Securing access, improving lives.

Strengthening patients' access to medicines in Europe

NEW ANGLE Simplicity in complex systems

SEPTEMBER 2025

REPORT

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ACRONYMS

AGCM	Autorita' Garante della Concorrenza e del Mercato (Italian Competition Authority)
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
ALBVVG	Act to Combat Drug Shortages and Improve Supply (Germany)
AMNOG	The Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganisation Act)
AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredients
ATC	Anatomical Therapeutic Chemical
ATMPs	Advanced Therapy Medicinal Products
BfArM	Bundesinstitut fur Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CEO	Chief Executive Officer
CMA	Critical Medicines Act
COG	Cost of Goods
CSRD	Corporate Sustainability Reporting Directive
DHSC	Department of Health and Social Care
EC	European Commission
EEA	European Economic Area
EHIF	Estonia Health Insurance Fund
EMA	European Medicines Agency
EPRS	European Parliamentary Research Service
ERP	External Reference Pricing
EU	European Union
EURIPID	European Medicine Database
EPRS	European Parliamentary Research Service
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FinStG	Financial Stabilization Act
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice

GKV	German Statutory Health Insurance Funds
HICP	Harmonized Indices of Consumer Prices
HTA	Health Technology Assessment
INN	International Nonproprietary Name
IRP	Internal Reference Pricing
MAH	Marketing Authorization Holder
MEAT	Most Economically Advantageous Tender
MFG	Medizinforschungsgesetz (Medical Research Act)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPF	Nordic Pharmaceutical Forum
OHE	Office of Health Economics
PHAS	Sweden's Public Health Agency
PPI	Purchase Power Parity
PPRI	Pharmaceutical Pricing and Reimbursement Information
PV	Pharmacovigilance
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
SEK	Swedish Krona
SGEI	Service of General Economic Interest
SHI	Staff Health Insurance
SMPA	Swedish Medical Products Agency
SNS	Serviço Nacional de Saúde (Portugal National Health Service)
SPMS	Serviços Partilhados da Saúde (Health Shared Services)
SSN	Serviço Sanitário Nacional (Italian National Health Service)
TLV	Tandvårds- och läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency)
UK	United Kingdom
UWWRD	Urban Waste Water Treatment Directive
VAM	Value-Added Medicine
VPAG	Voluntary Scheme for Branded Medicines Pricing Access and Growth
VPAS	Voluntary Pricing and Access Scheme
WHO	World Health Organization

I. INTRODUCTION

1. Why do off-patent medicines matter?

In disease areas with the highest public health impact, off-patent[1] medicines are typically the first treatment option. As a result, the effectiveness of public health initiatives in enhancing population health relies heavily on ensuring access to and proper use of these lower-cost medicines[1].

Antibiotics, selected as a case-study, are the cornerstone of modern medicine, essential for treating bacterial infections and preventing complications in various medical procedures, highlighting a problem faced by several other off-patent medicines. However, Europe has been grappling with recurring shortages of vital medicines, such as off-patent antibiotics, jeopardizing patient care and public health.

> *"Antibiotic resistance is one of the most urgent threats to public health. The development of antibiotic resistance can be reduced by the use of narrow-spectrum antibiotics that target specific bacteria, meaning that fewer non-harmful bacteria are killed and other harmful bacteria are not exposed to selection pressure."*[2]

In 2019, European Union (EU) countries reported over 1,300 cases of antibiotic shortages. These shortages can drive increased reliance on broad-spectrum antibiotics, potentially leading to long-term consequences. **When first-choice antibiotics are not available, and patients are instead provided with a suboptimal antibiotic with a different therapeutic spectrum**, this can lead to poorer patient outcomes and an increased risk of adverse effects. It can also contribute to a rise in antimicrobial resistance (AMR), particularly if the alternative has a broader spectrum, and increased healthcare costs[3,4].

Price pressures on off-patent medicines force manufacturers to prioritize efficient production to remain viable. This continued pressure contributes to market consolidation and reduced medicine availability, creating a vicious cycle. While price pressures have allowed health systems to reduce their expenditure on pharmaceutical products, it **has resulted in less**

[1] Off-patent medicines correspond to the mature medicines, branded, generic and biosimilar ones. They are medicines which launch happened several years ago (at least 10 years ago). In this report we will also use the term essential medicines due to the importance of off-patent antibiotics for populations and public health.

diversified and consequently more fragile supply chains, that are lean to the point of vulnerability.

Amoxicillin is an example, where availability has fluctuated, and shortages occurred frequently in recent years, due to price pressures and, consequently, concentration of manufacturers of active substance worldwide[4]. Some European Governments, worried about antibiotic shortages have tried to find ways to incentivize greater production in Europe such as the case of the manufacturing site in Kundl, Austria, with the aim to strengthen the long-term future of integrated antibiotics manufacturing in Europe[5,6].

Shortages can have multiple causes, such as: (a) supply chain vulnerabilities, mostly due to a small number of suppliers, geopolitical and trade risks; (b) regulatory and manufacturing limitations, due to regulatory barriers to market re-entry and reliance of few manufacturers of API; and (c) market concentration due to financial pressure, low prices, low volume and low profitability[4].

Most medicines that are permanently withdrawn from a particular market are **products with low or negative margins**, for which the Market Authorization Holder (MAH) faces **an unviable situation** as the revenue on the product doesn't support the costs of maintaining the product on the market. This might happen because market conditions no longer enable a sufficient profit margin on the product[4].

2. Overview of European Pricing Policies

External and Internal Reference Pricing (ERP and IRP) are widely used pharmaceutical pricing policies that significantly influence access to off-patent medicines, including antibiotics, but they also contribute to shortages and access problems in several countries. ERP often leads to price convergence at the lowest price among reference countries, which can drive prices down, through regular revisions. This can cause companies to withdraw products from markets where prices are too low, reducing availability and causing shortages. Also, ERP depends on transparent, comparable price data, which is often lacking or inconsistent. This can cause unpredictable price changes and complicate supply planning.

Internal reference pricing (IRP) is widely used in Europe to regulate the medicines market by setting a financing threshold, usually applied for groups of interchangeable medicines. In most

countries, IRP targets mostly reimbursable medicines totally or partially funded by national health systems or insurers. IRP works to group medicines with similar therapeutic effects or active ingredients and sets a maximum price based on either average or lowest-cost product within the group, often leading to very low prices, squeezing manufacturer margins and reducing incentives to supply or produce off-patent medicines. Also, tendering and rebate contracts can lead to a concentrated supply among few low-price suppliers, increasing vulnerability to supply disruptions[7].

Payback/clawback mechanisms applied to off-patent medicines, designed to have an extra-economic government funding or to control pharmaceutical spending, can inadvertently cause shortages and access problems for off-patent medicines by reducing manufacturers' incentives to supply these products. This issue is particularly prominent in the European Union, where diverse national pricing and reimbursement policies, combined with payback/clawback mechanisms, exacerbate the problem. The European Parliamentary Research Service (EPRS) highlights that many EU countries impose pricing and reimbursement controls, including payback schemes, which contribute to shortages and access problems[8]. When manufacturers face mandatory paybacks or rebates, especially on off-patent low-margin medicines, they may find continued production financially unattractive, or ultimately, unviable. This can lead to withdrawal or reduced supply of these medicines, causing shortages. Off-patent medicines generate lower profits than new originator medicines. Payback demands reduce profitability further, prompting companies to stop marketing these medicines in certain countries. Overall, payback mechanisms are part of broader cost-containment efforts that include price controls and reimbursement restrictions, which can reduce market attractiveness and availability[7].

The Union list of critical medicines highlights those whose shortage would cause serious harm. Many of these are off-patent medicines with low profit margins, vulnerable to supply interruptions driven by economic factors and cost containment policies [9]. **Antibiotics (e.g., Amoxicillin)** are among the medicine groups that are most affected by these cost containment policies[10], often resulting in shortages, such as the one that began in October 2022 due to increased respiratory infections driving demand and manufacturing capacity issues. Economic pressures including payback mechanisms reduce incentives for manufacturers to maintain production of low-margin antibiotics, contributing to supply gaps. Some intermittent supply problems persist across EU countries despite easing in others. Policy responses focus on

improving cooperation, transparency, and supply chain resilience, alongside efforts to balance cost containment with sustainable medicine availability.

Tendering mechanisms are procurement processes where public buyers (e.g., hospitals, health systems) invite suppliers to bid for contracts to supply medicines, often awarding contracts based primarily on the lowest price. While intended to reduce costs, these mechanisms can cause market concentration by favouring a single or very few low-cost suppliers. This reduces supplier diversity and resilience, increasing the risk of supply disruptions or shortages if a winning supplier faces production issues. Tendering also creates price pressure that may push manufacturers to exit or limit investment in manufacturing, leading to production delays. Lack of multi-winner tenders or flexible procurement rules further exacerbate vulnerability to shortages[7].

3. Other policies and factors affecting the prices

In addition to price policies, environmental, social, governance compliance and logistical aspects have impact on the prices.

Transport and Supply Chain

Rising **energy, materials and freight prices**, **logistics disruptions**, and **trade tensions** contribute to **higher input costs**, particularly for low-margin off-patent medicines—the industry can rarely pass these costs on[11].

Environmental regulations such as Extended Producer Responsibility require additional investments, for instance, on advanced wastewater treatment to remove pharmaceutical residues. A Swedish case study estimated these costs can add 0,5% to 4,5% to pharmaceutical budgets. When borne entirely by MAHs, up to 24% of product lines could fall below break-even pricing thresholds, which will critically affect off-patent medicines, which already have very low margins[12].

Environmental Compliance

New **EU environmental regulations** (e.g. Registration, Evaluation, Authorization and Restriction of Chemicals - REACH chemicals law, carbon emission pricing, expanded restricted substances lists) cost chemical firms, which supply the pharma industry, an estimated

€20 billion annually. These firms spend **up to 10% of capital budgets on compliance.** Pharmaceutical manufacturers face these indirect cost and other direct costs (eg, UWWRD, CSRD), escalating production costs. These costs disproportionately load onto **low-margin off-patent products**[13].

While green chemistry and sustainability initiatives can reduce waste and long-run costs, the upfront investment burden is significant—especially for low-margin off-patent medicines. Realized savings are often delayed or marginal compared to the capital outlay. Still, some firms view them as necessary for compliance and reputational reasons[14].

Regulatory Compliance

Regulatory compliance spans **GMP, GCP, PV, audits, traceability**, and documentation across clinical, manufacturing, logistics, and IT—adding overhead and indirect cost. E.g., Pfizer's latest impact report highlights intensive global audits across the product lifecycle[15]. Medicines in Europe face increasing **regulatory complexity** for labelling, batch release, pharmacovigilance, and environmental regulation, adding both cost and timeline burdens that disproportionately affect narrow margin off-patent products[16].

Implication for off-patent medicines

According to the *Critical Medicines Alliance strategic report*, the full cost of producing medicines in Europe can be **2,5–5 times higher** than in India or China; margins are eroded heavily by supply-chain and regulatory burdens. Off-patent products are typically low-volume and face **downward reimbursement pressure** (ERP/IRP) in Europe, making it **difficult to absorb rising upstream costs**[16].

4. Objectives and research questions

This study aims to examine the economic and policy factors affecting the viability and availability of off-patent medicines in Europe, mainly price-related, with the objective of identifying vulnerabilities and proposing actionable policy solutions. We chose to focus on antibiotic pricing, as a therapeutic case-study representing off-patent medicines, due to their critical importance to public health. The study covers 16 European countries (table 1) and is based on a mix of literature review (scientific and grey) and a quantitative analysis for off-patent antibiotics. Most antibiotics are off-patent medicines, and issues related to access and

availability are widespread across this therapeutic class. To ensure clarity and enable meaningful analysis, specific baskets of off-patent antibiotics were selected for in-depth examination.

Table 1: Scope of countries included in the study

Austria	Belgium	Croatia	Estonia	Finland	Germany
Hungary	Ireland	Italy	Norway	Poland	Portugal
Spain	Sweden	Switzerland	UK		

The main question we will answer with the study is:

What is the evolution of off-patent antibiotic prices and its relationship with the evolution of costs and economic indicators? Which policy solutions can be proposed to enhance access?

From this question we have derived four other questions that we explore in the study:

- What are the specific vulnerabilities and challenges faced by off-patent medicines, particularized in the baskets of antibiotics in Europe?
- How do changes in their prices compare with changes in inflation and COGs?
- Apart from direct COGs, which other costs are impacting the cost of medicines and contributing to price pressures?
- Which price policies have been implemented by European countries?
- What policy solutions can be proposed to enhance access to off-patent critical medicines, namely antibiotics, at the national level across Europe?

The table below clarifies the focus to be followed for each research question.

Table 2: Conceptual focus for each research question

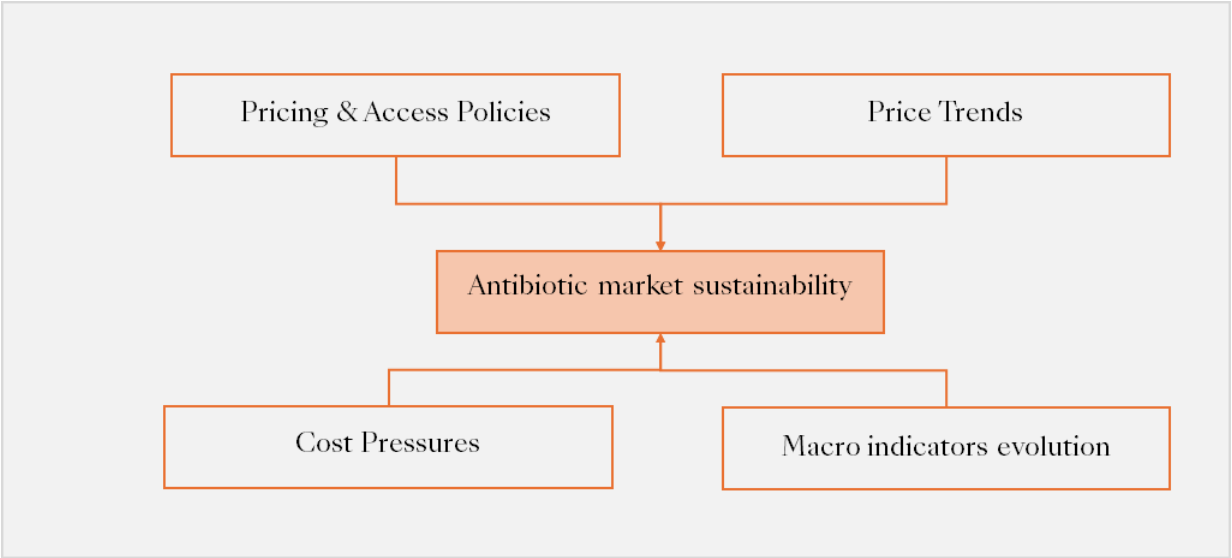
Research question	Conceptual focus
What are the specific vulnerabilities and challenges faced by off-patent medicines in Europe?	Analyse pricing mechanisms and their impacts. For off-patent antibiotics, analyse price evolution, market exit trends, structural fragility of supply chains, and shortages.
How do changes in antibiotic prices compare with changes in inflation and COGs?	Analyse price trends relative to inflation and COGs for a basket for the countries in scope.
Apart from direct COG, which other costs are impacting the cost of medicines and contributing to price pressures?	Analyse transportation costs, regulatory burden, quality compliance, ESG pressures.
Which price policies have been implemented by European countries?	Analyse study cases on pricing policies, procurement, and other approaches followed by selected countries, and measures undertaken to overcome problems, namely shortages and withdrawals of needed off-patent medicines.
What policy solutions can be proposed to enhance access to mature critical medicines at the national level across Europe?	Draft proposals for national or EU level policies that can promote access, resilience, and availability of critical off-patent medicines, with a focus on antibiotics.

II. METHODOLOGY

Off-patent medicines refer to mature medicines, branded, generic or biosimilar, whose period of exclusivity under intellectual property rights has expired, meaning that their patent and regulatory data protection no longer prevents competitors from marketing similar versions of it (even improved with new strengths or new pharmaceutical forms or fixed dose combinations). Usually, they are medicines originators launched several years ago (at least 10 years ago).

The image below depicts the conceptual framework for our analysis:

Fig. 1: Conceptual Framework



We have defined the following information and variables in relation to the key concepts that we will explore.

Table 3: Key concepts and variables

Concept	**Information / Variables**
Price trends	• Molecule (INN) and general ex-factory retail price trends
Pricing and access policies	• External and Internal Reference Pricing • Payback/ clawback and extraordinary contributions

Concept	Information / Variables
	• Mandatory discounts • Rebates • Price freezes and price cuts • Tender mechanisms • Pharmaceutical budget
Macro indicators evolution	Evolution of: • Harmonised Index of Consumer Prices (HICP) All Items • HICP Food and non-alcoholic beverages • Industrial Labor Cost Index • Industrial Producer Price Index • Other COGs costs, such as electricity, gas, aluminium and package materials
Cost pressures	Cost pressures such as transport costs, environmental and ESG compliance costs and regulatory compliance burden

A mixed methods approach was used:

- A quantitative method to explore antibiotic price trends for the period 2020 to 2024 for a basket of the top 10 antibiotics (chosen by sales value in 2024)[2] for each country, costs and economic indicators exploring the relationships between them.
- A qualitative method with a scoping review of literature on policies and issues related to pricing mechanisms and shortages and interviews with local professionals for four selected countries (Italy, Portugal, Sweden and United Kingdom).

[2] IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. Counting units is the smallest unit of measure defined by IQVIA for a product form. It represents the number of individual tablets, millilitres of liquid, grams of ointment, and so on for each product purchased. Similar product or pack dosage forms can be compared, and the effect of different pack sizes eliminated

Based on the defined methodology, we prepared the following analysis with the aim of answering our research questions:

- Trend comparisons: evolution of the price of antibiotics vs. inflation and cost indices, highlighting major issues and gaps.
- Description of policy mechanisms in place, withdrawals and potential resulting vulnerabilities.
- Deep dives into selected country cases or specific antibiotics pricing trends.
- Draft policy recommendations for improving the availability of off-patent medicines.

In Annex 1, the methodology is further described and detailed, including metadata on the indicators used.

