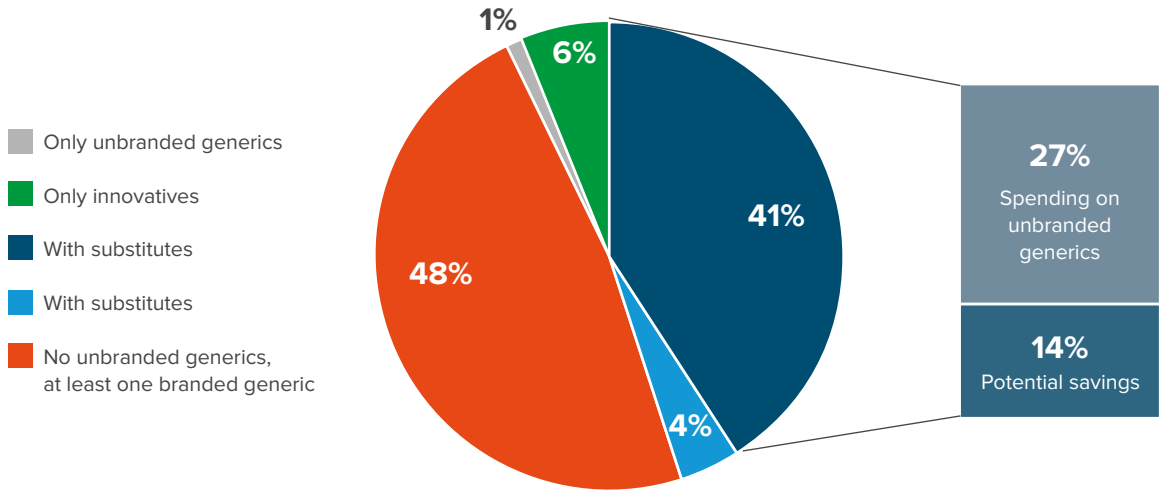
Third, substituting for unbranded generic drugs in segments where it is possible would result in potential annual savings of US$316 million in Chile[2] and around US$103 million in the Dominican Republic[3]. These savings represent close to 14 percent of total outpatient drug spending in each country. In other words, with the current availability of unbranded generics, each country could reduce its outpatient drug spending by 14 percent.

It is important to note the significant size, in both countries, of the segments where branded generics and innovators are present without the competition of unbranded generics for molecules that are no longer patent-protected (segment 1c in the above classification). This set represents 51 percent of total sales in Chile and 48 percent in the Dominican Republic. In these market segments, the innovator drugs are off-patent, meaning there could be unbranded generics, although there are currently none. **Therefore, additional savings could be obtained if the entry of unbranded generic drugs were promoted in these segments.**

Chile and the Dominican Republic could save at least 14 percent of their outpatient drug spending by purchasing unbranded generics instead of their branded equivalents, and even more if the entry of unbranded generics was promoted.

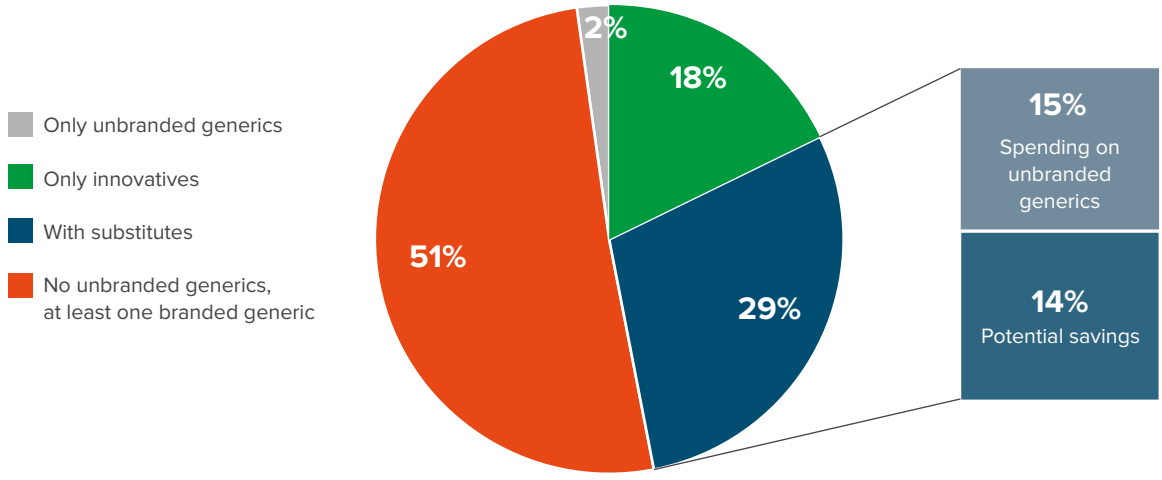
For Chile, the authors conducted an additional exercise on the market segments where no substitution is possible because only innovator drugs are available (set 1a of the classification, representing 18 percent of total sales). It was not possible to directly discern which products in this group were on-patent and which were off-patent, as the information on patent status was unavailable at the

FIGURE 1 **Distribution of sales value by market structure in the Dominican Republic, 2019 (million dollars)**



Source: Dominican Republic case study, Atal, J. P., et al. [4]

FIGURE 2 **Distribution of sales value by market structure in Chile, 2017 (million dollars)**



Source: Chile case study, Atal, J. P., et al. [2]

time. However, the authors found that for 58 percent of these products, two or more valid licenses existed, indicating that these innovator drugs are off-patent but do not face competition[4]. A systematic review by Vondeling *et al.* [10] finds that the average price of drugs falls significantly after generics enter the market, and proportionally to the number of generic entrants. This suggests significant additional potential savings if generic competition was promoted in this segment.