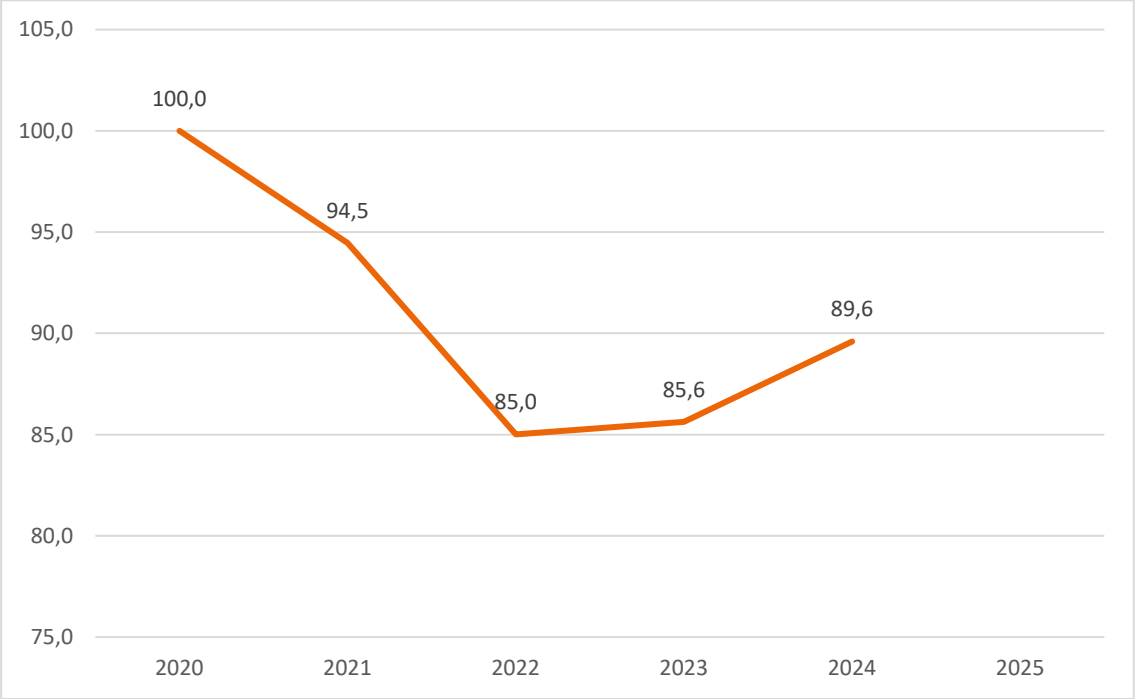
III. MAIN FINDINGS

1. Price evolution for off-patent antibiotics and their availability

We have analysed the price evolution of a basket composed of the top 10 antibiotic INNs for each country, selected based on the ex-factory retail revenue as of 2024. Thirty INNs were considered in total[3].

Our analysis shows that **for the top 10 most used INNs** in these 16 countries, **prices in 2024 are lower than they were in 2020.**

Figure 1: Price index for the top 10 INN in each country



Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. 2020 index=100. New Angle analysis.

On average, prices decreased by 15% from 2020 to 2022, followed by a 4,6% increase from 2022 to 2024 as certain measures began to be implemented in some countries. Overall, **the net decline in prices was 10,4%.** Extremely low prices have raised concerns about the viability and

[3] Amoxicillin, Amoxicillin Clavulanic Acid, Azithromycin, Aztreonam, Cefaclor, Cefadroxil, Cefalexin, Cefditoren Pivoxil, Cefixime, Cefpodoxime Proxetil, Cefprozil, Ceftriaxone, Cefuroxime Axetil, Ciprofloxacin, Clarithromycin, Clindamycin, Colistin, Dicloxacillin, Doxycycline, Erythromycin, Flucloxacillin, Levofloxacin, Lymecycline, Moxifloxacin, Penicillin V, Pivmecillinam, Sulfamethoxazole Trimethoprim, Sultamicillin, Tobramycin, Trimethoprim.

availability of certain molecules. **Amoxicillin, Amoxicillin with Clavulanic Acid, and Azithromycin**, together accounted for 52% of total sales revenue in 2024—**experienced price drops of 18,9%, 5,9%, and 7,9%,** respectively. Dicloxacillin, Trimethoprim (only commercialized in Norway), and the combination of Sulfamethoxazole and Trimethoprim (only commercialized in Poland, saw the largest price increases, but represented only 0,3% of total sales revenue. Overall, price increases were observed in medicines accounting for 19,6% of total sales revenue, while price decreases affected medicines representing 80,4% of total sales revenue.

Table 4: Price index evolution for the top 10 INNs (All countries), 2020-2024

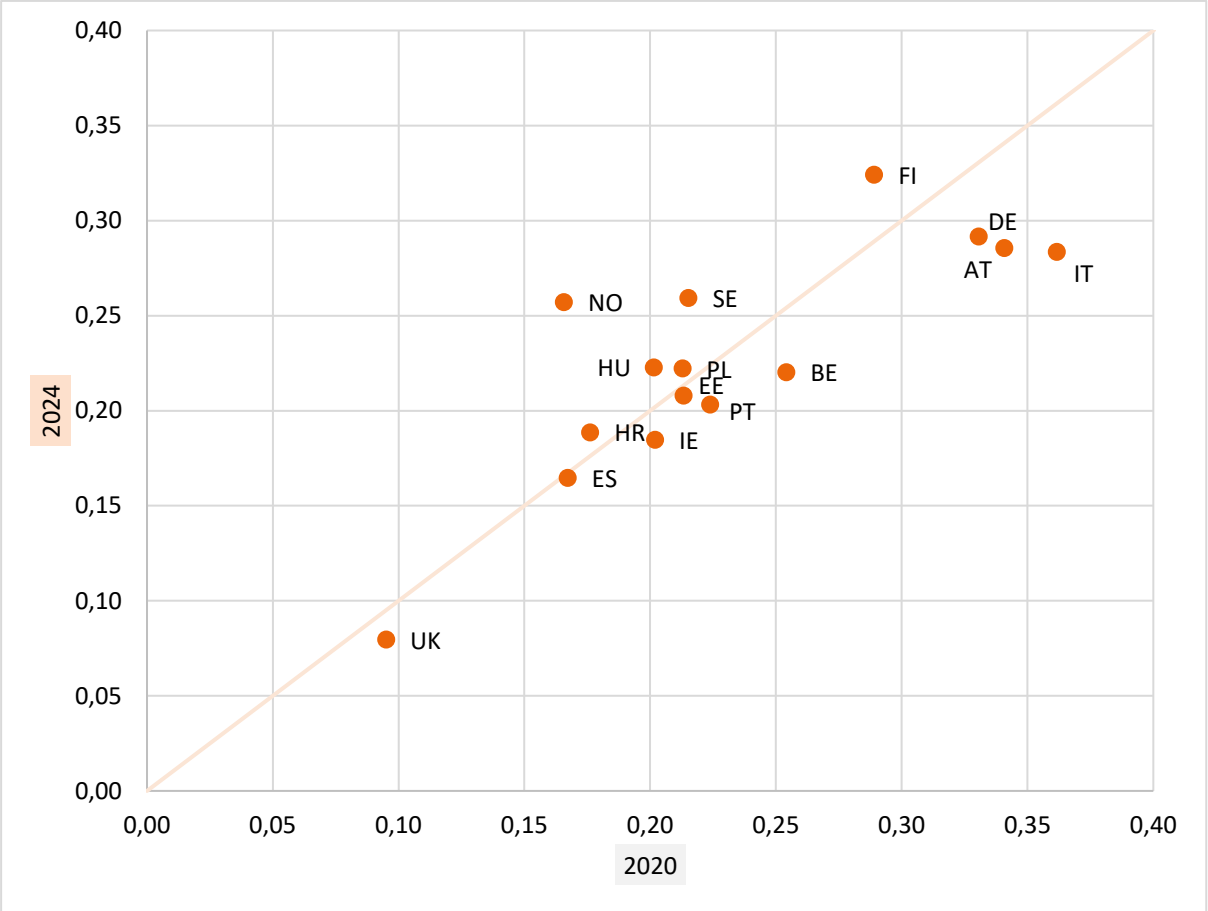
	INDEX					
INN	2020	2021	2022	2023	2024	TREND
DICLOXACILLIN	100,00	110,54	112,79	126,89	173,91	
TRIMETHOPRIM	100,00	102,66	111,92	129,72	149,14	
SULFAMETHOXAZOLE¦TRIMETHOI	100,00	81,23	83,63	116,20	141,33	
ERYTHROMYCIN	100,00	110,01	100,10	105,25	118,38	
CEFACLOR	100,00	111,41	94,05	88,89	115,83	
PIVMECILLINAM	100,00	99,96	93,80	99,13	113,84	
CEFUROXIME AXETIL	100,00	114,75	97,30	85,35	109,52	
CLARITHROMYCIN	100,00	93,36	87,14	107,01	102,19	
CLINDAMYCIN	100,00	98,07	102,13	105,12	102,18	
CEFDITOREN PIVOXIL	100,00	100,47	99,85	100,33	101,65	
CEFPROZIL	100,00	91,61	98,72	93,93	101,53	
CEFPODOXIME PROXETIL	100,00	86,50	89,50	75,55	99,83	
CIPROFLOXACIN	100,00	98,68	98,95	100,63	99,35	
PENICILLIN V	100,00	94,92	68,51	92,48	98,97	
LEVOFLOXACIN	100,00	96,83	99,08	101,39	98,43	
SULTAMICILLIN	100,00	96,77	88,14	88,94	98,28	
TOBRAMYCIN	100,00	95,41	91,18	98,63	97,71	
AZTREONAM	100,00	99,89	100,03	99,09	97,16	
MOXIFLOXACIN	100,00	96,82	95,83	95,80	95,55	
AMOXICILLIN¦CLAVULANIC ACID	100,00	97,48	90,46	90,54	94,11	
CEFTRIAXONE	100,00	100,76	99,70	96,06	93,52	
CEFADROXIL	100,00	71,77	63,73	50,53	93,39	
COLISTIN	100,00	100,62	106,92	99,19	92,38	
AZITHROMYCIN	100,00	93,34	93,77	92,03	92,11	
CEFALEXIN	100,00	94,93	79,60	91,26	90,66	
FLUCLOXACILLIN	100,00	88,97	77,74	92,35	85,98	
DOXYCYCLINE	100,00	86,08	70,42	73,10	85,95	
CEFIXIME	100,00	90,57	86,08	77,18	85,59	
AMOXICILLIN	100,00	90,60	82,54	84,83	81,11	
LYMECYCLINE	100,00	111,31	89,45	84,15	78,53	

Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. Baseline 2020 = 100. New Angle analysis.

In general, **most countries had price decreases** to their top 10 INNs in the period from 2020 to 2024. Although some countries had price increases over the period, notably Norway, Sweden and Finland, **most of them had price decreases, the highest being in Switzerland and Italy, with -26,5% and -21,6% respectively.** A few countries had price increases from 2023, as countries started to implement some initiatives to minimize the unstainable prices.

The graph below shows the countries for which prices have increased and those for which prices have decreased in the period from 2020 to 2024. All countries below the 45º line, have had price decreases for their top 10 INN during the period. Switzerland is an outlier as prices have dropped 26,5% in the period (not shown in the graph due to scale), the highest change in the countries analysed.

Figure 2: Price changes per country, 2020-2024



Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024. Price per counting unit. New Angle analysis.

In the last four years, several products have been withdrawn from the market, including molecules that belong to Union list of critical medicines list[9]. In some countries for some molecules, the number of suppliers and products in the market is very low, creating a greater risk of shortages and access to medicines. In total, 240 products for the top 10 INN in the 16 countries were withdrawn from the market. Only 7 INNs out of 20 didn't have any product withdrawal in the period, highlighting the potential vulnerabilities in the market.

Table 5: Medicines withdrawals from 2020-2024

INN	# OF PRODUCTS	PRODUCT WITHDRAWALS	% WITHDRAWALS	# OF SHORTAGES	CRITICAL MEDICINE
AMOXICILLIN	125	27	21,6%	29	YES
AMOXICILLIN&CLAVULANIC ACID	185	46	24,9%	60	YES
AZITHROMYCIN	182	31	17,0%	32	YES
AZTREONAM	2	0	0,0%	1	YES
CEFACLOR	8	0	0,0%	6	
CEFADROXIL	1	0	0,0%	2	
CEFALEXIN	19	4	21,1%	2	
CEFDITOREN PIVOXIL	4	0	0,0%		
CEFIXIME	19	3	15,8%	6	YES
CEFPODOXIME PROXETIL	20	1	5,0%	5	
CEFPROZIL	1	0	0,0%		
CEFTRIAXONE	42	6	14,3%	16	YES
CEFUROXIME AXETIL	60	16	26,7%	4	YES
CIPROFLOXACIN	137	24	17,5%	50	YES

INN	# OF PRODUCTS	PRODUCT WITHDRAWALS	% WITHDRAWALS	# OF SHORTAGES	CRITICAL MEDICINE
CLARITHROMYCIN	124	28	22,6%	48	YES
CLINDAMYCIN	53	4	7,5%	11	YES
COLISTIN	22	0	0,0%	1	
DICLOXACILLIN	4	2	50,0%		
DOXYCYCLINE	39	7	17,9%	21	YES
ERYTHROMYCIN	14	4	28,6%		YES
FLUCLOXACILLIN	23	6	26,1%	7	YES
LEVOFLOXACIN	90	11	12,2%	27	YES
LYMECYCLINE	14	1	7,1%	3	
MOXIFLOXACIN	5	1	20,0%	19	
PENICILLIN V	35	4	11,4%	14	YES
PIVMECILLINAM	12	2	16,7%		
SULFAMETHOXAZOLE &TRIMETHOPRIM	14	7	50,0%	5	
SULTAMICILLIN	10	2	20,0%		
TOBRAMYCIN	23	3	13,0%	16	YES
TRIMETHOPRIM	2	0	0,0%		YES
TOTAL	**1.289**	**240**	**18,6%**	385	

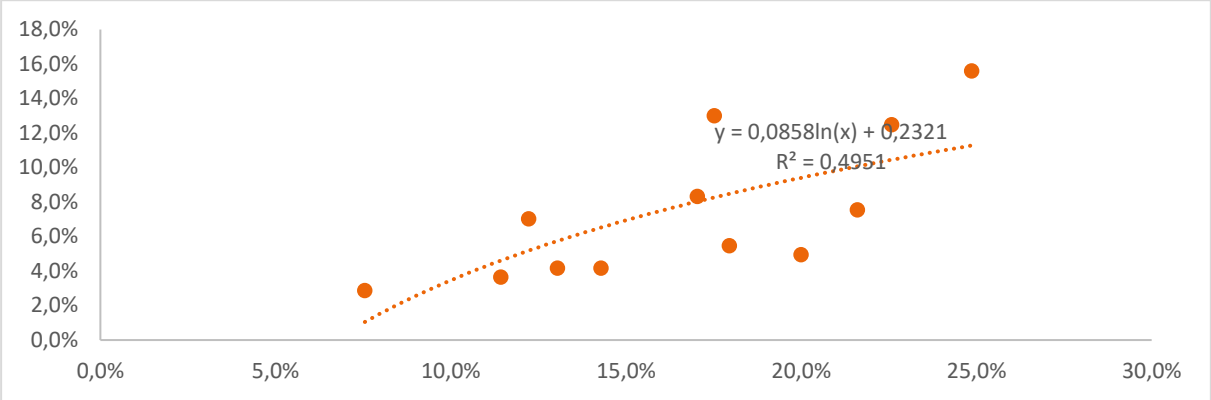
Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. Shortages were obtained from the national medicines' agencies in each country during the period from 23rd June to 7th July and they reflect shortages at a point in time. Information not available for Estonia. New Angle analysis.

A significant proportion of INNs (~77%) had shortages reported between 23rd June and 7 July 2025. Shortages were usually higher for molecules with withdrawals. About 74% of the shortages are in INNs that had more than 15% of their products withdrawn from the market.

That is the case for Amoxicillin, Amoxicillin and Clavulanic Acid, Azithromycin, Ciprofloxacin and Clarithromycin, which each had more than 25 shortages on those days.

The following graph highlights the trend between higher withdrawals and higher shortages (for all shortages that represent more than 2% of the shortages).

Figure 3: Shortages vs withdrawals



Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. Shortages were obtained from the national medicines' agencies in each country during the period from 23rd June to 7th July and they reflect shortages at a point in time. Information not available for Estonia. New Angle analysis.

Shortages per country are highlighted in the table below.

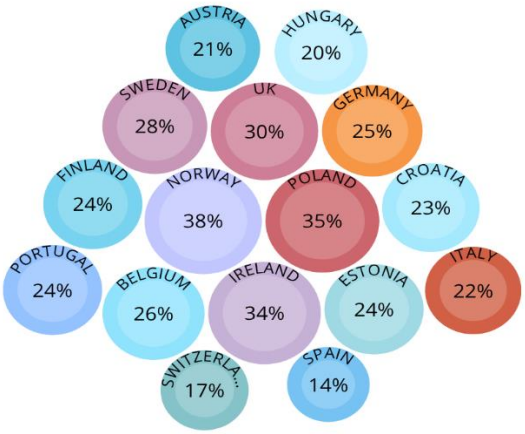
Table 6: Medicines shortages per country, for INN included in the basket

Austria	Belgium	Croatia	Finland	Germany
15	14	12	19	15
Hungary	Ireland	Italy	Norway	Poland
52	16	109	6	14
Portugal	Spain	Sweden	Switzerland	UK
40	17	31	24	0

Shortages were obtained from the national medicines' agencies in each country during the period from 23rd June to 7th July and they reflect shortages at a point in time. Information not available for Estonia. New Angle analysis.

If all retail products commercialized in the 16 countries were considered, 683 products, corresponding to 14%, have been withdrawn from the market from 2020 to 2024. Norway, Poland and Ireland had the most withdrawals, 38%, 35% and 34% of total products, respectively. The countries that withdrew the least products were from Spain and Switzerland with 14% and 17% of total products, respectively.

Figure 4: Percentage of products withdrawn from countries from 2020 to 2024



Source: IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. New Angle analysis.

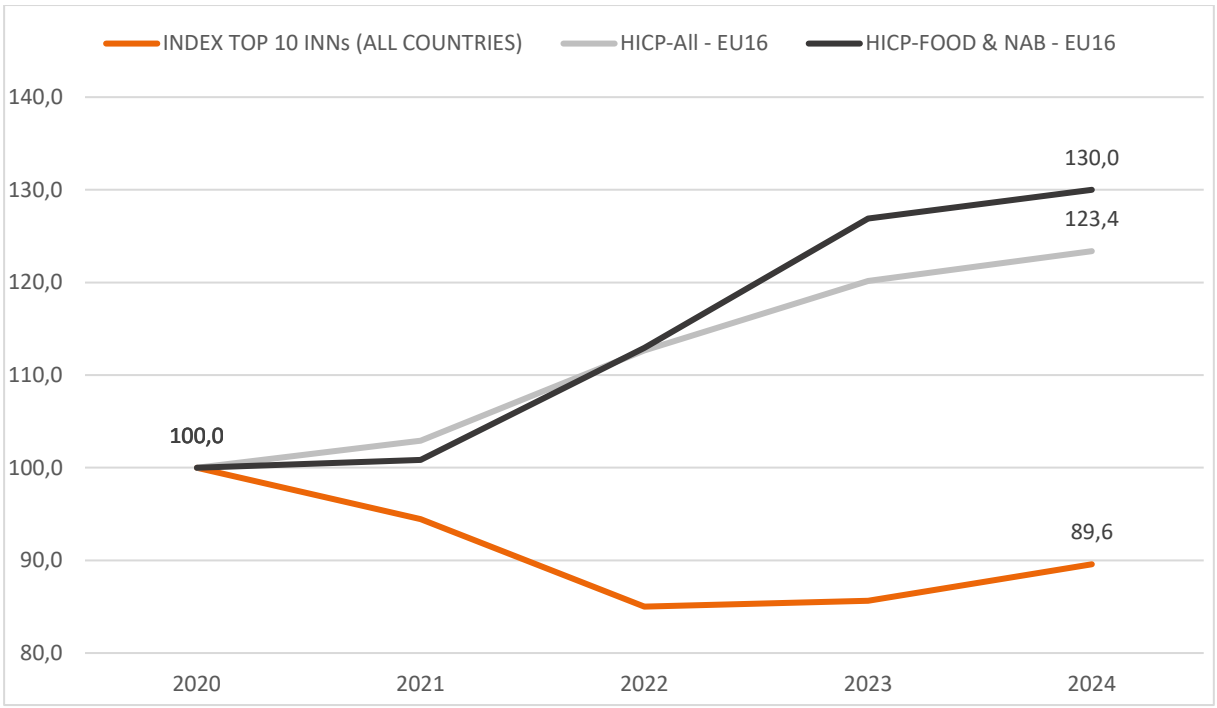
With withdrawals and for certain INNs that have a higher concentration of suppliers, shortages become a major problem. Even for INNs with many suppliers, such as Amoxycillin, shortages have been an issue in many countries.

2. Compared analysis with COGs and economic indicators

While off-patent medicines prices have decreased from 2020 to 2024, **most of the Cost of Goods used in production and inflation have gone up substantially**, generating a gap that risks viability and availability. In several countries, policies have been drafted to solve some of the problems that are surging due to low off-patent prices, as we will discuss further in this study.

From 2020 to 2024 **inflation grew by 30% and 23,4%** for food and non-alcoholic beverages and general inflation, respectively, while **off-patent antibiotic prices** for the top 10 INN, **decreased by 10,4%.**

Figure 5: INN average price index with HICP and HICP – Food and NAB indexes comparison

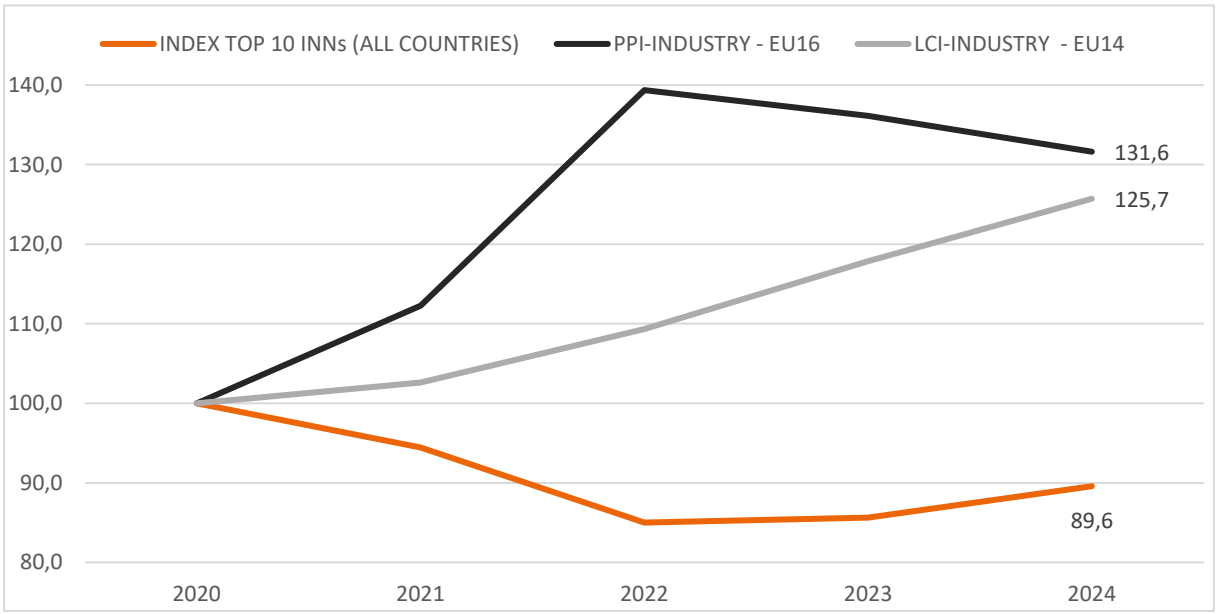


Source: (1) IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. (2) Eurostat and Office for National Statistics (UK). 2020 index=100. New Angle Analysis.

COGs with impact on medicine production costs have also increased substantially to a level that risks creating vulnerabilities in the supply chain, as companies find ways to optimize costs to be able to maintain their products in the market.

As information about production costs is not available, we have used the **production price index** for industry as a proxy, which **increased 31,6%** in the period. **Labor costs**, which are significant production costs for medicines, **increased 25,7%,** while prices dropped 10,4%, creating a significant pressure for off-patent antibiotics included in the basket.

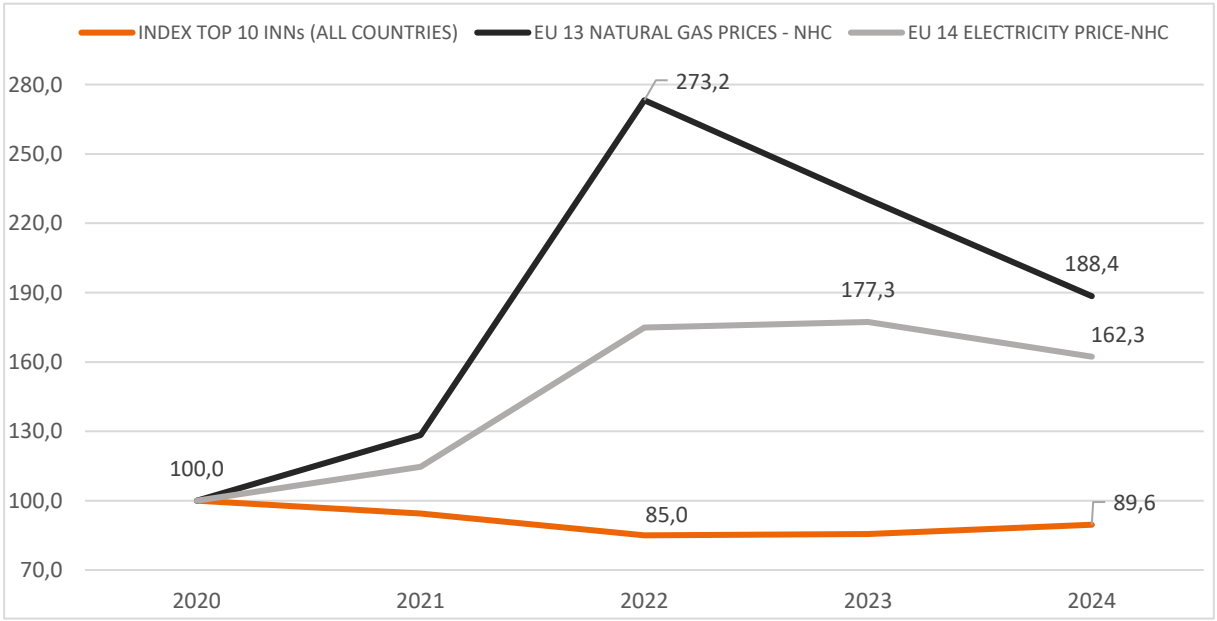
Figure 6: INN average price index with PPI industry and LCI industry indexes comparison



Source: (1) IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. (2) Eurostat and Office for National Statistics from each country (for industry PPI). 2020 index=100. Labor costs not available for Switzerland and Sweden. New Angle analysis.

Energy prices, electricity and gas, had huge increases during the period 2020 to 2024, mainly gas in 2022, which increased by 173,2%. Although prices have since stabilized somewhat, the increase in 2024 was still 88,4% and 62,3% for natural gas and electricity respectively.

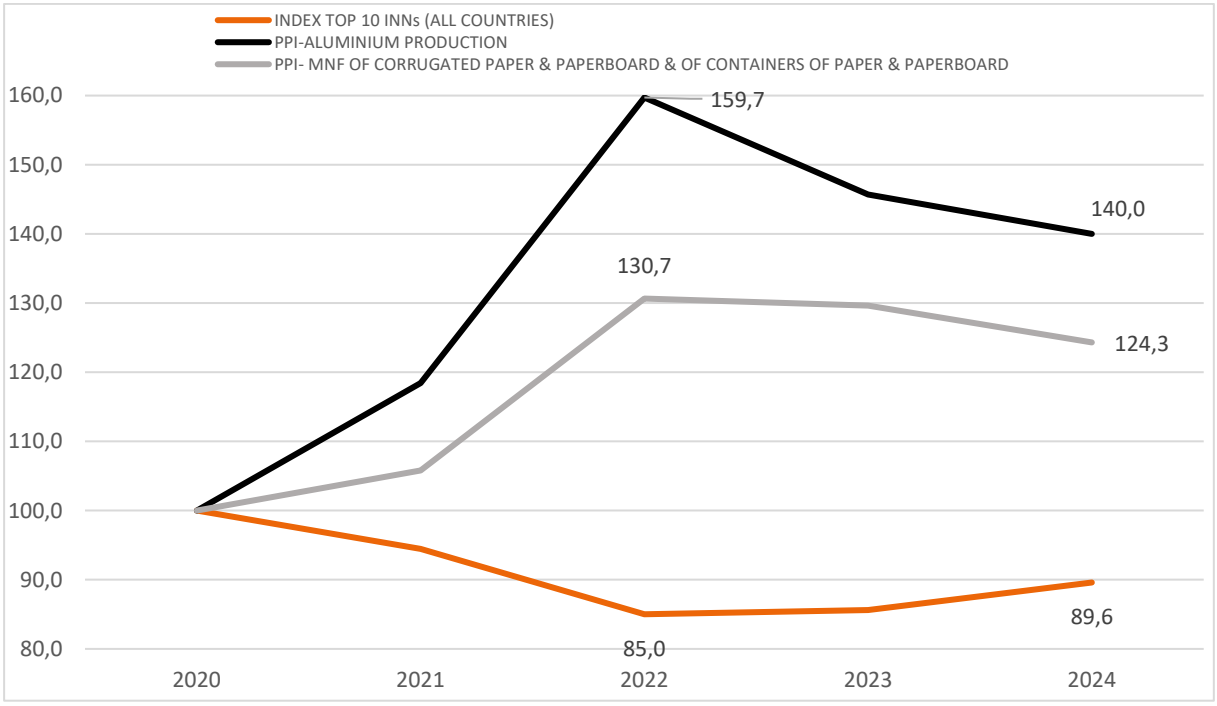
Figure 7: INN average price index with Electricity and Natural Gas prices for non-household consumers



Source: (1) IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. (2) Eurostat. Natural gas prices for non-household consumers not available for Norway, Switzerland and United Kingdom. Electricity prices for non-household consumers not available for Switzerland and United Kingdom. 2020 index=100. Analysis prepared by New Angle.

The following graph highlights **the increase in prices for aluminium production** and for **corrugated paper and paperboard**, which are also part of the costs to produce medicines. PPI for aluminium reached 159,7 index value in 2022 falling to 140 in 2024, representing a 40% increase from 2020. PPI for corrugated paper and paperboard, also increased by 24,7% by 2024.

Figure 8: INN average price index with PPI aluminium production and PPI of corrugated paper and paperboard



Source: (1) IQVIA Midas Data, Ex-Factory Price in EUR (LEU MNF) & Counting Units, FY 2020-2024, extracted on 31st May 2025. (2) Eurostat. PPI aluminium production and PPI-MNF of corrugated paper & paperboard & containers of paper & paperboard are presented for EU 27. 2020 index=100. New Angle analysis.

The significant increase in input costs has pressured the margins of medicines, particularly of off-patent medicines as they are already operating on the low margin side, to make them affordable and competitive to treat many diseases.

In the following chapter we will highlight some of the problems and issues felt in some of the countries, along with some interventions that have been tested or implemented with the aim of improving off-patent medicines' viability and availability.

3. Main policies pressuring off-patent medicines prices

3.A. Budget Controls (Including Payback/clawback, rebates, price cuts, extraordinary contributions)

Clawback (or payback or extraordinary contributions) policies require pharmaceutical manufacturers, wholesalers, or pharmacies to refund a percentage of sales or revenues, when public pharmaceutical spending exceeds predefined thresholds. While intended to contain costs, these mechanisms often apply broadly across reimbursable medicines, including off-patent medicines, such as antibiotics, which typically operate at very low margins. These policies disproportionately impact low-volume, low-margin medicines—notably off-patent medicines[7].

Clawbacks compound the effects of reference pricing and mandatory price cuts, driving down net revenues close to or below production cost – especially for injectable or small-volume medicines. **Clawbacks jeopardize supply continuity of mature medicines when applied without product-specific exemptions**[7].

Price freezes

In pharmaceutical policy, a **price freeze** (also known as a **price moratorium**) refers to regulatory restrictions that prevent manufacturers from **raising the list or reimbursement price** of certain medicines for a defined period. The freeze maintains prices at historical levels, often without periodic adjustment for inflation or cost increases – effectively locking them in[17].

Off-patent antibiotics, as other off-patent medicines, are already subject to aggressive cost-containment measures, and are often too low-priced to absorb inflation or manufacturing cost increases under a price freeze. Since these products are not frequently adjusted upward in price, profit margins shrink annually, discouraging manufacturers from maintaining supply.

Germany is one example who executed a price moratorium. Germany enforces a price freeze on drugs launched before August 1, 2009 (“price moratorium”), extended through 2026 under the GKV-FinStG reform. Prices subject to the price moratorium may be adjusted once a year according to the inflation rate[18].

Mandatory Price Cuts & Statutory Rebates

Some EU countries **mandate automatic statutory price cuts** for generics and originators upon patent expiry or fixed intervals. One example is Spain who introduced extensive price reductions to control pharmaceutical expenditure. By Royal Decree-Law 4/2010 (March 2010), **originator (brand-name) products older than 10 years**, with available generics, were subject to a **7,5% mandatory price reduction** on their industrial (ex-factory) price. If there was **no generic equivalent**, but the product had been on market for 10 years with an available equivalent in other EU countries, a **30% price cut** applied[19].

Germany levies a general rebate of 7–12% on manufacturer prices, plus additional 10% on generics (2023–2024), effectively reducing net revenues substantially[20]. **Portugal** has implemented the so-called "extraordinary contribution" between 2,5%–14,3% of the ex-factory price, applied to all reimbursable medicines for out-patient or inpatient use[21]. Noteworthy to say that Portugal experienced off-patent medicines shortages due to diminished financial incentives for the manufacturers, as small-volume, off-patent medicines—already low-priced—see net revenues shrink further under enforced cuts and rebates, often falling below production costs. Evidence from numerous Medicines for Europe and EC reviews notes unsustainably thin margins drive manufacturers to exit markets or drop specific antibiotic lines[7].

OHE, EU, and academic studies consistently link drug shortages—particularly off-patent antibiotics, to cumulative pricing pressures from rebates, freezes, and blanket cuts. In the past, multiple EU countries report decreasing supplier diversity, with around one-third of generic antibiotic molecules having disappeared in a 10-year period[22]. Essential antibiotics (paediatric forms, injectables) are frequently vulnerable, because their volume-based revenue cannot withstand enforced rebates.

Some selected cases from Europe are presented below.

Portugal Case

Challenge

In response to a high budget deficit and to rising pharmaceutical expenditures, **Portugal adopted a series of cost-containment measures to ensure both fiscal sustainability and continued access to essential medicines**[23]. These efforts intensified during the Troika

intervention period (2011–2014), which emphasized budgetary discipline within the healthcare system. Two central components of this policy framework are: (1) **an extraordinary contribution** for all medicines and (2) the payback mechanism applied to innovative medicines, aimed at controlling pharmaceutical spending within annually negotiated limits between the government and the pharmaceutical industry[21,24].

The extraordinary contribution for the pharmaceutical industry, established under the State Budget Law for 2015 (Law n.º 82-B/2014, of 31 December), defines contribution rates according to the classification of products. This contribution became **mandatory for almost all financed medicines** and health products sold to the National Health System (SNS) in Portugal and has been in place since then. The contribution is applied to the total sales volume for reimbursed medicines and other medical products. Rates vary from 2,5% to 10,4% (or 14,3% if sold to hospitals of SNS)[21].

While **these policies** help to control the National Health Service budget, it **can also exert downward pressure on net prices and margins for medicines,** with a great impact on low margin off-patent medicines. This, in turn, may disincentivize continued market supply or investment in low-margin, essential medicines. To mitigate shortage risks, Infarmed incorporates complementary measures such as mandatory safety stock requirements and real-time supply monitoring to guard against shortages, which further erodes margins for off-patent medicines[25,26]. In essence, given the narrow profit margins already present for off-patent medicines, the application of the extraordinary contribution further reduces economic viability for manufacturers and increases the risk that manufacturers will withdraw low-volume medicines, **jeopardizing their availability and continuity.** Reduced incentives to maintain off-patent antibiotic lines have the potential to lead to **supply shortages**, hindering patient access to critical essential medicines.

Overall, Portugal's extraordinary contribution policies reflect a broader strategy to balance cost-containment with medicines stewardship and market sustainability. Although off-patent medicines are not exempt from extraordinary contribution, severe shortages in some medicines have led to indirect safeguards aimed at maintaining availability, such as close monitoring of the market and stocks, as described in the following section.