THE OPPORTUNITY COST OF BUYING BRANDED DRUGS INSTEAD OF UNBRANDED GENERIC SUBSTITUTES

As observed, the potential savings from substituting for unbranded generic drugs in the Dominican Republic amount to US$103 million annually. While specific details on how these savings are distributed between households and the contribute regime are lacking, the authors estimate that approximately US$14.4 million (14 percent) would accrue to the social security system.

Using the country's cost-effectiveness threshold, the study determined that if these resources were redirected within the contributive regime to fund services covered by the SFS, members could collectively gain up to 3,994 years in perfect health annually. In other words, choosing branded drugs over their generic counterparts represents a missed opportunity, equivalent to a loss of 3,994 life years in perfect health for contributive regime members.

In countries where essential services are not fully covered, rather than comparing against the health system's average cost-effectiveness threshold, **it becomes crucial to consider reallocating resources toward addressing gaps in essential service coverage.**

The study in the Dominican Republic conducted this analysis by estimating gaps in two essential preventive services: cervical cancer screening and detection, and diagnosis and management of diabetes. It projected the potential health gains achievable if the savings from generic drug substitution were allocated to close these gaps. Based on reviewed literature, implementing a uterine cancer prevention and screening package for women aged 30 to 49 could yield an average of one additional life month per person covered. Similarly, each diabetes screening and management package is estimated to add seven healthy life months over a 20-year period.

By 2022, the gap in the timely detection of cervical cancer in the Dominican Republic was estimated at 54 percent, while the gap in the timely and comprehensive detection and non-pharmacological management of diabetic patients was at 61 percent. The estimated annual cost of closing these coverage gaps totaled US$16.6 million, with US$3.19 million needed for cervical cancer and US$13.5 million for diabetes). That is, with a savings of US$14.4 million through purchasing generics, the Dominican Republic could potentially bridge the entire gap in cervical cancer detection and 83% of the diabetes screening and management gap.

Drawing on the cost-effectiveness studies from existing literature, the authors projected that bridging the cervical cancer gap over a decade would yield 3,553 life years in perfect health. Closing 83% of the diabetes screening and management gap over 20 years was estimated to generate an additional 8,713 healthy life years, amounting to a total of 12,246 QALYs[5]. On average, this translates to an annual gain of 790 QALYs, potentially granting approximately 79 individuals a decade of life in perfect health each year.

With the savings obtained in one year, the Dominican Republic could bridge the entire gap in cervical cancer detection and 83 percent of the gap in diabetes detection and management. Closing these gaps would avoid the loss of 790 life years in perfect health annually.

The potential savings from substituting branded drugs with generics in Chile was estimated at US$315.5 million, including both prescription and over-the-counter drugs. Ninety percent of these savings (US$283 million) come from prescription drugs, over which prescribers and pharmaceutical policies have more control.

Using data from the 2017 household survey and the Encuesta de Caracterización Socioeconómica (CASEN) of 2017, the Chilean case study estimated the distribution of these savings by socioeconomic level. The analysis considered membership type (ISAPRE or social security) and the educational level of the household head.

On average, households with drug expenditures could reduce their health spending by 3.8 percent by opting for unbranded generic instead of branded drugs, with a 10 percent decrease in drug spending. In households with ISAPRE members, drug spending could decrease by up to 20 percent. The savings would be more significant in households where members have lower levels of

education: a 12 percent reduction for households with less than 9 years of education and a 19 percent reduction for households with 9 to 12 years of education.

Chilean households could reduce their out-of-pocket drug spending by 10 percent if they bought unbranded generics instead of innovators and branded generics.

Another way to understand the opportunity cost that households incur through buying branded drugs is to estimate what alternative expenses they could cover with the potential savings. The study found that, on average, households could use these savings to cover two months of transport costs to work per year, nearly a fifth of their total transport to work costs. This is significant, especially for lower-income households, where transport is a major expense. Additionally, in households where individuals have less than 12 years of education, the savings could notably increase spending on other items. For example, the savings could boost recreational budgets by just over 10 percent.

Overall, the estimated savings represent 1.1 percent of total national health spending, indicating that the share of out-of-pocket expenses could be reduced by one percentage point. Savings would be larger if unbranded generics were available in other segments of the market were brand names are off-patent.

3. THE OPPORTUNITY COST OF FUNDING HIGH-COST DRUGS: THE CASES OF COLOMBIA AND THE DOMINICAN REPUBLIC

High-cost drugs (HCD) are increasingly consuming a larger share of health budgets worldwide, with pharmaceutical spending expected to continue its growth.