Policy intervention

Portugal, to address and mitigate the risks of shortage of off-patent medicines, including antibiotics, implemented some measures[25,26]:

- Maintain at least a **two-month safety stock** of essential medicines by Marketing Authorization Holders (MAHs). Any potential shortage must be **declared at least two months in advance** to Infarmed, enabling early intervention.
- **Supply Assurance Plans** by MAHs to proactively assess and manage risks across production and distribution chains.
- **Stock Management Plans** will be developed by Infarmed, with support from MAHs, in the case of critical shortage scenarios, including controlled medicine distribution, therapeutic alternative identification, and regional stock allocation supervision by Infarmed,
- T**emporary export bans or prior-notification requirements** for critical medicines (often including off-patent antibiotics), ensuring domestic supply is prioritized over exports. During shortages, Infarmed implements controlled distribution and prioritization, allocating available stocks to critical healthcare facilities first.

The above-mentioned measures do not address prices, margins or financial pressures on the manufacturers of off-patent antibiotics, rather, they are focused on how a possible shortage can be managed and mitigated through operational measures. Nevertheless, Portugal has a list of essential medicines, and the manufacturer can apply for a set of supportive measures for such medicines, as example, apply for exceptional price review[27] .

Spain Case

Challenge

Since the financial crisis of 2010–2012, Spain has implemented a series of cost-containment measures in response to rising public pharmaceutical expenditures. Among these, **IRP has led to very low prices that in many cases don't allow to recover from increasing costs.** In Spain **more than 50% of generics volume is sold below the reference price threshold (established at € 1,6).** There is no price increase regulatory recognition and current fixed discounts for off-

patent medicines[28,29] . **Spain implemented broad austerity reforms** that were codified through successive Royal Decrees, such as RD 4/2010, RD 8/2010, and RD 9/2011, which **mandated price reductions and tightened reimbursement systems for a wide range of pharmaceutical products**—including off-patent antibiotics. Spain's National Health Service (SNS) continues to face financial pressure, requiring policies that ensure budget sustainability while maintaining access to essential medicines. [19,30–32].

Key features of the mechanism include **mandatory discounts** as set in Royal Decree-Law 8/2010 Article 8 where a **7,5% deduction** on the **industrial price** (manufacturer's ex-factory price) of non-generic reimbursed medicines sold through **retail pharmacies** is mandated. **Article 9** extends the **same 7,5% deduction** to hospital, health centre, and primary-care pharmacy **procurements**, applied to the **tender award price** rather than the retail markup. In hospital or primary care **purchases,** the **price used is the agreed tender award price**. This applies even if the award price is significantly below the standard **retail pharmacy price**, since hospitals use their own purchasing channel. In the case of orphan medicines, the discount applied is only 4%. For off-patent medicines for which a generic is not marketed in Spain, a 15% discount applies[19,30,31].

This policy led to significant consequences for the viability and availability of off-patent medicines, such as:

- **Margin Erosion**: Off-patent medicines, already sold at low prices, faced additional margin pressures due to both reference pricing and clawbacks.
- **Supply Shortages**: Spain has experienced shortages of critical antibiotics, such as paediatric amoxicillin. These have been partially attributed to low profitability under the current pricing and clawback structure.
- **Market Withdrawal Risk**: Small-volume suppliers tried to exit the market due to reduced net revenues, jeopardizing the supply of essential off-patent antibiotics.
- **Accessibility Challenges**: Given the critical role of antibiotics in public health, such pressures raised serious concerns about ensuring continued patient access to these therapies.

Policy Intervention

Spain has been moving towards new pharmaceutical pricing reforms with some very relevant positive steps taken recently, seeking sustainability and innovation:

- Exceptional 40% price increase of paediatric antibiotics applied in 2023[33] .
- Incremental Innovation (Value-Added Medicine – VAM) recognition at an amendment of Spanish Law for State Agency Creation, approved July 2024 modifies for the first time article 98 of Spanish Medicines Law. Enabling reference price exceptions & price increase in, amongst other[34]:
    - Medicines Incremental innovations proving patient value: new combinations, indications.
    - Strategic Medicines and Paediatric Presentations

The concept of strategic medicines for which regulatory or economic measures might be needed to guarantee its presence in the market due to clinical motives or vulnerabilities in the supply chain, has been introduced[35].

Sweden Case

Sweden's Challenge: *Low sales volumes undermining profitability*

Sweden is a small market which uses older narrow-spectrum antibiotics more frequently compared to other countries[36]. Low sales volumes for several of the older antibiotic products imply that costs of regulatory compliance and administrative efforts are relatively high compared with a product with high sales volumes. Sweden faced significant challenges with access to critical antibiotics, that resulted not only from a small market size but also from payback/clawback mechanisms for off-patent medicines such as antibiotics, which contributed to shortages. The consequence of shortage may be that an antibiotic with a broader spectrum must be used, which entails an increased risk for antibiotic resistance[36].

These challenges stemmed from the financial disincentives making it economically unsustainable to enter the Swedish market or keep older, off-patent medicines on the market. This situation led to manufacturers withdrawing antibiotics (for example **Ceftibuten Category A** was withdrawn from the Swedish market in **2017** and few paediatric narrow span ones pulled afterwards)[2], prioritizing larger markets like Germany or the UK instead, thus causing shortages in Sweden[37].

Sweden's policy intervention: *Annual revenue guarantees for antibiotics targeting priority pathogens, securing minimum revenues*

A low sales value is an important indicator that a product risks leaving the market and to prevent and overcome possible shortages, Sweden designed a novel reimbursement model aimed at ensuring the availability of medically important antibiotics. This followed a pilot where The Public Health Agency of Sweden (PHAS) was mandated to test and evaluate a new reimbursement model aiming to ensure that particularly important antibiotics for hospital use are made available in Sweden. During the preparation stage, PHAS defined the foundational principles of the reimbursement model intended for testing.

The pilot was conducted with e**ligible products that include** activity against **carbapenem-resistant** pathogens (WHO priority pathogens) with defined clinical indications and with stock and delivery-time along with certain **environmental** requirements. During the pilot study, the **state guaranteed pharmaceutical companies a minimum annual revenue** in exchange for maintaining a buffer stock of antibiotics included in a list of antibiotics of special medical value. This model partially delinked reimbursement from sales volume, providing financial incentives for companies to enter the Swedish market[38,39].

The mechanism of pilot study (Phase 1)[39]**:** The designed reimbursement model mainly operates as a pull mechanism, wherein revenue is **partially** delinked from actual sales. Under this scheme, pharmaceutical companies receive financial compensation contingent upon quarterly verification that a distributor maintains a buffer stock equivalent to six months of standard consumption for each specified product. The mechanism can be seen as a two-component approach: (1) A top-up as a revenue guarantee by the government in case the sales remain low and (2) A stock incentive.

The guaranteed annual revenue for each antibiotic was calculated using the following formula:

Minimum Revenue = Defined Stock Volume × Template Price per Pack × 1,5

- **Defined Stock Volume**: Based on estimated medical needs in a "worst-case scenario" to handle unpredictable global delivery issues.
- **Template Price per Pack**: A standardized price assigned to each antibiotic pack.
- **Multiplier (1,5)**: Applied to cover additional costs associated with maintaining buffer stocks and ensuring readiness.

The state guaranteed a minimum revenue of **SEK 4 million** per product annually. If regional sales fell short of this amount, the state compensated the difference. In case actual **annual sales revenue for the selected product remains below a guaranteed floor**, the **state is to pay a top-up** up to the guarantee (SEK **4.000.000 per product/year** in the pilot).

The **"stock incentive"** (10% of the guarantee) is **paid regardless of sales**, to compensate the cost of maintaining an agreed **in-country security stock** and **24-hour delivery** capability. Accordingly, **10% of the annual guaranteed minimum revenue** is provided as an extra incentive for all products, even if annual sales exceeded the reimbursement level. This aimed to cover costs for maintaining availability as per the agreement.

The pilot included agreements with four companies to stockpile and deliver specific antibiotics within set time frames, which proved effective in improving availability.

A closer look at the conditions of pilot enrolment: Pharmaceutical companies participating in the **pilot** were required to:

- **Ensure Prompt Delivery**: Guarantee delivery of the antibiotic within 24 hours of ordering.
- **Meet Specific Criteria**: Antibiotics included in the pilot had to be approved by the EU Commission and demonstrate good activity against at least one of the following carbapenem-resistant pathogens: *Enterobacterales, Pseudomonas aeruginosa,* or *Acinetobacter baumannii.* They should have a bactericidal effect and possess a safety profile similar to β-lactam antibiotics. Also, they should be approved for treating infections in patients with limited treatment options or for at least two of the following conditions:
    - Complicated intra-abdominal infections.
    - Complicated urinary tract infections.
    - Hospital-acquired pneumonia.
- **Adhere to Environmental Considerations**: Comply with environmental requirements set forth in the agreement.

Failure to meet these conditions could result in reductions to the guaranteed revenue. The pilot study involved agreements with four pharmaceutical companies supplying five antibiotics:

- **MSD**: Recarbrio (imipenem/relebactam) and Zerbaxa (ceftolozane/tazobactam).
- **Pharmaprim**: Vaborem (meropenem/vaborbactam).

- **Unimedic Pharma**: Fosfomycin Infectopharm (fosfomycin).
- **Shionogi**: Fetcroja (cefiderocol).

Key results of the pilot implementation included[39,40]:

- **Enhanced Availability**: Sweden achieved availability of the selected antibiotics under the program.
- **Targeted Use**: The antibiotics were used for a limited but critically ill patient group who had few treatment options.
- **Cost-Effectiveness**: Average top-up the government paid to fill gaps between actual sales and guaranteed income remained at a level of just SEK 2 million per product (The difference comes from variability in actual market sales of the antibiotic products.).
- **Market Impact:** Introduction of new antibiotics led to reduced sales of certain older antibiotics, possibly due to medical replacement.
- **Stock Management**: A relatively large cancellation of unsold products indicated that stock volume requirements might need adjustment.

The evaluation concluded that the reimbursement model effectively ensured the availability of critical antibiotics and recommended its continuation with potential refinements.

Consequences for off-patent antibiotics and expansion (Phase 2): After the pilot, by end of June 2023, the Public Health Agency of Sweden was commissioned to carry out a preliminary study of a new reimbursement model where pharmaceutical companies receive compensation for providing a buffer stock of certain prioritised **off-patent antibiotics**. Hence, Sweden is exploring a **separate track** for **older off-patent antibiotics** focused on **keeping them in the market** and a **buffer-stock reimbursement** (a national buffer-lager model). That **buffer-stock** proposal is **distinct** from the 2020–2022 **revenue-guarantee pilot** and aims specifically at paying for **stockholding** of prioritised older products. The agency has established criteria and procedural guidelines for the proposed reimbursement model and has identified a set of prioritised off-patent antibiotics recommended for inclusion. The selection methodology draws upon a previously published **priority list of clinically significant antibiotics deemed at risk of limited availability**. From this list, specific delineations were applied—giving precedence to older antibiotics that are recommended as first-line therapies and lack interchangeable alternatives. **The model is intended to incentivize continued market**

availability of the selected products in Sweden. An annual stockholding compensation of SEK 400.000 per selected product is defined. For products generating less than SEK 850.000 in annual sales, supplementary compensation is to be provided to bridge the gap[40,41].

In summary, Sweden addressed the challenges posed by clawback/payback mechanisms and market withdrawal of mature antibiotics by introducing a reimbursement model guaranteeing minimum revenues for stockpiling, exploring government-supported storage incentives, and planning state-involved production to stabilize antibiotic availability and prevent shortages.

UK Case

UK's Challenge: Structural weaknesses, spending caps, and low margins undermine supply resilience

The UK's recurring shortages of mature off-patent medicines arise from structural weaknesses—very low margins, rigid low-cost procurement, concentrated globalised supply, and limited incentives for building resilience. These vulnerabilities mean demand surges or production disruptions can rapidly trigger shortages, for which some recent measures are being proposed[42] . While the UK recognises free market principles and uses price concessions to raise reimbursement temporarily during shortages, this reactive approach cannot secure long-term stability[43–45] . Under the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS[4]), branded medicine manufacturers are required to repay a percentage of their revenues to the Department of Health and Social Care (DHSC) when NHS spending exceeds an agreed cap. Although intended to control NHS drug expenditure, this uniform rebate mechanism (regardless of therapeutic area or medicine importance) created economic disincentives for companies selling low-margin, essential antibiotics, especially older ones (which reached 26,5% in 2023)[43,44].

Some highlights from the interview with a UK local representative reveals key challenges:

- *The generics market has effectively a free pricing market.*

[4] From 2024, there were changes in the scheme, now Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG).

- *Prices of off-patent antibiotics are very low, hence there is limited antibiotics portfolio in the UK.*
- *There is an ongoing boom-bust supply cycle, which is mainly based on small number of suppliers: scarcity of suppliers leads to supply issues and then suppliers drop out as it becomes unprofitable. Then the prices spike and then the government must effectively pay more to get suppliers to come back into the market. Suppliers drop out because it's not profitable and the price goes up, then they come back in again.*
- *There is a phenomenon such as concessionary prices. Accordingly, when pharmacies report back that they're not able to buy the product, the government then implements concessionary pricing. This is a* ***reactive price increase mechanism*** *when market prices fall so low that products become unavailable.*

Subscription Model: Netflix of Antibiotics

This model implemented by the UK does not target off-patent medicines, rather, focuses on novel antibiotics. However given the innovative and inspiring nature of the model, it is included as a case study in this report.

In 2022, the UK experimented with a "Netflix-like" subscription model (Antibiotic-Specific Procurement Pilot or "Netflix Model"), paying a fixed annual fee to pharmaceutical companies for antibiotics regardless of sales volume, aiming to decouple revenue from sales and incentivize supply stability. Accordingly, antibiotics targeting drug-resistant infections, especially those caused by WHO-priority pathogens are selected. Drugs are then categorized into four bands, with annual payments ranging from £5 million to £20 million, reflecting their assessed value. This approach is piloted by NHS England, initiated in 2019, in collaboration with NICE and DHSC and for two antibiotics:

- **Cefiderocol (Fetcroja)**: A novel siderophore cephalosporin effective against multidrug-resistant Gram-negative bacteria.
- **Ceftazidime-avibactam (Zavicefta)**: A combination therapy targeting resistant bacterial infections.

NICE evaluated each antibiotic's value based on criteria like clinical effectiveness, supply security, stewardship, and environmental impact. Both antibiotics were awarded subscription

contracts in July 2022, each valued at up to £10 million annually. Initial contracts span three years, with options extending to 15 years, aligning with the product's exclusivity period. These agreements provide manufacturers with predictable revenue streams, encouraging continued investment in antibiotic development[46–49].

Although this approach is not yet scaled to off-patent antibiotics, it reflects recognition of the flaw in using volume-linked pricing mechanisms for low-demand but high-value antibiotics. In May 2024, following the pilot's success, the model was expanded to include more antibiotics, with the NHS launching tenders for contracts estimated at £1,9 billion over 16 years[49]. The UK's approach has inspired similar initiatives in other countries, such as the pilot program in Sweden.

This **subscription model for antibiotics** provides a novel and stable revenue mechanism that **directly incentivizes the development and supply of new antibiotics**, counteracting the negative effects of traditional pricing pressures. This model has been recognized as a promising solution to the antibiotic market failure and is designed to align public health goals with commercial viability[50].

In addition to the abovementioned pilot implementation, **UK has been debating on the Voluntary Pricing and Access Scheme (VPAS) Reforms**, as during consultations for the 2024 successor to VPAS, industry and public health advocates (e.g., the AMR Industry Alliance) argued for exemptions or reduced rebate rates for essential, off-patent, or low-volume medicines such as off-patent antibiotics. While the full implementation of such reforms is still evolving, it reflects pressure on policymakers to avoid applying flat rates that deter supply of essential medicines.

Further **to address the shortages, price concessions are offered by Department of Health and Social Care (DHSC) to temporarily allow wholesalers to be reimbursed more than the standard NHS tariff price during shortage periods**—effectively offsetting commercial losses. This mechanism has been used for certain antibiotics (e.g., phenoxymethylpenicillin during the 2022/23 strep A outbreak), acting as an ad hoc buffer to clawback-driven supply exits[51].

Findings from countries with and without payback/clawback/extraordinary contribution mechanisms

Some countries choose to implement payback/clawback/extraordinary contribution policies to prevent and to control the expenses with medicines, while some countries do not implement such mechanism on off-patent medicines to secure better access to these medicines. Accordingly, Belgium, Hungary, Italy, Portugal and Spain implement payback/clawback/extraordinary contribution on off-patent medicines, while others do not. In essence,

- Countries with industry-level payback/clawback/extraordinary contribution mechanisms (Belgium, Hungary, Italy, Poland, Portugal and Spain) lead to reduced profitability and increased exit risk from the market[23].
- Countries without payback/clawbacks or where they are product-level and include only innovative medicines and/or some off-patent medicines (Austria, Croatia, Estonia, Finland, Germany, Ireland, Norway, Switzerland[5], Sweden, UK) provide a less punitive environment—although low reimbursement prices remain a challenge[23].
- UK uniquely protects generics, as payback/clawbacks apply only to branded presentations under VPAG/Statutory schemes[23].

Below is a summary of countries with respect to their position on payback/clawback/extraordinary contribution policies:

Country	Industry- wide Payback/ Clawback/extraordinary contribution?	Applies to Off- Patent Medicines?[23]	Implication for Off-patent Antibiotic Supply
Austria	No (except for products not included in the national reimbursement list)	No (except for products not included in the national reimbursement list)	While most products are not subject to a clawback, medicines not included in the reimbursement list (Code of Reimbursement) that exceeds a 750 k€

[5] With the implementation of the Cost Containment Package 2, planned for 2027, a significant volume-based clawback mechanism is planned, which will further erode revenues and margins for off-patent medicines.

Country	Industry- wide Payback/ Clawback/extraordinary contribution?	Applies to Off- Patent Medicines?[23]	Implication for Off-patent Antibiotic Supply
			cost for 12 months for social security will be retrospectively subject to ERP added by a 6,5% discount to be paid back[52]. Although not implementing a sector wide payback/clawback helps sustainability yet does not stop shortage risks completely.
Belgium	Yes	Yes	Further pressures prices down
Croatia	No (only product-specific)	No	Low prices still challenge
Estonia	No	No	Access unstable due to low market prices
Finland	No	No	Better sustainability
Germany	Yes	No	Not subject to payback/clawback; only standard rebates apply
Hungary	Yes	Partial	High burden; unstable supply
Ireland	No	No	Access risk due to low margin
Italy	Yes	Yes	Risk of exit of low-profit antibiotics
Norway	No	No	Stable supply likely
Poland	No	No	Reference price only; moderate viability

Country	Industry- wide Payback/ Clawback/extraordinary contribution?	Applies to Off- Patent Medicines?[23]	Implication for Off-patent Antibiotic Supply
Portugal	Yes, extraordinary contribution is applicable to almost all medicines. Yes, clawback for new innovative medicines with ceiling for sales	Yes (just the extraordinary contribution)	Puts additional burden on MAH; may challenge supply of low-margin products.
Spain	Yes	Yes	Market unattractive for low-profit antibiotics; supply risk remains.
Sweden	No	No	Favourable environment for off-patent antibiotics. No retrospective clawback burdens off-patent antibiotics; retains higher likelihood of continued availability.
Switzerland	No typical clawback, although the Cost Containment Package 2, planned for 2027, will introduce it	No	Some cost pressure exists, but no universal clawback, which will change with the new package further eroding revenues and margins for off-patent medicines.
UK	Yes (generics exempt)	No	Mature generics safe; branded suppressed

3 B Tendering

Tendering is a competitive procurement process in which public (or hospital) buyers request bids from manufacturers or suppliers for a defined set of medicines. The aim is to award a

supply contract—often to the lowest bidder, though other criteria (e.g., delivery guarantees, quality) may also be considered. Tendering is recognized as a key procurement instrument across Europe[7] and is used widely at the:

- National level (e.g., centralized public procurement).
- Regional level (e.g., decentralized purchasing).
- Hospital level (e.g., single-facility or consortium purchasing).

Tendering can cover:

- **Single-winner tenders**: only one supplier is selected (most cost-saving but higher risk).
- **Multi-winner tenders**: multiple suppliers are contracted (higher resilience but less saving).

Tendering is widely adopted because of its ability to:

- **Drive down medicine prices**, especially for **generic or off-patent products.**
- Improve **budget predictability** for payers.
- Enable **bulk purchasing power.**
- Promote **transparency** and **efficiency** in procurement.
- In some cases, secure **supply commitments and penalties** in the contract to reduce shortage risks.

It is particularly prevalent in countries with **strong public healthcare financing systems**, such as Sweden, Norway and Croatia. Off-patent medicines are **prime targets for tendering** as:

- They are many times high-volume and often produced by multiple manufacturers.
- Patents have expired, allowing generic entry.
- Governments seek to maximize cost savings in essential medicine classes.

Tendering has potential risks regarding the sustainability of supply from manufacturers' perspective[3,7]:

- **Race to the bottom in pricing**: Tendering incentivizes ultra-low pricing, which may undercut production costs, especially when manufacturing is complex (e.g., for injectables or sterile antibiotics).

- **Winner-takes-all risks**: Single-winner tenders, common in hospital procurement, eliminate competition and increase dependency on one supplier. If that supplier exits or has a disruption, shortages occur.
- **Short tender cycles**: Short-term contracts (1–2 years) discourage manufacturers from investing in supply stability, especially for low-margin mature medicines.
- **Volume unpredictability**: In some systems, tender volumes are not guaranteed, but pricing is fixed, further eroding predictability and profitability.
- **Reduced manufacturer participation**: Companies may choose not to participate in tenders if expected margins are too low, leading to fewer suppliers and increased vulnerability to shortages.

The **cumulative effect** of tendering and other policies (e.g., IRP/ERP, mandatory rebates, clawbacks) leads to:

- **Margin squeeze**: Some antibiotics, particularly **older injectable beta-lactams**, become **commercially unattractive.**
- **Disincentivized production**: Manufacturers may **divert capacity to more profitable markets or products** (e.g., oncology).
- **Market exits**: Documented cases where companies withdrew from tenders due to unsustainable pricing (e.g., amoxicillin suspension shortages in Spain, Portugal, and Ireland).
- **Supply disruptions**: Over-reliance on a **single winner** can backfire if that supplier faces API shortages, manufacturing quality issues, or recalls.

Spain's paediatric amoxicillin shortages (2022–2023) was partly attributed to unsustainable pricing and lack of competition due to aggressive hospital tendering. In **Ireland**: Tender-based purchasing has led to **low prices** but **limited manufacturer interest.** For **Croatia,** World Bank 2023 policy note warned that excessive reliance on tendering may **undermine supplier diversity** for essential generics like antibiotics. **In Sweden**: Multiple actors requesting **reform of essential medicine tendering**, including longer contracts, dual supplier models, and non-price criteria.

Some examples across Europe include:

Country	Tendering Level	Specific Notes Related to Off-Patent Antibiotics
Norway	National	Multi-supplier tenders used for hospital procurement; includes off-patent antibiotics; criteria include quality and delivery.
Croatia	National and hospital level (occasionally)	Tenders used only for hospital procurement conducted by MoH on national level or individual hospital in some cases. Price is a primary criterion; has led to market exits for low-margin medicines.
Estonia	National	Electronic procurement system; generic antibiotics are tendered widely; few bidders in some cases.
Finland	Hospital (decentralized)	Hospital districts manage tenders; short contract cycles; low participation for some injectables.
Germany	Limited to SHIs	SHIs can conduct rebate contracts. The ALBVVG requires health insurance companies to issue tenders for antibiotics separately for active ingredient manufacturers from mainly Europe and other countries, thereby strengthening European suppliers.
UK	Regional/hospital	NHS Supply Chain manages tenders; off-patent antibiotics included in hospital framework contracts.
Portugal	Hospital-focused	Hospital purchasing centralised under SPMS; Hospitals direct purchasing under strict budget controls; bid prices, when competition is in place, drop significantly and very fast.
Sweden	Regional	County councils organize periodic tenders; pricing for essential antibiotics medicines heavily constrained.

Some cases for a closer look are presented below:

Belgium Case

Aggressive austerity-driven price cuts combined with tendering have led to supplier exits and shortages, especially in hospital procurement. Belgium is exploring price-volume trade-offs

and multi-winner tendering to improve supply security. Belgium has been a key player in advocating for better policies for critical medicines:

- **Critical Medicines Alliance and Strategic Leadership (Since 2024)**[53]**:** Belgium played a central role in establishing the Critical Medicines Alliance in April 2024 during its Presidency of the EU Council. The Alliance brings together policymakers, industry, healthcare stakeholders, and EU Member States to identify supply chain bottlenecks and recommend sustainable solutions to medicine shortages, including those caused by tendering mechanisms. Belgium's Federal Agency for Medicines and Health Products (FAMHP) has been deeply involved, with its CEO serving as vice-chair of the Alliance's Steering Board and experts contributing to all thematic working groups. The Alliance's strategic report (February 2025) forms the basis for the EU Critical Medicines Act, which aims to improve procurement frameworks to enhance supply security beyond lowest-price tendering.
- **Advocacy for Resilient Procurement Policies**[16,54]**:** Belgium has explicitly called for procurement reforms under the EU's proposed Critical Medicines Act to ensure procurement decisions prioritize long-term supply security, environmental sustainability, and geographic diversification over price alone. The FAMHP advocates for legally binding criteria within the Most Economically Advantageous Tender (MEAT) framework to move away from purely lowest-price tendering, which has contributed to supplier exits and shortages. This approach aims to create a more sustainable and competitive environment for European medicine producers, reducing supply vulnerabilities caused by aggressive price-based tendering.
- **Support for 'Buy European' Procurement Principle**[55]**:** Belgium supports the EU Commission's new 'Buy European' mechanism proposed in the Critical Medicines Act, which prioritizes suppliers manufacturing critical medicines within the EU in public procurement contracts. This policy aims to reduce dependence on external suppliers, diversify supply chains, and strengthen domestic production capacity, directly addressing tendering-related shortages caused by over-reliance on low-cost third-country manufacturers.
- **National Stock Monitoring and Shortage Management**[56]**:** Belgium's FAMHP operates the PharmaStatus platform, an official tool for monitoring medicine shortages and stock

levels, which supports early detection and proactive management of supply disruptions. The platform is integrated into legislation, enabling pharmacists to substitute medicines or compound magistral formulas to maintain treatment continuity during shortages. This system enhances transparency and responsiveness in the supply chain, mitigating the impact of supply interruptions.

- **Broader Health Reform and Pharmaceutical Strategy**[57]: Belgium's new government (2025) has unveiled a wide-ranging health reform agenda including pharmaceutical measures aimed at securing medicine supply and accelerating innovation. The Roadmap Medicines initiative focuses on modernizing reimbursement and procurement procedures to improve efficiency and access, indirectly supporting sustainable supply.

Due to price pressures on certain antibiotics, which pose a risk to their availability on the Belgian market, a government initiative was launched at the beginning of 2024 inviting pharmaceutical companies to request price increases for these medicines. As a result, starting October 1, 2025, prices for approximately 105 antibiotic packs will be increased.

Germany Case

Tendering and rebate contracts favour the lowest-price suppliers in the drug market, leading to a limited number of suppliers. This concentration has caused unpredictable shortages of off-patent antibiotics such as amoxicillin and paediatric formulations. Pharmacies and insurers face challenges as reimbursement is capped at reference prices linked to tender outcomes, limiting flexibility to source alternatives during shortages. The German Federal Institute for Drugs and Medical Devices (BfArM) has officially declared critical supply shortages linked to these procurement practices[58].

Policy Intervention

Germany has taken the below steps to address the shortage issue due to tendering practices:

Act to Combat Drug Shortages and Improve Supply (ALBVVG) – Enacted July 2023[59]: The ALBVVG law requires statutory health insurance funds to favour manufacturers with production facilities in the EU or EEA in tendering processes for off-patent medicines. Specifically, **at least half of the lots in tenders must be awarded to suppliers with European**

production, aiming to reduce dependence on third-country manufacturing (notably India and China), which has been a key vulnerability causing shortages. The law also mandates mandatory stockpiling by manufacturers to ensure several months' supply availability. While stockpiling improves resilience against supply disruptions, it increases the costs for the manufacturers and may have negative effects on other countries. The first procurement contracts under this law were signed in 2024 for eight antibiotic active substances, awarding multiple contracts per substance (multi-partner model) to promote supply security rather than single-winner lowest-price tenders. This tendering approach balances cost containment with supply chain robustness by encouraging supplier diversity and European manufacturing.

Legal Flexibilities for Pharmacists to Manage Shortages (2024–2025)[60]**:** Pharmacists in Germany have been granted a **legal basis to deviate from medical prescriptions without consulting prescribers under certain conditions** (e.g., package size, strength) during shortages. This regulatory flexibility helps mitigate the impact of tendering-induced shortages by allowing therapeutic or generic substitution and partial dispensing, improving patient access despite supply constraints.

Italy Case

Procurement in Italy is largely regional, run by *Soggetti Aggregatori* (regional central purchasing bodies) and at national level, CONSIP also runs framework agreements and a very large Dynamic Purchasing System (SDA Farmaci) that regions can call off. For **standardised, off-patent medicines** (which typically includes many antibiotics), contracting authorities frequently rely on **lowest price** awards; **MEAT** (quality and price) is used mostly when meaningful qualitative differences exist (e.g., biologics, complex services). Italian hospital pharmacy literature and guidance reflect this split of practices[61].

Italy created a multi-winner obligation for biosimilars (National Budget Law 232/2016 and subsequent guidance), but there is no nationwide rule requiring multiple winners for small-molecule antibiotics; regions often structure lots with one winner per lot.

The tendering system's focus on cost containment has been criticized by political actors and stakeholders for undermining supply security. Recent years have seen a **decline in the number of offers submitted**, an increase in **unfilled tender lots**, and **failures to fulfil awarded**

contracts, especially for off-patent medicines. This has led to **supplier concentration, market exits, and irregular supply**, contributing to medicine shortages and regional disparities in access[62].

Regional tendering pressure has contributed to irregular supply and regional disparities in access to off-patent medicines. The number of unavailable drugs more than doubled between 2018 and 2024, partly due to tendering-driven supplier exits and production challenges[63].

Policy Intervention

Below initiatives are implemented to overcome these above-mentioned challenges:

- **Improved Tendering Procedures**[64]**:** Efforts are underway to refine tendering processes, including better splitting of lots and more transparent contract award criteria, to encourage supplier participation and reduce unfilled lots.
- **Increased Monitoring and Oversight:** The Ministry of Health and CONSIP have increased monitoring of tender procedures and contract fulfilment, with involvement from the Italian Competition Authority (AGCM) to ensure fair competition and prevent tender failures.

Also, Italy supports the European Commission's Critical Medicines Act (CMA) proposed in March 2025, which aims to adapt public procurement rules to prioritize supply chain resilience over lowest price alone and promote joint procurement among EU Member States to leverage collective purchasing power and diversify suppliers. These EU initiatives align with Italy's national challenges and are expected to complement domestic efforts to reform tendering and improve medicine supply security.

3.C. External and Internal Reference Pricing

External Reference Pricing

ERP is a pricing policy where the price of a medicine in a country is set or capped based on the prices of the same medicine in a basket of selected reference countries. It aims to control pharmaceutical costs by importing price discipline from other markets and to align prices with international benchmarks. Typically, the lowest or average ex-factory price among reference countries is used. Reference baskets commonly include neighbouring or economically similar countries. Commonly applied to both on-patent and off-patent medicines, including off-patent

antibiotics. The frequency of price reviews varies: some countries conduct quarterly, or annual price adjustments based on updated reference country prices.

ERP is widely used across Europe, either as a main or supportive pricing tool. Although it is applied to both on patent and off-patent medicines, current expert consensus views ERP as unsuitable for off-patent antibiotic markets[7,65]: parts of Europe use it but recognize its limited dynamic impact in off-patent medicines environments. For off-patent medicines, ERP helps set price ceilings aligned with international markets, indirectly controlling national expenditures. ERP is rarely the primary driver for off-patent medicines, instead, it influences prices during the post-patent, pre-generic phase, and fades after generics enter.

Given that off-patent medicines are typically low-margin, highly competitive medicines, often sold as generics or biosimilars and the market dynamics for these medicines are driven more by **competition, volume, and tendering** rather than pricing benchmarks, their prices tend to erode rapidly, making rigid price referencing less meaningful. This leads to limitations of ERP when applied to off-patent medicines. Some key considerations are[3,65,66]:

- **ERP relies on list prices in reference countries, which often do not reflect actual transaction prices**, rebates, discounts, or clawbacks frequently negotiated for generics, including antibiotics. This makes ERP price reference artificial and disconnected from real market prices.
- Since **generic and off-patent medicines operate in highly dynamic and competitive markets**, policies like ERP - which are often static, external benchmarks—cannot adequately reflect or respond to the rapid price changes and market entry/exit phenomena common in these segments.
- ERP **can inadvertently drive prices down excessively**, especially when referencing countries with aggressively low prices, potentially making mature antibiotic markets economically unsustainable.
- ERP may **stifle supplier incentives** because it limits price flexibility, which can exacerbate supply shortages of essential off-patent medicines due to low profitability.
- Due to **launch sequence strategies**, companies may delay market entry of off-patent medicines, such as generics, in some countries to avoid triggering low ERP benchmarks that affect prices in larger markets, worsening timely access.

- **ERP also does not account for local market differences in clinical needs**, e.g. antibiotic stewardship priorities, or public health imperatives – factors critical for off-patent medicines availability and use.

Key features of ERP with respect to the relevant parameters of policy can be summarized as below:

Aspect	Explanation
Market dynamics	Off-patent medicines exist in competitive, rapidly evolving generics markets.
Price erosion risk	ERP can push prices to unsustainable levels, threatening supply and market participation.
Lack of price flexibility	ERP's rigid external price referencing conflicts with the need for local pricing dynamics.
Launch delays and access impact	ERP influences market entry timing adversely, delaying access to affordable medicines.
Better alternatives	Competitive domestic pricing, volume-price agreements, and stewardship measures work better for off-patent medicines.

Several countries (e.g. Italy) use ERP at launch but rely predominantly on IRP thereafter[7].

Internal Reference Pricing

IRP can have two purposes: (a) to compare a new medicine (even an off-patent one) with the price of the reference product in the country and (b) to establish reimbursement levels by grouping medicines within the domestic market according to therapeutic equivalence or the same active substance and setting a reference price for each group. This approach is employed essentially to (a) ensure that new medicine is cost-effective vs. the standard or care and (b) encourage price competition within groups by incentivizing use of lower-cost alternatives and to cap public reimbursement expenditure.

In a typical IRP application, for generic medicines, medicines are clustered based on active substance or therapeutic equivalence (often at ATC-5 level). The reference price is typically

the lowest or average price within the cluster. Patients pay the difference (co-payment) in case they select medicines priced above the reference[7]. National systems recalculate reference groups periodically (e.g. annually or quarterly), adjusting reimbursements accordingly. IRP primarily affects reimbursement and co-payment structures domestically.

Discounts are often tiered by generics entry order (e.g., first generic 50% off originator, next generics further cuts such as second generic 18% below first; third 15% below second; by third generic, all products match lowest price, as an example)[67].

IRP is known to produce better results when paired with demand-side incentives (e.g., substitution rules) to stimulate competition. Without these, IRP can flatten price but not promote ongoing competitive pricing. Indeed, IRP-driven policies result in steep price reductions rendering low-volume medicines financially marginal. By setting a maximum reimbursement level, IRP encourages patients and prescribers to switch to lower-cost generics or biosimilars within the medicine group. In essence, IRP introduces some key characteristics including:

- **Market transparency and competition:** Creates an environment fostering price competition within therapeutic or substance groups, **enabling clearer pricing signals** for manufacturers and providers.
- **Cost containment:** IRP generally leads to price reductions within groups by incentivizing use of lower-cost medicines, helping to control pharmaceutical budgets. Evidence from systematic reviews reports insurer expenditure reductions around 18% post-IRP implementation[68].
- **Policy Flexibility:** IRP can be combined with other pricing policies for a comprehensive framework.

IRP has some potential shortcomings, including some very serious consequences:

- **Potential supply and availability risks:** Excessive price pressure within IRP may **reduce manufacturer incentives**, especially in low-margin off-patent medicines, potentially leading to **market withdrawal or shortages**. The price ceiling may compress profit margins unsustainably for low-volume or older medicines. IRP-driven pricing reductions often drop medicines prices substantially, eroding margins. Short-term price declines from originator to generic entry average 61% over time. Emergence of

single- or dual-supplier markets for many medicines increases vulnerability: ~33% of older antibiotics exited the EU market in past decade[7,69].