In Latin America and the Caribbean, pharmaceutical spending is projected to rise by up to 50 percent between 2022 and 2027 [11]. A significant portion of this increase will be driven by new biological drugs and oncologic treatments, with oncology spending alone expected to double in the same period [11]. While some advancements offer substantial benefits, especially for patients with untreatable conditions, others may only provide moderate improvements. This creates a real risk that funding high-cost drugs could displace other investments with higher health benefits or slow the closing of gaps in essential services that persist in the region.

Like most countries in the region, the Dominican Republic and Colombia cover high-cost drugs for various chronic conditions (Table 2 describes coverage in both countries). The case studies analyzed the opportunity cost for ten high-cost drugs, selected based on the annual treatment cost per patient and budget impact.

The selected drugs are used for orphan diseases, cancer treatments and immunosuppressors. In the Colombian case, the authors included an anti-diabetic drug with a high budgetary impact. Some of these drugs have generic or biosimilar alternatives, others have alternatives within their same therapeutic class and a few have little to no therapeutic alternatives.

TABLE 2 High-cost Drugs Coverage in the Dominican Republic and Colombia

	Coverage
Dominican Republic	All insured individuals have a right to an explicit health benefits plan –the Plan de Servicios de Salud, PDSS, or Health Services Plan– that covers some high-cost drugs. Financial coverage is structured through maximum ceilings per member per year. In addition to the drug coverage in the basic health plan, the Dominican ministry of health (Ministerio de Salud Pública) has the Programa de Medicamentos de Alto Costo y Ayudas Médicas (PMAC, High-cost Drugs and Medical Aids Program). The PMAC assists over 14,000 members and annually invests approximately RD4.4 billion (US$815 million). The program currently covers 113 drugs. Drugs on this list are either not covered by the PDSS or, due to their high-cost and existing coverage ceilings, copayments or moderating fees, result in high out-of-pocket expenses that lower-income members cannot afford. The study focused on ten drugs covered by the PMAC.
Colombia	Colombia also has an explicit benefits plan (Plan de Beneficios en Salud, PBS, Health Benefits Plan) that covers most available technologies. The PBS is funded through a per capita premium paid to the Empresas Administradoras de Planes de Beneficios (EAPB, Benefits Plans Managing Companies) by each member. Health system members can also access goods or services not covered by the explicit benefits plan through a mechanism that requires a special request by the attending physician or a court order, as long as the prescription is not in a list of excluded exceptions. These goods and services are funded through another resource fund known as “maximum budgets”. The bulk of spending in this fund is made up of high-cost drugs. The study focused on ten high-cost drugs covered through prescriptions not covered by the explicit plan.

Source: The authors.

Tables 3 and 4 present the studies' results. In the Dominican Republic, the annual cost of treatment per patient ranges from US$10,000 to US$251,000. Compared to the best existing alternatives, the additional spending throughout the treatment period for the ten drugs and the 1,807 people under treatment totals US$155 million[6]. Treatments have an average duration of 4 years (ranging from 17 weeks to 47 years) and provide an average of 0.83 QALY, equivalent to 43 weeks of perfect health per patient, ranging from 1.5 weeks (regorafenib) to nearly 2 years (golimumab).

In Colombia, the annual cost per treated person ranges from US$614 to US$179,000. Treating the 23,261 people covered with these drugs, instead of their therapeutic alternatives, results in an additional total spending of US$543.5 million over the entire treatment period. The benefits in terms of life years in perfect health range from 2 weeks (aflibercept) to one and a half years (ibrutininb).

Comparing the cost-benefit ratio of the high-cost drugs with the average cost of producing one QALY through the services provided by the health care system (the CET), both countries are paying relatively high prices for each additional life year in perfect health. Each QALY obtained with agalsidase beta costs 1,300 times more than the average cost of obtaining a QALY in the health system. In Colombia, eculizumab is 275 times more expensive than the cost-effectiveness threshold.

The studies find that funding high-cost drugs instead of their therapeutic alternatives results in an additional cost of US$155 million in the Dominican Republic and US$543,5 million in Colombia. If these resources were invested in health services provided by the system, almost 35,000 QALYs would be gained in the Dominican Republic and 88,000 in Colombia. In other words, if these countries continue to divert funding from other services to fund these high-cost drugs, their populations are losing 35,000 and 88,000 life years in perfect health[7], respectively.

Funding ten high-cost drugs costs the Dominican Republic 35,000 healthy life years and Colombia 88,000.

For example, palbociclib, used for advanced stage breast cancer, costs US$64,135 per patient per year. Compared to its existing therapeutic alternative, letrozole, it provides 0.7 additional QALY (equivalent to 36 weeks in perfect health) for an additional cost per person per year of US$99,394. The opportunity cost is 8,177 QALYs that are lost if resources are diverted from the health system to fund palbociclib, or that are not gained if additional available resources are allocated to this high-cost drug instead of the best existing alternative (letrozole or fulvestrant).