- **Can lead to market distortions induced by originator strategies:** Originator companies may engage in 'product hopping' ("evergreening" practices) or introducing pseudo-generics to circumvent reference pricing or maintain market share, potentially weakening IRP effectiveness.

Key features of IRP with respect to relevant policy parameters can be summarized as below:

Aspect	Details
Policy Role	Sets maximum reimbursement within therapeutic/substance groups
Advantages	Controls costs, generic medicines with more affordable price, incentivizes their uptake and supports competition
Shortcomings	Risk of supply shortages
Mitigation Strategies	Combine IRP with stewardship, volume-price agreements, and supply monitoring

Evidence links aggressive pricing to supply withdrawal and drug shortages[7,69]. Global supply shocks (e.g. factory explosion in China and India) emphasize compounded risk: low margins plus fragile supply chains lead to critical shortages[69].

Clawbacks, rebates, and mandatory cuts amplify IRP effects. In examples such as Portugal, Hungary and Spain indiscriminate paybacks on top of reference-based pricing led to further squeezing margins. Also, in some countries, parallel trade pushes domestic prices down via arbitrage.

Medicines destined for low-price markets often resold across borders has the potential to undermine the local supply. Finally, lack of demand-side incentives (e.g. weaker generic substitution rules in some countries) dampens uptake, reducing the competitive pressure IRP relies on[7]. Below are some country examples of reference pricing have been implemented and what were the consequences.

Summary of findings from countries with respect to their approach to ERP and IRP

ERP remains a central tool in many EU systems but often targets originator or patent-exclusivity medicines more than off-patent medicines only, despite some countries across Europe, mainly in Eastern EU, still apply ERP to off-patent products. Countries with well-established ERP systems IRP is widespread, with ATC-5 groups applying in virtually all countries. Germany and several others focus instead on internal reference pricing (IRP) or negotiated discounts, frequently excluding generics and other off-patent medicines from ERP constraints entirely. Per the EURIPID assessment (2024/2025), ERP guidance has been adopted widely, but its scope and intensity vary significantly species-to-species and country-to-country - particularly off-patent medicines.

ERP and IRP combined exert the strongest downward pressure to prices, increasing supply risk. **Countries without ERP usage** for generics offer moderate sustainability, but all face narrow margins under IRP. Consequences that are encountered by the countries who implement ERP can be summarized as below:

- **Reduced pricing flexibility**: Mandatory caps at lower international price levels limit ability to adjust to inflation or cost changes (e.g. Austria, Hungary).
- **Low profitability**: off-patent medicines when sold at low volumes are disproportionally impacted by ERP pricing constraints.
- **Disincentivization**: Strong ERP rules combined with reference pricing and payback policies create a market risk that may lead manufacturers to withdraw low-margin medicines.
- **Potential strategic response**: Some manufacturers delay product launch or avoid small markets due to ERP-related spillback effects across markets (notably Germany delaying new launches when used as reference country)

Below is a summary of the approach of countries to ERP and IRP[23,52].

Table 7: Approach of Selected Countries to Reference Pricing (Summary)

Country	ERP on Off-Patent Medicines	IRP Benchmark Method	Consequences for Off- Patent Medicines	Mitigation Measures
Austria	Yes Outpatient reimbursed prices capped at EU-average ex-factory price minus mandatory discounts	Generic/biosimilar medicines prices are set percentage below originator price	Limits revenue growth; tight margin on low-volume off-patent medicines	General PPRI guidelines
Belgium	Yes ERP (supportive) and IRP coexist; basket-based pricing	Lowest of group or average	Off-patent medicines priced at or below EU median; reduced incentives for small volumes	No specific mitigation measures
Croatia	ERP applied	Generic price linkage to originator	Low IRP maintains low reimbursements	Focus on stewardship and local procurement
Estonia	ERP applied	Standard national IRP	Low price but stable within IRP limits	Stock monitoring, tender processes
Finland	ERP applied	IRP average or generic price-link	Tight pricing for mature medicines; limited profitability	HTA-based reimbursement flexibility

Country	ERP on Off-Patent Medicines	IRP Benchmark Method	Consequences for Off- Patent Medicines	Mitigation Measures
Germany	No ERP for generics	Internal group within Germany	Mature medicines set via IRP stable; no ERP erosion	Manufacturer rebates used instead of ERP
Hungary	ERP applied once at launch National law enforces ERP with dynamic basket; payback mechanisms also apply	ERP "launch-only"; IRP thereafter	Severe price erosion; extra paybacks; high risk of market exit	R&D offset incentives; strict cost-control
Ireland	ERP limited to originators	Internal price capping; percentage below originator price	Low generic reimbursement levels; no ERP pressure	Stewardship, procurement policies
Italy	ERP used; plus, IRP for generics; basket includes EU peers; pricing defined centrally	Generic price link with progressive tiers	Margins very low; risk of supplier exit	Tender systems and formulary prioritization
Norway	No ERP	Lowest within group	Minimal pricing pressure via IRP, stable supply	National procurement and tendering

Country	ERP on Off-Patent Medicines	IRP Benchmark Method	Consequences for Off- Patent Medicines	Mitigation Measures
Poland	ERP combined with IRP; basket consistent; price re-evaluated per EURIPID guidance	ERP + IRP cap; EURIPID basket	High price pressure via combined ERP & IRP	IP-led generics
Portugal	ERP has limited impact on generic medicines, but not on non-generic such as branded and biosimilar medicines, which are subject to annual price review.	ERP supportive; core pricing via IRP, mainly to establish the maximum financed price	Low margins via IRP; ERP might indirectly affect the price of off-patent medicines, through changes in the external reference price.	Discretionary price reviews were applied for low price medicines
Spain	ERP for only informative purposes, used with IRP	Generic price link to originator (although in process to be changed as referred to previously in this study)	ERP-informed and IRP regime keeps prices contained	Managed formularies, stewardship programs
Sweden	With basket revision every few years; 15-year price reductions for old drugs via TLV 15-year rule.	Internal TLV 15-year reduction policy (7,5%)	Mature drugs face enforced price reductions; persistent low margins	Substitution enforcement and supply resilience efforts

Country	ERP on Off-Patent Medicines	IRP Benchmark Method	Consequences for Off- Patent Medicines	Mitigation Measures
Switzerland	ERP conducted for the same medicine (compound) in 9 defined reference countries. No comparison with generics. Generic pricing is determined by the Swiss market volume of the originator. Triennial review occurs for both.	IRP conducted with other off-patent medicines. Negotiations take place between the manufacturer and FOPH.	Little room for negotiation of IRP and ERP when patent expires (or later). The price for generics is usually set below the originator price with a fixed rebate based on the originator revenue of previous years.	Coverage via a positive list. Mandatory stockpiling of essential medicines. Suspension of the triennial price decreases or price increases in very exceptional cases if there are no therapeutic alternative.
UK	No ERP for generics	Pricing for generics left to competition	Mature antibiotics priced via IRP or substitution policy	VPAS rebate structure separate from IRP

For countries who apply ERP or IRP to off-patent medicines, a few case studies are presented below.

Germany Case

Challenge: *Price erosion from reference pricing*

Germany has long applied Internal Reference Pricing (IRP) to off-patent and therapeutically interchangeable medicines, including mature antibiotics, via the so-called "reference pricing groups" (*Festbetragsgruppen*), which:

- Group medicines with similar therapeutic effects or same active substances.
- Set a maximum reimbursement price (reference price).
- Patients pay the difference if a product is priced above this limit.

IRP directly affects mature antibiotics, which are often grouped with generics and subject to the lowest price pressure. In Germany, IRP has been in place since the 1989 and is regularly updated by the GKV-Spitzenverband (National Association of Statutory Health Insurance Funds). IRP, together with the other cost-containment measures such as the mandatory manufacturer discounts (e.g., 7% rebate), additional rebates in tenders and lack of exemption for critical low-margin products like off-patent antibiotics, led to **supply shortages** and **manufacturer exits**, especially for low-volume, low-price antibiotics like amoxicillin and penicillin V[20,58].

Policy Intervention: *Exemption of critical antibiotics from internal reference pricing, accelerated benefit assessments*

To address the risk to mature antibiotics, the German government implemented[20,70]:

- Shortage mitigation ordinance updates: introducing exemptions for certain low-price, critical antibiotics.
- 2023 Statutory Health Insurance Financial Stabilization Act (GKV-FinStG): limited rebate amounts for essential drugs and supported local production.
- Selective pricing flexibility for essential antibiotics: manufacturers can apply for higher reimbursement prices for mature antibiotics if shortage risk is documented.

Removal of ERP from Price Negotiations and Introduction of Confidential Pricing (2025)[71]**:** As of January 1, 2025, Germany legally removed international reference price as a criterion in price negotiations between pharmaceutical companies and statutory health insurance funds (GKV) under the Medical Research Act (Medizinforschungsgesetz, MFG). This means that actual sales prices in other European countries are no longer considered when setting reimbursement prices for medicines in Germany. This change aims to reduce the downward price pressure caused by referencing low prices in other countries, which had contributed to supply shortages of off-patent medicines, including antibiotics[20].

Italy Case

Italy maintains a Reference Price ("prezzo di riferimento") & Transparency List. Medicines with the same active ingredient, formulation, dosage, and pack size are bundled into reference groups. Accordingly, for reimbursed Class A off-patent medicines (which includes most community antibiotics), the National Health Service (SSN) reimburses up to the lowest-priced equivalent in the cluster. Transparency List is published and updated monthly with clusters and reimbursement ceilings[72]. If a higher-priced brand is dispensed, the patient pays the difference. Unless the prescriber marks the prescription "non-substitutable," the pharmacist is mandated to dispense the lowest-price equivalent; if the patient insists on a higher-priced brand, they pay the top-up above the reference price. For new off-patent entrants, Italy uses simplified procedures to include equivalents into reimbursement and align them to the reference-price system (2019/2021 AIFA procedures). In practice, the reimbursement ceiling governs what SSN pays; any list price above that becomes out-of-pocket.

The reimbursement price is set as the lowest price among equivalent products available locally, updated monthly. Patients pay the difference if they choose more expensive products. This tends to **push prices down** and incentivizes manufacturers to lower prices to maintain market share. Italy imposes **mandatory price reductions for generics**, where generic antibiotics must be priced at least 20% lower than branded originators to qualify for reimbursement, with successive entrants required to offer further discounts. Such steep mandatory discounts create strong price pressure on generics. INN (International Non-proprietary Name) prescribing encouraged.

For hospital-only antibiotics (Class H) – regional procurement prices, no national retail price applies; prices are discovered via regional tenders/frameworks run by Soggetti Aggregatori or via the national Consip dynamic purchasing system (SDA Farmaci). **Manufacturers must provide cumulative mandatory discounts** (e.g., 5%+5%) on reimbursed medicines, and there are **payback mechanisms if expenditure ceilings are exceeded**[72] .

The combination of reference pricing and mandatory substitution drives retail antibiotics toward the lowest price in the cluster; higher-priced packs shift the gap to patient copay and lose share. This is by design of the Transparency List system[73].

Policy Intervention

A 2025 law introduced incentives for innovative antibiotics under patent or data protection that are listed as WHO reserve or priority antibiotics. These benefit from[74,75]:

- A dedicated fund of up to €100 million per year.
- Exemption from the payback mechanism, expected to increase annual revenues by around 15%.

Although not focused on off-patent antibiotics, it opens discussions for key critical off-patent medicines. **Off-patent antibiotics and critical medicines remain vulnerable** under Italy's rigid reference pricing and procurement rules, unless specific incentives are introduced.

Portugal Case

Challenge: Highly demanding reference price policies

Portugal employs both ERP and IRP to regulate pharmaceutical prices, and their use has been instrumental in controlling pharmaceutical expenditures. However, these pricing mechanisms have also contributed to challenges in maintaining the availability of certain off-patent medicines, including antibiotics[67].

Historically, Portugal has used ERP extensively to contain pharmaceutical expenditures and promote affordability within the National Health Service (SNS). Generic medicines are not directly affected by ERP, but can be indirectly affected by it, as it influences the price of reference medicine used in IPR[67]. In Portugal, ERP used to be implemented by referencing the average of the lowest four prices from other countries to set domestic prices for retail

medicines (or the lowest one from other countries, to set the domestic hospital exclusive medicines[76]. While this approach aimed to contain costs, it led to unintended consequences. For instance, if reference countries have significantly lower prices, this can result in reduced profit margins for MAH in Portugal, potentially discouraging them from supplying certain medicines, especially those with lower profitability. **The price set for retail medicines in Portugal is the average price observed in the reference basket**, enforced through legal price ceilings and reimbursement conditions.

The ERP system is updated periodically with price revisions triggered by changes in referenced country prices, budgetary needs, or policy adjustments. ERP is coupled with payback mechanisms, - **almost all medicines are subject to an extraordinary contribution** as explained previously[21].

Portugal also implements Internal Reference Pricing (IRP) alongside External Reference Pricing (ERP). Portugal's Internal Reference Pricing system groups medicines into "homogeneous groups"—usually medicines with the same active substance composition, pharmaceutical form, and therapeutic indication (or interchangeable medicines). IRP is also used for copies, new dosage, new pharmaceutic forms of patented medicines. **For each homogeneous group, a reference price is set.** An off-patent medicine can't have a higher price than the reference medicine. If it is a generic one, its price must be 50% lower than the reference medicine, for the first four generic medicines entering the group. All other generic medicines that enter the reference group must be 5% cheaper than the cheapest medicine in the group with a market share greater than 5%, **until a reduction limit to 80% of the price of reference medicine is achieved**[24,77].

Patients pay the difference if they choose medicines priced above the reference price. The IRP system influences reimbursement levels and encourages use of lower-priced medicines within these groups, fostering price competition and controlling public pharmaceutical expenditure.

Portugal's ERP and IRP policy faced typical challenges affecting off-patent medicines globally. **The strict reference pricing can lead to continuously lowered prices, threatening profitability for off-patent medicines** and discouraging manufacturers from commercialising these low-margin products domestically. Further, ERP and IRP combined with the extraordinary contribution added financial pressures that sometimes triggers supply risks for off-patent medicines.

Policy Intervention

Persistent concerns about the impact of pure ERP policies on off-patent medicines availability and market sustainability motivated INFARMED and policymakers to refine the policy framework. To mitigate the adverse effects of reference pricing on medicine availability, Portugal has implemented below strategies:

- **Adjusting Reference Pricing Methodologies**[67]**:** Portugal has refined its ERP calculations by considering, for the retail market, the average of the lowest four prices rather than the absolute lowest which is still applied for medicines with exclusive hospital use. This approach aims to prevent excessively low pricing that could deter manufacturers from entering or remaining in the market. Accordingly,
    - The reference countries for ERP were updated for 2025 to include Spain, France, Italy, and Belgium, to reflect a move toward referencing countries with comparable markets and pharmaceutical pricing environments[78].
    - **Ad-hoc and discretionary measure in the last 3 years** without guarantee to continue in the future, Portugal **has introduced limitations in annual price revisions for low price medicines.** For 2025, according to Ordinance 293/2024/1 from 15th November, medicines with a price equal to or lower than 16€ are allowed to be increased in line with inflation, by 2.6%. At the same time these medicines are exempt from annual price reviews. Additionally, any price reduction resulting from the ERP comparison with reference countries may not exceed 5% (for prices between €16 and €30) or 10% (for prices above €30) to brake excessive downward price pressure[78].

Price controls in Portugal have maintained relative affordability of off-patent medicines in a cost-constrained health system. However, the unmitigated application of price controls reduces manufacturer commercial and concurrence conditions, leading to **serious risks of potential shortages and limited product availability.** As a consequence of shortages, health authorities actively monitor medicine availability and have established mechanisms to address shortages promptly, ensuring that all medicines remain accessible to patients.

Sweden Case

Challenge: Price erosion from reference pricing of old medicines

Sweden does not use classic ERP for generic or mature medicines. Instead, price regulation hinges on an internal substitution rule[36,79]:

- Under TLV's regulation FS 2018:30, **pharmaceuticals that have been marketed for more than 15 years may face an automatic 7,5% price reduction** once they reach the 15-year milestone. This applies regardless of competition status, including off-patent antibiotics.
- After this reduction, **they remain priced below the European average**—often ~40-50% lower, especially in the 15-25-year window.
- For generic medicines within ATC-5 groups, **internal reference pricing (IRP) applies.** Reimbursement is capped within therapeutic groups based on substitution rules and group ceilings defined by TLV[80].

Sweden encountered some challenges in relation with these policies. Accordingly**, the 15-year rule effectively forces older medicines into low price territory** (≈ 38% reduction), regardless of usage or volume. **Off-patent antibiotics are low-volume products in the region, so revenue declines sharply when prices are cut while costs remain stable**, threatening manufacturer retention. Small or niche medicines were impacted by the insufficient financial return, especially when combined with conservative IRP ceilings across ATC-5 groups[80].

Policy Intervention: Revenue guarantee model

Significant price reduction in mature antibiotics leading to low margins and further to supply risk called for a change in policy to secure availability of antibiotics. As detailed in Section 3A, Sweden started a pilot program for better compensation of selected antibiotics, which is now being considered to expand to cover off-patent antibiotics. Additionally, regular international price comparison reports by TLV (2023–2024) to monitor price levels and trends relative to other countries were introduced, along with an initiative that includes multiagency collaboration (TLV, SMPA, Folkhälsomyndigheten) to examine antibiotic availability and strengthen supply of older, essential antibiotics[36,81].

3D A Wholistic View of the Policies

Sections 3A, 3B, and 3C examine the evolution of key policy measures affecting the pricing, margins, and ultimately the viability and availability of off-patent medicines. These sections highlight not only how individual policies have developed over time but also what lessons have been learned in the process. The complex interplay between distinct policy interventions is evident in several country case studies—where in some instances, one policy amplifies the negative effects of another, while in others, the weaknesses of a given policy are mitigated by complementary measures, as seen in the Swedish example. Additionally, certain initiatives extend beyond national boundaries, exemplified by the Nordic Collaboration Policy, which represents a coordinated regional effort rather than isolated national programs.

Nordic Collaboration

Small national markets, low antibiotic consumption, and low resistance rates make Nordic countries unattractive markets for small-volume, old antibiotics. In 2024, fewer than 20 of 36 clinically important antibiotics were available in Denmark, Iceland, Norway and Sweden; Finland had just 14[3,82]. To combat supply shortages, market withdrawal, and limited registration, Nordic policymakers commissioned a joint study to identify priority policies for antibiotic access[82]. Main reasons to start the initiative are:

- Recognition that **traditional market forces fail to ensure availability** for low-margin off-patent antibiotics crucial in treating multi-drug-resistant infections.
- EU-level approaches focus mainly on innovation (new antibiotics), but **post-approval access** of existing medicines needs parallel policy solutions[3].

Also, Sweden's Public Health Agency (PHAS) received government mandates to **pilot new reimbursement mechanisms** for selected antibiotics that haven't found attractive to enter the Swedish market[41].

Key Developments Under the Initiative

Policy Roadmap for Nordic	Uppsala University's commissioned report identified ten policy options, prioritizing six for implementation: 1. Improved shortage monitoring & supply chain transparency

Collaboration (June 2024)[82]	2. Nordic-harmonised packaging/e-leaflets 3. Mutual recognition of approvals of old antibiotics 4. Good purchasing practices and parallel sourcing 5. New reimbursement models (revenue guarantees) 6. Mapping of production capacity in/near Nordic region
Swedish Pilot – Partial De-Linked Reimbursement (2020–2022)[83]	• PHAS pilot model (July 2020–December 2022): pharmaceutical companies guaranteed minimum revenue (based on buffer stock and template price ×1,5), independently of low sales. Additional 10% incentive for inventory maintenance. • Five antibiotics were included (e.g. Recarbrio®, Zerbaxa®, Vaborem®, Fetcroja®, fosfomycin). Coverage included supply within 24 hours and guaranteed revenue (~SEK 4 million/year per product). (Details of implementation are presented in the country analysis of Sweden above.)
Expansion of Reimbursement Guarantees (2023–2025)[41]	A new assignment (May 2023) studied the extension the reimbursement model to **at-risk off-patent antibiotics** following several criteria. Proposed guarantee: SEK 400k for buffer stock + SEK 850k-actual sales for revenue guarantee.

Key programs under the initiative include[82]**:**

- **Harmonization of Essential Medicine Lists and Market Approvals:** The Nordic countries work on harmonizing essential antibiotic lists, including dosage forms and strengths. This aims to reduce market fragmentation, which was identified as a key barrier to supply as different countries prioritized different formulations, often smaller national demand sizes complicating sustainable supply.
- **New Reimbursement Models with Income Guarantees:** To encourage suppliers to maintain or re-enter the antibiotic market, innovative reimbursement models with income guarantees are explored to reduce financial risks to manufacturers of mature

antibiotics. These models will aim to provide predictable income despite low sales volume typical of narrow-spectrum agents. This is still in planning stage.

- **Mutual Recognition of Market Approvals:** The Nordic collaboration aims to promote mutual recognition of regulatory approvals to streamline market entry and reduce duplication in administrative burden, enhancing timely availability of essential antibiotics across the region.
- **Strategic Stockpiling and Supply Security Measures:** Nordic countries coordinate on stockpiling essential antibiotics strategically to manage shortages and supply interruptions.
- **Antimicrobial Stewardship and Surveillance Cooperation:** Joint efforts on antimicrobial stewardship programs (promoting prudent use of antibiotics) and surveillance of antimicrobial resistance (AMR) patterns enhance both demand management and resistance control.
- **Political and Institutional Support Via Nordic Council of Ministers:** The Nordic Council of Ministers supports strategic groups and declarations (e.g., "One Health" strategy) that unify efforts under shared health security and AMR reduction goals, reinforcing the collaborative framework.
- **Joint Procurement and Purchasing Strategies:** The Nordic Pharmaceutical Forum (NPF) facilitates joint purchasing collaborations especially for hospital medicines, including antibiotics, to increase negotiating power and ensure supply reliability. Joint pooled procurement of older hospital medicines (including antibiotics) is Implemented by Denmark (Amgros), Norway (Sykehusinnkjøp) and Iceland (Landspítali/Icelandic Medicines Agency) via the Nordic Pharmaceutical Forum (NPF). Joint tenders were run in 2019/2020, 2022–2024, and 2024 (contracts from 1 Apr 2025); Finland and Sweden are members of NPF but did not participate in these specific joint tenders[84].

Impact

As of August 2025, only results of the joint tenders are visible and the rest of the initiative are still in progress. For the joint procurement practice, immediate results include[85]:

- **Improved Access in Iceland:** Some antibiotics became available to Icelandic patients for the first time, as manufacturers had previously not applied for marketing authorisation there.
- **Vendor Participation Increased:** Across the first two tenders, **at least two bids were received for 59% of the product-country groups**, indicating a healthy level of competition and a modest increase in supplier engagement.
- **Supply Resilience:** Awarding contracts to **two separate suppliers**—one for Denmark and Iceland, and another for Norway.

In this section, in addition to the detailed analysis of some critical country cases that are addressed earlier, a summary of policies and their interaction for selected countries is presented.

Table 8: Key Policies, Impact and Interventions by Selected Countries

	Key Policies	Impact of Policies	Interventions
Austria[7,23,52,86]	**External Reference Pricing (ERP):** For **retail (outpatient)** medicines, the **Austrian reimbursement code (EKO)** mandates **external price referencing (ERP)** for new medicines based on an EU ex-factory average price cap. **Internal Reference Pricing (IRP):** The pricing of generics and biosimilars follows a step-down system with discounts: the 1st generic medicine is set at 50% of the reference drug, the 2nd generic medicine is set 18% of 1st generic medicine and 3rd and subsequent generic medicine is set at 15% of previous generic medicine. Originator medicine must also reduce its price by 30% after three months from the introduction of the 1st generic medicine and follow analogue reductions to the 3rd generic price. To keep prices balanced, some generic medicines	ERP-driven mandatory price along with cuts when generics enter the market, drives medicines prices down sharply. Austria's generic pricing model subjects low-margin products (e.g. off-patent antibiotics) to risk of withdrawal and supply instability. **Price reductions** for off-patent originators on generics entering the market leads to **price stagnation** or low absolute pricing for off-patent molecules.	No new interventions in place

	Key Policies	Impact of Policies	Interventions
	with the same active ingredient cannot cost more than 20% above the cheapest option. **Clawback / Pay-back Mechanisms:** While most products are not subject to a clawback, medicines not included in the reimbursement list (Code of Reimbursement) that exceeds a 750 k€ cost for 12 months for social security will be retrospectively subject to ERP added by a 6,5% discount to be paid back. **Tendering:** **Hospitals don't conduct tenders. Hospital's procurement** occurs via offers submitted by pharmaceutical companies, which doesn't bound hospitals to buy from a specific company.		
Belgium[7,23,68,87,88]	**Internal Reference Pricing (IRP):** Belgium uses (bio)reference reimbursement clusters: mature originators and subsequent generics are grouped, and automatic reimbursement reductions (20–35%) are applied based on turnover after cluster entry. This "old drugs cliff" is triggered 12 years post-inclusion or upon	**Reference pricing clusters:** Steep price cuts ("reference reimbursement" 44,75% - 51,52% + "old drugs cliff" 20-35%) post-generic entry leads to limited margins.	Belgium exerts strong downward reimbursement pressure on off-patent medicines primarily through IRP cluster rules.

	Key Policies	Impact of Policies	Interventions
	the first generic launch. Products within the group must align with the least costly category; prescribers and pharmacists are required to adhere to these lowest-cost options. **External Reference Pricing (ERP)** Belgium employs external reference pricing at ex-factory price level. Basket methodology is defined legislatively, and ERP is integrated into the formulation of the maximum public price. However, it is primarily applied to newer products with limited generic competition; off-patent antibiotics are typically subject to IRP-centric downward pressure. **Payback / Clawback Mechanisms** **Belgium** applies a payback mechanism to pharma companies marketing innovative medicines under a temporary reimbursement. **There is also a clawback mechanism (overshoot of the budget)** applied to pharma companies marketing reimbursed medicines (no exemption for generic	**Mandatory low-cost prescribing:** Sets prescribing and dispensing behaviour favouring cheapest products. **ERP:** Minimal downward pressure beyond initial launch phase. **Clawback mechanism** adds pressure to off-patent antibiotics	ERP contributes to initial price setting but is not the main driver for long-term off-patent medicines pricing. Strategic positioning within reimbursement clusters, combined with volume planning and regulatory monitoring, is essential for maintaining sustainable access and supply in Belgium.

	Key Policies	Impact of Policies	Interventions
	medicines). In 2020 post-patent products were exempted but afterwards again applied on all reimbursed medicines. Belgium maintains a mandatory clawback/payback mechanism however generics and off-patent antibiotics—are explicitly exempt from generic-specific clawback.		
Croatia[23,67,89]-	**Tendering Framework** Hospital procurement (in-patient) of off-patent medicines in Croatia is conducted through competitive tenders, typically issued for 6-12 months contracts. These tenders are based on criteria such as price, supply reliability, and therapeutic equivalence. This mechanism dominates hospital purchasing and applies to mature off-patent medicines. Outpatient sector, particularly ambulatory generics, is managed under reference pricing and reimbursement list controls—tendering does not apply directly. **Payback / Clawback Mechanisms**	**Price compression**: Off-patent medicines typically fall within the IRP groups at ATC-5, facing steep price constraints driven by generic competition and ERP-based ceilings. **Limited profitability**: Since the first generic triggers 30% cut and subsequent entrants further compress pricing, manufacturers have minimal margins on off-patent medicines.	**Tender monitoring and reliability criteria**: Tenders include supply reliability and continuity obligations. **Rational prescribing and stewardship**: National guidelines promote antibiotics stewardship, moderating volume and controlling expenditure indirectly supporting sustainability. **Negotiated procurement exceptions**: For essential or shortage-prone antibiotics, Croatia has occasionally employed **direct procurement exceptions** to ensure supply continuity.

	Key Policies	Impact of Policies	Interventions
	Croatia does not operate a general clawback or payback mechanism for pharmaceutical manufacturers based on budget overruns. Categorical mandatory rebates are also not enforced across reimbursed products. ERP Croatia continues to apply external reference pricing: the maximum wholesale price for medicines is set at the 100% of the average ex-factory price of a selected EU peer basket. Basket specifics (country list) are updated annually by the Agency for Medical Products and Medical Devices - HALMED. For off-patent antibiotics, ERP provides initial price caps especially when originator references are still cited, although savings are modest (~8–10% reduction expected per updated regulations). IRP Croatia uses internal reference pricing at ATC Level III to V for outpatient reimbursed medicines. Off-patent medicines grouped by identical active substance (ATC-5) are capped at a reimbursed price; higher priced products	**Supply risk**: Low financial return may discourage introduction or continued supply of low-volume medicines in Croatia.	

	Key Policies	Impact of Policies	Interventions
	fall into a supplementary list, requiring patient co-pay. After initial listing, entry of successive generics triggers reference price reductions. The first generic must be priced 30% lower, the second and third generics 5% lower than the first, with further reductions for additional entrants. The originator drops price accordingly.		
Estonia[23,67,90–94]	IRP Reference prices are applied to homogeneous groups defined by identical active substance and administration route (i.e. ATC-5 level) The second-cheapest package price determines the reimbursement ceiling for the entire group. Patients pay any excess, creating pressure for manufacturers to remain competitive. With each new entrant, reference prices are recalculated, which typically leads to downward adjustments—especially relevant for off-patent medicines where multiple off-patent suppliers exist.	In essence: Estonia employs **rigorous reference pricing systems combining IRP and selective ERP-linked negotiations**, which exert significant pressure on prices of off-patent medicines. The structure effectively minimizes public drug spending, but at the risk of undermining producer incentives to supply low-margin, low-volume medicines. **Price caps via IRP:** Reference pricing tightly binds	**Mandatory substitution** at pharmacies steers uses toward the cheapest reimbursed antibiotic within an IRP group. Estonia's **digital reimbursement system** ensures real-time outpatient claims tracking and rapid reflection of price changes in patient cost-sharing. **Socioeconomic protection**: If annual out-of-pocket prescription spending exceeds thresholds, EHIF compensates up to 90% automatically,

	Key Policies	Impact of Policies	Interventions
	External Reference Pricing (ERP) & Price-Volume Agreements Estonia uses ERP in conjunction with internal pricing, especially for single-supplier products or originators: manufacturers negotiate a price-volume agreement with the Estonian Health Insurance Fund (EHIF), referencing prices in Latvia, Lithuania, and Slovakia These agreements require provision of local cost-effectiveness data and may lead to price reductions if volume exceeds forecasts or if referenced market prices fall. **Tendering and Procurement Practices** Hospital procurement remains largely facility based. Procurement criteria emphasize price, delivery reliability, and equivalence, which may indirectly favour cheaper generic medicines suppliers. Broader centralized tenders are rare except for biosimilars, which are procured at national level.	reimbursement levels to the second-cheapest package, limiting revenue potential for off-patent medicines. **ERP-linked agreements:** Exclusive-supplier medicines face external price pressure via benchmarks in neighbour countries; price-volume contracts may further compress net prices. **Frequent recalculation:** New generic entries or price competition lower ceilings continuously, compressing margins over time.	thereby maintaining access for critical medicines.

	Key Policies	Impact of Policies	Interventions
Finland[23,67,95]	**IRP** Finland operates a **formal IRP system** where therapeutically equivalent products (typically ATC-5 level substitution groups) dictate reimbursement ceilings. These reference price groups are **determined quarterly** by the Pharmaceuticals Pricing Board (HILA), based on the **VAT-inclusive price of the cheapest product plus €0,50**. Medicines priced above this ceiling are eligible only for partial reimbursement or require full patient co-pay. **ERP** ERP is **not applied** to off-patent medicines in Finland. New or innovative medicines may reference prices in other EEA countries, but off-patent medicines are priced based solely on Finnish IRP and statutory rules. **Statutory Price Formation and Mandatory Price Cuts** Retail prices are fixed by regulation and adjusted twice yearly (§1 Jan and 15 Jul), based on a regulated markup over the wholesale price. For example, price tiers apply	**IRP ceiling:** Reimbursement is capped at reference price; manufacturers must compete at price floor levels. **Statutory price adjustments:** Biannual adjustments and mandatory reductions erode margins, especially for long-market products. **No ERP for off-patent medicines:** Limits external price pressures but allows local downward pricing mechanisms. **Facility-level tendering:** Hospital contracts may exclude higher-cost suppliers, favouring low-cost generics.	**Mandatory substitution** ensures pharmacies dispense the cheapest reimbursed equivalent within IRP groups. **Conditional reimbursement schemes** are negotiated for structurally important but low-volume medicines, sometimes with confidential paybacks or volume guarantees. **Social insurance protections** cap out-of-pocket patient expenses, shielding consumers. While public affordability is maintained, the combination of IRP caps, mandatory reductions, and limited hospital contracts significantly compresses margins—posing challenges to the viability of low-volume off-patent medicines supplies.

	Key Policies	Impact of Policies	Interventions
	varying multipliers and fixed additives depending on price brackets. **Off patent medicines**, defined as products marketed over a certain period (typically >15 years), may be subject to **mandatory wholesale price reductions**—often 1,5% or more—especially for originators in low competition segments. Recent HILA rules reaffirm this for medicines with minimal competition. **Tendering and Hospital Procurement** Hospital procurement remains **decentralized.** Local or regional hospitals run **facility-level tenders**. There is no national tender specifically targeting off-patent medicines across hospitals.	The combined effect is **substantial margin compression**, constrained revenue potential, and **high supply risk** for low-volume, off-patent medicines.	Strategic manufacturer engagement through **conditional reimbursement agreements** and **proactive price negotiation** is essential to support continued market presence under these constraints.
Germany[20,58,59, 67,70,71]	**Market Access & AMNOG Framework** Under the **AMNOG** regime (Pharmaceutical Market Reorganization Act, effective since 2011), pharmaceutical pricing is initially **unregulated** for the first six months post-launch.	AMNOG Reference Pricing: Limits reimbursement to lowest-cost comparator; margin squeeze on generics.	**Supply Shortage & Pricing Reforms (ALBVVG Law)** As of **July 2023**, Germany amended the **German Social Code V (SGB V),**

	Key Policies	Impact of Policies	Interventions
	During this period, manufacturers can set their price freely. Then, a **health technology assessment (HTA)** by **G-BA** determines whether the product adds therapeutic benefit. From month seven, a **negotiated reimbursement price** with the **SHI funds (GKV-SV)** takes effect. If negotiations fail, an **arbitration committee** sets the reimbursed price. **Internal Reference Pricing & Cost-Sharing** For medicines judged to have **no additional benefit**, **reference pricing applies**: the statutory reimbursement is capped at the **cost of the cheapest comparator therapy** in the same indication. Many mature antibiotics fit this profile and enter the reference pricing system. Reference groups and reimbursement limits are recalculated at least **annually**, influencing pricing for off-patent medicines. ERP	Free-Pricing Phase (0–6 mo): Short window for higher pricing before reference cap takes hold. **Removal of ERP** (from 2025): Decreases pressure on domestic reference ceilings but affects launch-incentives. **Shortage exemptions** (ALBVVG): Excludes certain reserve antibiotics from price cuts or rebate obligations. Off-patent brand medicines are generally allocated to reference pricing groups, limiting reimbursement to the cost-effective price band. Margin pressure intensifies once comparator generics enter the reference cluster.	**Sections 35 and 130b**, to introduce new exceptions and incentives: **Reserve antibiotics** (targeting multi-drug resistant pathogens) and **paediatric medicines** are **exempted** from reference pricing constraints and rebate contracts. Manufacturers may set a **launch price up to 50% above** the last reference price, with insurance carriers covering the difference. If only a few suppliers remain for a critical medicine, reference price ceilings can be **increased by up to 50%** to ensure market viability. **Mandatory Stock-Retention & Supply Commitments** **Rebate contract holders** must maintain **minimum stock levels** (six months' average volume), with

	Key Policies	Impact of Policies	Interventions
	Historically, Germany used **ERP as a legal obligation** in price negotiations; manufacturers and SHIs referenced prices in other European countries. However, as of **January 1, 2025**, the **new Medical Research Act (MFG)** removes ERP from pricing negotiations, instead moving toward a model of **confidential reimbursement prices**. For off-patent medicines ERP historically had limited impact and is now being phase-out. **Supply-Shortage Mitigation Adjustments** The **ALBVVG** ("Act to Combat Supply Shortages and Improve Medicine Provision") passed in mid-2023 introduces: • Mandatory **early-warning systems** for drug shortages (via BfArM). • **Exemptions from reference pricing and rebate contracts** for **reserve antibiotics and critical paediatric medicines.**	With ERP gone, pricing is increasingly domestically regulated—ERP had minimal effect on off-patent medicines. Through ALBVVG, pharmaceuticals considered critical (e.g., paediatric antibiotics) may temporarily escape reference-based pricing or rebate constraints.	mandatory EU/EEA–based manufacturing supply lines prioritized. Pharmacies and wholesalers must fulfil stockpile requirements for **parenteral medicines and ICU antibiotics**, aiming to reduce risk of supply gaps. **Early-Warning & Transparency System** **BfArM** (Germany's regulatory agency) is required to operate a **public supply-shortage alert system**, collect data from manufacturers/wholesalers about stocks and supply issues, and publish a **monthly list of essential paediatric and antibiotic products at risk.** **Substitution authority** extended to pharmacists—enabling emergency dispensing of therapeutically