Some drugs provide less than 5 additional weeks of life in perfect health. For instance, regorafenib offers only 1.5 weeks of perfect health compared to its alternative treatment (palliative care), but at a cost of US$252,000 per person per year. This is 1,000 times higher than the Dominican Republic's cost-effectiveness threshold. In Colombia, aflibercept provides the equivalent of two additional weeks in perfect health compared to its alternative treatment (bevacizumab), at a cost of US$2,104 per person per year, resulting in an opportunity cost of 17,000 QALYs lost.

These findings underscore the importance of conducting economic evaluations and considering opportunity costs in decision-making, not only to determine what to fund but also to negotiate better prices from manufacturers. An effective pricing policy can significantly reduce the opportunity costs associated with high-cost drugs. The Colombia case study examined the impact of price dispersion on opportunity cost for the same drugs. In some cases, the price dispersion is so substantial that, when using the lowest prices, the high-cost drug becomes both more economical and more effective than its comparison. This is the case, for instance, with lenalidomide and factor VIII, highlighting the importance of price management in funding high-cost drugs.

As previously mentioned, in countries with gaps in essential service coverage, an important question arises: **what would happen if the additional resources used to fund high-cost drugs were instead allocated to bridge these gaps?** An additional exercise conducted as part of the Dominican Republic study estimated the QALY that could be gained if resources used to fund the ten analyzed drugs were redirected to close gaps in preventive services for cervical cancer detection and screening, as well as the timely diagnosis and management of diabetic patients.

TABLE 3 Opportunity Cost of Funding High-cost Drugs in the Dominican Republic, 2022 (dollars)

High-cost drug (HCD)	Condition	Annual treatment cost per patient	Additional cost per patient of covering the HCD vs its alternative throughout the treatment	Life years in perfect health provided per patient by the HCD throughout the treatment	Price paid per QALY gained with the HCD	Net benefit per patient in additional years in perfect health (QALY)	Number of treated people	Total net benefit (NHB per patient * number of cases)
Palbociclib	Breast cancer	64,135	99,394	0.70	141,992	--23.50	348	-8,177
Golimumab	Psoriatic arthritis	15,063	84,408	1.91	44,309	-18.64	370	-6,898
Ocrelizumab	Relapsing-remitting multiple sclerosis	32,114	210,496	0.66	318,934	-49.43	97	-4,795
Etanercept	Psoriatic arthritis	10,077	49,629	1.74	28,563	-9.93	442	-4,390
Pembrolizumab	Non-small cell lung cancer (NSCLC)	72,703	104,262	1.04	99,931	-24.34	153	-3,724
Atezolizumab	Non-small cell lung cancer (NSCLC)	83,889	158,222	0.85	185,417	-37.66	62	-2,335
Enzalutamide	Prostate cancer	27,082	36,836	0.37	99,289	-8.60	263	-2,261
Agalsidase beta	Endocrine disorders (Fabry disease)	115,537	3,815,005	0.70	5,450,008	-928.04	2	-1,856
Regorafenib	Colon cancer	251,917	102,901	0.03	4.116.041	-25.03	25	-626
Sorafenib	Renal cancer	37,630	18,970	0.26	74.393	-4.36	45	-196
Total							**1,807**	**-35,258**

Source: Dominican Republic case study, Jorgensen, N., et al. [3].
Note: the cost-effectiveness threshold for the Dominican Republic has been estimated with local data at US$4,108.

TABLE 4 Opportunity Cost of Funding High-cost Drugs in Colombia, 2022 (dollars)

High-cost drug (HCD)	Condition	Annual treatment cost per patient	patient of covering the HCD vs its alternative throughout the treatment	Life years in perfect health provided per patient by the HCD throughout the treatment	Price paid per QALY gained with the HCD	Net benefit per patient n additional years in perfect health (QALY	Number of treated people	Total net benefit (NHB per patient * number of cases)
Liraglutide	Type 2 diabetes	614	2,322	0.23	10,096	-0.21	10,562	-2,199
Abatacept	Adult rheumatoid arthritis	1,830	24,818	1.43	17,355	-3.25	1,365	-4,442
Lenalidomide	Multiple myeloma	10,286	32,023	1.47	21,784	-4.57	3,146	-7,052
Ibrutinib	Acute lymphocytic leukemia	28,727	518,822	1.49	348,203	-96.43	168	-16,200
Adalimumab	Ulcerative colitis	1,732	28,242	0.18	73,927	-5.15	569	-1,336
Eculizumab	Paroxysmal nocturnal hemoglobinuria	135,200	1,216,842	1.08	1,459,535	-228.58	102	-30,235
Nusinersen	Spinal muscular atrophy	178,604	1,576,298	1.43	850,938	-296.07	42	-9,586
Pembrolizumab	Chronic lymphocytic leukemia	28,432	-24,977	0.32	HCD dominates, less costly and more effective	5.03	168	846
Aflibercept	Macular and posterior eye pole degeneration	2,104	15,598	0.04	380,429	-2.90	5,856	-16,999
Plasmatic factor VIII	Hemophilia	20,189	2,832	-0.16	HCD is dominated, more costly and less effective	NA	1,283	-891
Total							**23,261**	**-88,095**

Source: Colombia case study, Gutiérrez, C. et al. (2023) [5].
Note: the cost-effectiveness threshold for Colombia has been estimated at US$5,298 for 2021.

TABLE 5 Opportunity Cost of Funding HCD Instead of Closing Essential Services Coverage Gaps, 2022 (dollars)

HDC	Condition	Additional cost of HCD vs alternative, for each QALY	Additional QALY provided by the HCD relative to its comparison fore very patient	Incremental treatment cost for all patients	Comparison intervention	Cost per QALY of essential service	% of the gap covered with resources allocated to 10 HCD	Additional QALY of gaps closing	Net Health Benefit of funding HCD
Agalsidase beta	Endocrine disorders (Fabry disease)	5,450,008	1.40	7,630,011	Cervical cancer detection (time frame: 10 years)	910	100%	8,382	-8,380
Regorafenib	Colon cancer	4,116,041	0.63	2,572,525				2,826	-2,825
Ocrelizumab	Relapsing-remitting multiple sclerosis	318,934	64.02	20,418,142				22,430	-22,366
Atezolizumab	Non-small cell lung cancer (NSCLC)	185,417	52.91	9,809,778	Diabetes detection and management de diabetes (time frame: 20 years)	1,288	46%	7,614	-7,561
Palbociclib	Breast cancer	141,992	243.60	34,589,137				26,848	-26,604
Pembrolizumab	Non-small cell lung cancer (NSCLC)	99,931	159.63	15,952,012				12,382	-12,222
Enzalutamide	Prostate cancer	99,289	97.57	9,687,934				7,520	-7,422
Sorafenib	Renal cancer	74,393	11.48	853,660				663	-651
Golimumab	Psoriatic arthritis	44,309	704.85	31,231,026				24,241	-23,536
Etanercept	Psoriatic arthritis	28,563	767.98	21,935,975				17,027	-16,259
Totals			**2.104**	**154,680,199**				**129,932**	**-127,828**

Table 5 presents the results, showing that the gaps in these prevention and promotion services could be bridged with the resources needed to fund high-cost drugs instead of their alternative treatments. With these resources, the Dominican Republic could close the entire gap in cervical cancer detection and 46 percent of the gap in diabetes detection and management. This reallocation would result in a net gain of 127,828 QALYs. **Additionally, since most of these gaps in essential services affect vulnerable populations, reallocating resources would also lead to equity gains.**

With the additional resources allocated to fund high-cost drugs, the Dominican Republic could completely close the gap in cervical cancer detection and 46% of the gap in diabetes detection and management of diabetes, with a net gain of 127,828 years lived in perfect health.

4. CONCLUSIONS AND POLICY RECOMMENDATIONS

The case studies highlight the importance of efficient resource allocation. Inefficient allocation can lead to a direct loss in population health or/ and lower household wellbeing. Table 6 summarizes the results of the four case studies.

Funding high-cost drugs when more cost-effective therapeutic alternatives exist and allocating public or out-of-pocket resources to branded drugs instead of unbranded generics, results in significant health opportunity costs for the Dominican Republic and Chile. Many policies could improve resource allocation in these countries and throughout the region. **The following section summarizes the main policy recommendations from our review of existing literature and from these case studies.**

TABLE 6 The Impact of Funding High-cost and Branded Drugs on Health and Spending

Health Systems' and Households' Savings by Substituting for Unbranded Generics	By substituting for unbranded generics, Chilean households could reduce their out-of-pocket drug spending by 10 percent. Estimated savings are higher for lower education populations. The savings could cover, for example, two months' worth of transportation to work per year. » By substituting for unbranded generics, the Dominican Republic's contributive system could save **US$14.4 million annually**, equivalent to 14 percent of outpatient drug spending. » In both countries, sales of branded generics and off-patent innovators that do not face unbranded competition are significant, representing 51 percent of total sales in Chile and 48 percent in the Dominican Republic. This suggests that there is space for additional savings if the entry of unbranded generics in these segments is promoted. » If instead of funding innovator and unbranded drugs the Dominican Republic's contributive system funded their generic equivalents, and distributed the savings within its health system, it would obtain **3,900 life years in perfect health annually.** These gains would significantly increase if it directed savings to highly cost-effective essential interventions. For example, it would **gain 12,000 life years** in perfect health if the savings were directed over ten years to timely cervical cancer detection and bridging the coverage gap in screening and managing diabetes patients over 20 years.
The Opportunity Cost of Funding High-cost Drugs	In Colombia, funding the ten high-cost drugs that were studied instead of their therapeutic alternative generates: » A **loss of 88,000 life years** in perfect health by diverting those resources from its health system. » An additional spending of **US$543 million.** In the Dominican Republic, funding the ten high-cost drugs that were studied instead of their therapeutic alternative generates: » A **loss of 35,000 life years** in perfect health by diverting those resources from its health system. » An additional spending of **US$155 million.** » A **loss of 127,000 life years** in perfect health by using the incremental resources to funding the ten selected high-cost drugs instead of allocating these resources to cover gaps in diabetes detection and management as well as cervical cancer screening.

POLICIES TO PROMOTE THE ENTRY AND USE OF UNBRANDED GENERIC DRUGS

Many policies designed to promote the adoption of generics can also specifically promote the substitution for unbranded generic drugs. Some policies expand supply, while others drive demand.

Policies Promoting the Demand of Unbranded Generic Drugs

» **Setting therapeutic equivalences.** A necessary prerequisite for promoting the substitution for generic drugs is the trust of prescribers, patients and dispensers in the quality and interchangeability of the drugs. Health agencies have the authority to set the necessary standards for a drug to be interchangeable with another, which is especially important for unbranded generics. The WHO has established guidelines for interchangeability and technical criteria to determine when a pharmaceutical product can be safely and effectively used instead of another. Ojeda and Cristiá (2016) [14] find significant differences in the regulatory paths and the required evidence to ensure interchangeability across Latin American countries. The first step to promoting generics, especially unbranded ones, is to set universally accepted criteria and standards to certify an unbranded generic as interchangeable with its branded counterpart and to strengthen the regulatory agencies to guarantee the products' safety, quality and effectiveness. The Dominican Republic has been making progress in this direction, and it should continue to strengthen regulation and enforcement.

» **Pharmaceutical packaging and labelling.** Regulations can set guidelines for the labelling of generic products, unbranded generics and their innovator counterparts. For example, mandating the inscription of the international nonproprietary name on the packaging of all products with the same active ingredient, concentration and presentation (pharmaceutical form) could clear any confusion created by branding. It is even possible to mandate a smaller font size for the brand name relative to the international nonproprietary name to facilitate identification by end-users [15]. Packaging can also clearly show the interchangeability of unbranded generic products. For example, Chile mandated the "yellow stripe" labelling, which certifies interchangeability, along with a campaign to "demand the yellow" that informed consumers of lower prices for these products as well as their equivalent quality and interchangeability.

» **Prescription.** Prescribers play a key role in the adoption of generics and unbranded generics. A first step in this direction is to mandate prescriptions using the drugs' international nonproprietary name. Additionally, there is evidence that education and promotion programs for prescribers that spread information about the quality and interchangeability of generics will increase their prescription. These programs can also raise awareness about price differences between branded and unbranded generics. Utilization and prescription reviews are also important; these are authorized, structured and systematic quality improvement programs providing information and feedback to the medical community regarding observed prescription patterns relative to guidelines and recommendations. Feedback can include the prescription pattern of unbranded generics, branded generics and innovators with information on potential savings for the system or the end-user.

Electronic prescription and dispensation systems can function as quick, simple guides for an effective prescription and facilitate precise and updated knowledge on generic drugs. In Holland and Australia, demand for generics increased after the introduction of electronic databases that provided physicians with comparative information on price and interchangeability between pharmaceutical products [16]. In the United Kingdom, when a physician enters the name of a branded drug in the electronic system, it automatically provides the generic name [16].

» **Substitution for generics at the pharmacy.** Generic substitution authorizes the pharmacist to dispense a drug's generic version (usually unbranded), even when the physician has prescribed it by its brand name. Depending on the policy, the dispenser can have complete freedom to substitute or face some restrictions; for example, requiring an authorization or only substituting when the prescribed drug is not available. For generic substitution to be effective, the dispenser's incentives must align with the policy goals; if pharmacies' profit margins depend on sales value, the pharmacist will be incentivized to dispense the higher-margin drug, which is usually the most expensive one [16]. Generic substitution policies should be paired with regulations on sales

margins or other incentives that reward generic dispensing. For generic substitution policies to be effective, substitution should be monitored, and effective penalty mechanisms for non-compliance should be established.

» **Price definitions.** If the main goal of a policy for promoting generic drug substitution is to improve patients' accessibility and reduce the budgetary impact on health systems, price policies should not be neglected. Generic promotion is ineffective if their prices are not significantly lower than those of innovators. This is especially true in countries with high branded generic penetration and few market competitors. Some countries impose maximum prices on generic products relative to the price of the innovator. For instance, France stipulates that the price of generics entering the market must be lower than 70 percent of the innovator drug's price [16]. Additionally, a maximum reimbursement price can be set for a drug to be funded with public resources; if a pharmaceutical product's price is above the reference price, the insured, the insurer or the provider must pay the difference. Alternatively, the formulary of covered drugs might only cover the unbranded generic, with the price differential for prescribing branded products assumed by the user, provider or insurer. This could be useful in contexts where providers and insurers have their own pharmacies and receive margins from drugs sales.

It is also important to consider the interactions of innovator product price policies and their effect on the price of branded or unbranded generics. For example, setting price ceilings for innovator products can result in generic drug prices or those in the same therapeutic group converging toward the ceiling. The review by Puig-Junoy [17] reveals that applying maximum price regulation is generally associated with an increase in the price of generic drugs (contrary to that of the innovators). In Colombia, Bardey, Harker and Zuluaga [18] finds that the maximum prices policy resulted in a net 30 percent increase in the aggregate pharmaceutical spending of the 2,000 products it analyzed.

Public tenders granting the entire market to a single competitor can significantly reduce the prices but can also discourage the entry of new competitors. An alternative is to tender the market to a reduced number of providers offering the lowest prices.

Policies Promoting the Supply of Unbranded Generic Drugs

Promoting generic entry, sale and manufacturing. Competition is a key determinant of drug prices. The case studies for Chile and the Dominican Republic revealed that a significant share of the market comprises segments where branded generic drugs face no unbranded generic competition (51 percent in Chile and 48 percent in the Dominican Republic). Additionally, in Chile, it was found that 18 percent of the market consists solely of innovator products, with at least 51 percent of these being off-patent. This suggests ample space to promote the entry of generics in both countries, which may also apply to other countries in the region.

Striking a balance between promoting competition and keeping prices low is challenging. To promote the entry of unbranded generics, countries could allow an expedited mechanism to authorize commercialization and verification of the bioequivalence, reducing the time and possibly the fees for market entry authorization requests. This could be achieved, for instance, by homologating international certifications for generic or biosimilar products [19].

Promoting private-public partnerships or introducing tax incentives for the local production of unbranded generics can promote competition and reduce prices. Creating "peoples' pharmacies" so that the public health system can guarantee the availability of unbranded generics is another strategy implemented by Chile and the Dominican Republic. Home delivery and internet sales can also increase access to unbranded generics [19].

POLICIES TO MITIGATE THE OPPORTUNITY COST OF HIGH-COST DRUGS

There are several tools to reduce the opportunity cost of high-cost drugs. Some strategies are more effective depending on the drug type, available market alternatives, nature of the health condition and the institutional context.

No single policy is sufficient; rather, countries should implement a series of complementary policies. These policies can be classified as those modulating coverage and use, and those seeking to obtain better prices.

Policies Acting on Coverage

- **Financial coverage.** To maximize return on investment, countries could regulate high-cost drug coverage by setting criteria that patients must meet to receive the drug, such as disease stage, age, probability of health benefits or adverse effects. Clinical outcomes should be monitored, and treatment suspended if there is no evidence of progress or clinical benefits. Another approach is to limit the prescription of high-cost drugs and patient follow-up to specialized providers, ensuring optimal use and avoiding harm or ineffective spending. Countries should also discourage funding drugs with reduced additional clinical effectiveness, limited benefit in terms of QALY compared to other therapeutic alternatives and high opportunity cost. Reconsidering their coverage with public resources is advisable, as many high-income countries have already done. Additionally, it would be worthwhile to design a system to clinically monitor and make informed decisions for patients who receive high-cost drugs, ensuring access and adequate use of these technologies. Colombia follows this approach for diseases such as hemophilia and various kinds of cancer.

- **Making the opportunity cost of HCD visible.** Countries could start by making a list of high-cost drugs based on budgetary impact, price or other explicit criteria. After this definition, economic evaluations should be conducted to make the opportunity costs visible in terms of population health gained or lost and their incremental cost-effectiveness. These results should be incorporated into decision-making, price definition and drug procurement policies. Results must be communicated clearly and concisely to a non-specialized audience and be publicly available for consultation. This transparency would allow courts, populations and medical communities to justify the decision to fund or not to fund a given high-cost drug.

- **Promoting informed prescription.** Physicians play a key role in substituting toward lower-cost drugs, but they rarely have information on opportunity costs or price differences between options. As with unbranded generics, it could be useful to engage in a combination of information and outreach efforts with medical societies, including prices and an estimation or approximation of the opportunity cost of different commercial presentations of the same active ingredient.

Clear rules on the conditions to start and end high-cost drug treatments should be established, as Colombia did with nusinersen. These rules should be informed through guidelines for specialist physicians, with input from respective scientific societies and clear information on budgetary impacts and opportunity costs.

Price Policies

- **Price policies and control.** Price control mechanisms using international references for on-patent innovator products are a first step to setting more equitable and sustainable prices. However, these mechanisms should be carefully designed to avoid unintended consequences, such as other products in the same therapeutic group escalating to prices near the ceiling. It's also important to verify that the resulting price from international references is actually lower than the local price.

- In monopolistic markets, one effective strategy is setting the price based on the drug's therapeutic value, as practiced in Brazil, Germany and other countries. Under this strategy, an innovator drug can only obtain a higher price than others in the same therapeutic group if it provides an additional benefit, and that price is proportional to that additional benefit. Colombia is moving in this direction, though the regulation has not yet been approved.

» **Intelligent procurement mechanisms.** Latin America and the Caribbean should adopt intelligent procurement mechanisms for high-cost drugs that exert significant pressure on health systems. As we have seen, opportunity costs can be high. Given budgetary restrictions, the changing epidemiologic profile and the increasing entry of innovator therapies, continuing to purchase drugs at any cost is unsustainable, especially considering technologies with high financial and/or clinical uncertainty.

Managed entry agreements (MEA) between drug manufacturers and payers can play a key role. These agreements require a strategy including: (1) prioritizing drugs for MEAs; (2) rigorous negotiation incorporating economic evaluations, budget impact analysis, payment linked to clinical outcomes and designing clinical pathways for appropriate technology use; 3) monitoring and data collection at the patient level; and (4) result evaluation.

Despite technical and political challenges, the region should move toward centralized regional procurement to increase negotiating power and achieve lower prices. PAHO has successfully done this for antiretrovirals for hepatitis C patients.

In segments with one or two generic or biosimilar alternatives, governments should consider inverse tenders, funding only the drug from the manufacturer offering a lowest price. This method, used in New Zealand, could be beneficial for drugs like adalimumab and lenalidomide.

In markets where the innovator drug's patent has expired and the active ingredient has various alternatives with significant price dispersion, a tender with a reduced number of competitors could be a solution. Alternatively, more transparency could be given to drug transactions between buyers and distributors or suppliers, disclosing the prices paid for each active ingredient and the distribution chains' margins.

» **Promoting the entry of biosimilars**. Expediting the approval process and promotion for biosimilars can help reduce prices for some high-cost drugs. Clear processes and criteria must be set to determine that a biosimilar is interchangeable with the innovator.

» **Mandatory licenses.** Vincent Rajkumar [20] posits that countries "should be more willing to use compulsory licensing to lower the cost of specific prescription drugs when negotiations with drug manufacturers on reasonable pricing fail or encounter unacceptable delays. This process permitted under the Doha declaration of 2001, allows countries to override patent protection and issue a license to manufacture and distribute a given prescription drug at low cost in the interest of public health." Both Colombia and Brazil have adopted this approach in specific instances.

ANNEX

TABLE A1 Potential Savings as a Percentage of Total Spending, Health Spending, Drug Spending and Spending on Other Household Items by Substituting for Generic Drugs in Households that Buy Drugs

	Potential savings (million dollars)	% of total spending		% of health spending		% of drug spending	
		Potential savings (%)	95% CI	Potential savings (%)	95% CI	Potential savings (%)	95% CI
Total	283.2	0.4%	[0.4 - 3.5]	3.8%	[4.1 - 3.5]	10.4%	[10.8 - 10]
Breakdown by insurance type							
FONASA	174.8	0.3%	[0.4 - 0.3]	3.7%	[3.9 - 3.5]	9.2%	[9.7 - 8.8]
ISAPRE and others	108.4	0.7%	[0.8 - 0.7]	6.3%	[8.5 - 4.9]	20.7%	[22.8 - 19]
Breakdown by education level							
< 9 years of education	49.2	0.6%	[0.6 - 0.6]	5.9%	[6.6 - 5.3]	12.4%	[13.7 - 11.3]
9-12 years of education	111.6	0.7%	[0.7 - 0.7]	7.3%	[7.9 - 6.7]	17.7%	[19.2 - 16.4]
> 12 years of education	122.4	0.3%	[0.4 - 0.3]	3.4%	[4.0 - 3.0]	10.0%	[10.7 - 9.4]

	% of spending on transport		% of spending on food		% of spending on recreation	
	Potential savings (%)	95% CI	Potential savings (%)	95% CI	Potential savings (%)	95% CI
Total	2.4%	[2.5 - 2.3]	2.1%	[2.1 - 2.0]	5.1%	[5.4 - 4.9]
Breakdown by insurance type						
FONASA	2.3%	[2.4 - 2.2]	1.8%	[1.9 - 1.7]	5.1%	[5.4 - 4.8]
ISAPRE and others	4.8%	[5.4 - 4.4]	5.4%	[5.8 - 5.0]	9.3%	[10.6 - 8.3]
Breakdown by education level						
< 9 years of education	4.9%	[5.6 - 4.4]	2.1%	[2.3 - 2.0]	10.2%	[12.6 - 8.5]
9-12 years of education	5.1%	[5.5 - 4.8]	3.0%	[3.2 - 2.8]	11.7%	[13 - 10.6]
> 12 years of education	2.1%	[2.3 - 2.0]	2.4%	[2.6 - 2.3]	4.6%	[4.9 - 4.3]

NOTES

[1] In principle, branded drugs should have no additional clinical benefit over their unbranded generic equivalents; both should possess the same quality and clinical benefit to be available on the market. This assumes that drugs undergo a rigorous approval process to ensure their equivalence before they are allowed into the market.

[2] For Chile, the estimation was conducted for 2017 and is presented in current dollars. For the Dominican Republic, the savings estimation was conducted for 2019, with results presented in 2022 dollars. The cost of covering the mentioned gaps was calculated in 2022 dollars.

[3] For the Dominican Republic it was assumed that the savings for the contributive regime are proportional to the savings reported for the entire retail market, based on calculations from IQVIA data.

[4] More specifically, the authors conducted an exhaustive revision of licenses from the Instituto de Salud Pública de Chile, valid for 2017, covering 70 percent (in value) of markets where IQVIA only records sales of innovators. This review found that segments with licenses of non-innovative products represented 58 percent of total sales in this set. It is also worth noting that a smaller fraction of these segments with no generic licenses in Chile have generic health records in the United States.

[5] The 10- and 20-year time frames are in line with the time frames in the clinical cost-effectiveness studies for both diseases.

[6] The spending throughout the treatment is discounted at rates ranging from 3 to 5 percent depending on the rate used by the original study.

[7] The case studies further detail the calculations.

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