	Key Policies	Impact of Policies	Interventions
	These safety clauses may reduce pressure on mature antibiotics considered critical, temporarily shielding them from standard price constraints.		equivalent products without prescriber consultation
Hungary[7,23,67,96,97]	**Internal Reference Pricing and Stepped-Price System** Hungary operates a tight internal reference pricing framework with ATC-level groups: reimbursement is capped at the price of the lowest-priced medicine in the group, subject to a minimum volume (DOT) threshold to define the reference. A statutory stepped-price reduction system applies when generics enter the market: • First generic: –40% • Second generic: –20% • Third generic: –10% • 4th to 6th generics: –5% • Beyond 6: reduced to minimum 1 HUF price (~€0,003)	**Implications:** Off-patent medicines lose large margins after generic entry. Deep price erosion over time threatens revenue viability—even for higher-volume drugs. **IRP:** Market ceilings tied to lowest-price peers; large post-generic cuts. **Stepped Generic Discounts:** Price erosion triggers severe margin compression over time. **ERP (initial only):** Limited long-term influence after generics enter market.	Government introduced **windfall tax relief** (Decree 317/2023) allowing up to 50% reduction in clawback if manufacturers reinvest in R&D or tangible assets by 2024–2025. **Volume contracts** within tenders may include reliability clauses or buffer stock requirements to preserve supply continuity. For manufacturers, Hungary represents a high-risk viability environment for mature medicines due to **combined internal pricing, generous clawback obligations, and competitive tender dynamics**. That said, **2023–2024 policy tweaks**, particularly clawback

	Key Policies	Impact of Policies	Interventions
	For biosimilars, a similar staggered discount applies: 30%, 10%, 10%, then minimum price. **External Reference Pricing (ERP)** ERP is also applied but acts as a supportive mechanism: Hungary applies ratio-based ceilings using EU price baskets upon initial listing. However, once generics enter, domestic IRP and stepped-price rules dominate. **Clawback and Payback Mechanisms** Hungary imposes sector-wide payback **mechanisms** tied to budgetary overshoot: pharmaceutical manufacturers must pay back a percentage of revenues if reimbursements exceed caps. **Windfall tax and clawback** obligations have escalated up to 40%, although from the beginning of 2025 it was reduced to 20%. Some **tax relief** measures introduced in 2023 allow producers investing in R&D or tangible assets to **halve clawback liabilities**.	**Clawback/Payback Obligations:** Reduced from 40% to 20% clawback, but still eroding profitability. **Central Tendering:** Low-price focused procurement pressures small or higher-cost suppliers.	relief tied to R&D investment, offer a potential lever to maintain economic viability. Proactive strategies—such as aligning with hospital tenders, maximizing days of therapy thresholds, and engaging early with pricing regulators—are essential to mitigate supply risk.

	Key Policies	Impact of Policies	Interventions
	Crucially, this applies broadly across reimbursed medicines, including off-patent antibiotics—intensifying margin pressure. **Tendering & Procurement Practices** Centralized tendering is common in hospital and specialized sectors; mature medicines are included within **multi-year contracts (1–3 years)**. Suppliers often offer **confidential discounts or rebates** to win contracts. Hospitals may prioritize bidders offering **reliable supply and stable pricing** amid tightening margins.		
Ireland[23,67,98–100]	**Reference Pricing & Substitution Rules (IRP)** Ireland operates a formal generic substitution and internal reference pricing (IRP) system, under the Health Pricing and Supply of Medical Goods Act 2013, amended as recently as 2024. The system applies to all ATC-5 therapeutically equivalent products. Reference prices are periodically updated with substitution obligation imposed on lower-cost	**Compressed margins**: IRP ceilings and downward rebates significantly reduce net fixation prices for off-patent medicines. **Supply challenges**: The combination of price pressure and lack of ERP cushioning may discourage manufacturers from supplying low-volume medicines.	**Mandatory substitution** ensures pharmacists dispense the least costly approved medicine within a reference group. **Patient cost caps**: **Medical Card Scheme**: low flat charge per item (typically €1–€1,50, capped per month) for lower-income patients.

	Key Policies	Impact of Policies	Interventions
	therapeutically equivalent agents, driving price competition. **ERP** Ireland's use of **ERP is limited** to **originator or newly launched patented medicines**. Mature medicines, being off-patent and multi-source, generally are excluded from ERP mechanisms. Their pricing is driven by IRP and framework rebate policies. **Framework Agreements & Mandatory Price Rebates** Under Framework Agreements between government, the Irish Pharmaceutical Healthcare Association and Medicines for Ireland in 2024, 812 medicine lines downwardly re-aligned, including price reductions for patent-expired, non-exclusive products (which includes off-patent antibiotics), resulting in substantial savings. These agreements include annual, downward-only pricing realignments, reinforcing IRP pressure on mature medicines. **Tender Policies & Hospital Procurement**		**Drug Payment Scheme**: general maximum patient contribution (€80/month), with reimbursement based on reference price. **Pharmacy shortage monitoring**: the **PGEU Medicine Shortages Report 2023** flagged antibiotics as consistently among the classes facing supply disruptions in Ireland, prompting early-warning enhancements and industry coordination.

	Key Policies	Impact of Policies	Interventions
	Off-patent medicines are rarely centrally tendered at national level. Instead, hospital procurement is decentralized with each hospital or regional group conducting independent tenders, commonly emphasizing price, continuity, and therapeutic equivalence.		
Italy[7,23,67,73]	**Reference Pricing & Co-Payment Regime** Italy applies a reference pricing (RPS) system: the Servizio Sanitario Nazionale (SSN) reimburses only the price of the lowest-cost equivalent (same active substance, form, dosage). If patients opt for a more expensive branded or off-reference product, they pay the price difference plus, in some cases, a prescription fee (from 2-4€) applied at regional level. But, in many regions, the off-patent medicines are exempt from paying this prescription fee. **ERP** ERP exists as part of Italy's pricing system, but is primarily applied to patented, high-priced medicines. Off-patent medicines generally fall under reference	**Off-patent medicines** in Italy are predominantly governed by reference pricing, limiting reimbursement and driving low-cost margins. While ERP and paybacks minimally affect off-patent medicines, price and access pressures stem from central and regional reimbursement rules.	**Pull-Incentive Fund (2025 Budget Law)** Starting 2025, Italy allocates €100 million/year in a national pull-incentive fund for reserve, WHO-priority or AWaRe Category Reserve antibiotics. These antibiotics—though innovative or new—will be exempt from payback and can enter SSN reimbursement directly, bypassing traditional reference pricing constraints. **Reform of Therapeutic Notes & Plans** **In mid-2024, AIFA initiated a review of "therapeutic notes"** affecting

	Key Policies	Impact of Policies	Interventions
	pricing, not ERP. ERP serves as an initial reference mechanism but has limited relevance for off-patent medicines. **Payback / Clawback Mechanism** Italy employs clawback obligations for all medicines, but obligations are lighter for off-patent and generic medicines. Also, small companies with annual turnover under €3 million are exempt from payback obligations, not based on product type, but company size. Generic companies are required to contribute to the payback based on market share of reimbursed medicines. As of 2023, payback procedures were initiated with percentages around 1,8% to 5%, applied across all reimbursed products, including generics. **Procurement & Regional Variability** Italy's pharmaceutical system is decentralized, with 21 regional health systems independently managing formularies and procurement. Regional therapeutic plans (note AIFA "nota AIFA") and prescribing guidelines can		prescribing of antibiotics, to simplify access and reduce administrative burdens (e.g., relax restrictions on certain core antibiotics). **Active Shortage Monitoring** Though formal shortage incentives are limited, Italy reports rising shortages (>3,700 drugs affected by 2024), prompting calls for improved demand forecasting, supply analytics, and simplified dissent for essential off-patent drugs.

	Key Policies	Impact of Policies	Interventions
	influence antibiotic reimbursement—some regions place mature antibiotics under restricted prescribing directives to control overuse.		
Norway[3,23,67,82,101,102]-	**Statutory Maximum Price System (ERP-style Policy)** In Norway, all prescription-only medicines must have a maximum pharmacy purchase price, established by the Norwegian Medicines Agency (NoMA). This maximum price is calculated as the mean of the three lowest ex-factory prices of the same product across a designated basket of European countries: Sweden, Finland, Denmark, Germany, UK, Netherlands, Austria, Belgium, and Ireland. This effectively acts as a regulated ERP mechanism, applying equally to new and mature medicines, regardless of patent status. **Internal Reference Pricing (IRP) and Stepped-Price Regulation**	**ERP-style maximum pricing:** Caps maximum purchase price at lowest EU-tier averages, limiting pricing flexibility. **Stepped price reductions:** Successive generic entrants face mandatory discounts, compressing margins over time. **Volume-based hospital contracts:** Larger suppliers favoured; small-volume or niche medicines may be excluded. **No price reversion flexibility:** Once reduced, maximum prices remain fixed unless renegotiated at product level.	**Pull-incentive discussions**: As part of Nordic policy reviews (e.g., PLATINEA, EHO), Norway has explored **unit price increases** or **societal value-based premiums** for antibiotics deemed critical to counteract margin collapse. **Flexible procurement exceptions**: **Norwegian Hospital Procurement Trust.** occasionally accommodates essential antibiotic suppliers with reliability-of-supply clauses in contracts to prevent shortages. Norway's system blends **statutory ERP-like price ceilings** with **automatic stepped pricing**, ensuring

	Key Policies	Impact of Policies	Interventions
	Once **generic competition emerges**, Norway applies a **stepped-price regulation.** Prices are gradually reduced in **set increments** (tiers), with tiered discounts applied to successive generic entrants. This ensures rapid price erosion for off-patent medicines following loss of exclusivity. Reimbursement remains based on these statutory price points—there is **no additional IRP group system** as observed in other countries. **Hospital Procurement & Tiered Discounts** In the **hospital sector**, the four Regional Health Authorities coordinate through the **Norwegian Drug Procurement Cooperative (LIS).** LIS negotiates **volume-based discount contracts** with suppliers for hospital medicines. Pricing for hospital supply is negotiated and is not bound by outpatient ERP ceilings.		robust price control on off-patent medicines. While effective in containing pharmaceutical expenditure, **the approach compresses margins**, especially for low-volume products, and may deter sustainable supply. Policy dialogue continues regarding **societal-value compensation or targeted incentives** to support antibiotic availability. For manufacturers, aligning early with LIS contracts and planning for predictable price decline is essential to ensure continued market participation in Norway.

	Key Policies	Impact of Policies	Interventions
Poland[7,23,67,103]	**IRP** Poland employs formal IRP. Medicines are grouped by identical active substance and dosage form (ATC-5). The reimbursement cap is set at 100%-75%-50% of the price of a single reference product within the group—usually the cheapest. The remaining difference is borne by the patient as a surcharge. IRP is recalculated every 24-36 months, although in practice coverage updates are more frequent due to health ministry revisions. Generic entry further decreases group ceiling prices. **ERP** ERP operates as a "supportive criterion", predominantly used for initial ceiling price setting and first launch products—not for generics. Poland references prices from 31 EU and EFTA countries, including Hungary, Croatia, Slovakia, and Estonia.	**IRP:** Ceiling constrains reimbursement; leads to steep revenue erosion. **ERP reference linkage:** Some initial ERP influence remains, but no sustained pressure post-generic entry. Without clawback obligations, revenue erosion is limited to IRP tools, but margin viability remains low. **Access depends heavily** on generic substitution practices and inclusion in hospital tenders, necessitating strategic engagement by manufacturers. **Decentralized hospital tenders:** Supply reliability favoured in tender scoring.	**Mandatory generic substitution** is enforced at pharmacy level, directing patients to the lowest-priced products in each group. **Shortage prevention protocols** include delivery reliability clauses in hospital tender terms and in retail declaration (mandatory) to sustain supply continuity.

	Key Policies	Impact of Policies	Interventions
	In theory, initial caps for mature medicines entering the system may reflect this ERP, but long-established products default to IRP-based reimbursement levels. **Payback / Clawback Mechanisms** Poland does not impose unconditional clawback or payback obligations on manufacturers based on spending growth. **Tendering & Procurement Practices** Hospital procurement is managed at regional or institutional level. Tender contracts prioritize price, supplier reliability, and comparable therapeutic efficacy. Mature medicines fall under facility tenders; no national framework specific to antibiotics exists. Contractual requirements for delivery continuity and shelf-life buffer may support supply of low-margin medicines.		
Portugal[7,21,23,24,67,76,78]	**ERP:**	**ERP-linked mandatory deep discounts** can depress off-patent	Regulatory adjustments to reduce frequency or intensity of mandatory

	Key Policies	Impact of Policies	Interventions
	Portugal uses ERP to set maximum reference prices for medicines entering the market for the first time and for annual price reviews. **IRP**: IRP is used for reimbursement purposes. An off-patent medicine can't have a higher price than the reference medicine. If it is a generic one, its price must be 50% lower than the reference medicine, for the first four generic medicines entering the group. All other generic medicines that enter the reference group must be 5% cheaper than the cheapest medicine in the group with a market share greater than 5%, until a reduction limit to 80% of the price of reference medicine is achieved. **Extraordinary contribution**: Since January 2015, an extraordinary contribution is applied for almost all commercialized medicines. **Tendering**: Applies to **hospital procurement only**.	pricing to unsustainable levels. The combination of ERP, IRP and extraordinary contribution often compresses margins, leading to significant withdrawals in off-patent medicines.	price cuts for selected critical off-patent medicines.

	Key Policies	Impact of Policies	Interventions
Spain[19,23,30–32,35,67,104,105]	**IRP**: Internal reference pricing is used within therapeutic exchange groups (INN-based and administration route). **Tendering** Used at **regional level** by Autonomous Communities, especially for hospital medicines. **Other tools**: Fix discounts are applied for off patent medicines. Together with "Disposición adicional sexta" enforced payment to laboratories for every retail pharma dispensing, aimed to be expanded to hospital pharmacies in Medicines Law Reform. Spain uses price freezes after initial entry and caps—including fixed maximum reimbursement levels, for innovative medicines	**Profitability Concerns**: Static prices and aggressive IRP have led to **reduced margins**, discouraging manufacturers. **Shortages**: Off-patent antibiotics and medicines have faced **supply issues**, especially in retail pharmacies.	There is growing governmental interest in **allowing price differentiation** among off-patent drugs—to enable undercuts in reference prices upon generic entry, without forcing originators to keep prices unsustainably low. **2025 Medicines Law Reform under consultation phase**: • Introduces **flexible pricing bands** for off-patents. • Reinforces **supply chain resilience** measures. In July 2024 reference prices were allowed to increase in case of incremental innovation and for strategic medicines.

	Key Policies	Impact of Policies	Interventions
Sweden[7,23,67,80,81]	**ERP/IRP** Sweden applies a monthly tender/auction system for all off-patent and interchangeable medicines: each month, pharmacies must offer the lowest-priced product in each substitution group as the default option. This constitutes Sweden's version of internal reference pricing (IRP), where the product-of-the-month functions as a dynamic, competition-based substitution model. ERP plays a limited or indirect role; pricing control is achieved through substitution systems rather than reference to other countries.	Swedish off-patent medicine prices are among the **lowest in Europe**—approximately **44% below the European average** for products with generic competition and still significantly low for those off-patent but non-generic. Extremely low prices **limit profitability** and discourage continued supply, especially in small-volume molecules like older off-patent antibiotics.	In **2023**, Sweden raised **ceiling prices** for select substitution groups to **align more closely to EU averages**, providing more margin flexibility for suppliers and reducing extreme price compression. Sweden engaged in Nordic Collaboration and run the pilot implementation.
Switzerland[7,23,67,68,106,107]	**Pricing Framework & Reimbursement Listing** Reimbursement under Switzerland's mandatory health insurance requires a product's inclusion on the List of Specialities (LS), maintained by The Swiss Federal Office of Public Health (FOPH). For many products, the FOPH seeks advice from the Federal Drug Commission (FMC).	Switzerland employs a **dual-pricing system combining ERP and IRP** with mandatory discount schedules and periodic review to maintain financial affordability. For off-patent medicines, this leads to **incremental margin erosion** and leads to increasing	Switzerland has partially implemented some few **targeted policy interventions** to address pricing-related challenges, especially those impacting **off-patent medicines**. These interventions aim to balance **cost containment** with **supply security**,

	Key Policies	Impact of Policies	Interventions
	LS listing demands demonstration of Effectiveness, Appropriateness, and Cost-effectiveness (so called WZW criteria). Products that do not meet these criteria may face price adjustments, additional reimbursement restrictions or removal from LS. **Internal Reference Pricing (IRP)** Switzerland uses internal reference pricing via therapeutic cross-comparison. FOPH compares treatment costs of therapeutically equivalent medicines used in the same disease to assess fair pricing and subsidy levels. This is updated on a three-year review cycle, where IRP and ERP are both used to adjust public pricing for reimbursed medicines. **ERP** Switzerland applies ERP by comparing ex-factory prices with an approved basket of nine comparable countries (including Belgium, Finland, Sweden, Denmark,	supply issues of essential medicines. While low-cost product exemptions and individual case mechanisms exist to prevent market withdrawals or supply issues, they are applied very restrictively and require a long onerous administrative process. This leads to **low-volume essential medicines remaining vulnerable to market exits**. **Price erosion is systematic**: originator pricing drops at generic entry (off-patent price review), and again at triennial reassessments. **Margin compression** occurs rapidly—especially when generics	particularly for **essential low-margin medicines**. **Reform of the Triennial Price Review System:** Every three years, the Federal Office of Public Health (FOPH) reviews the prices of reimbursed medicines. In 2022–2023, **stakeholders** (trade association vips) agreed with the FOPH to **suspend price review** for some selected products with **already low prices** or **supply-critical roles**. In some cases, this measure allowed **flexibility for medicines below a certain threshold** or without therapeutic alternatives. A few exemptions are still in place today.

	Key Policies	Impact of Policies	Interventions
	Netherlands, France, Germany, UK, Austria). ERP is explicitly integrated in three-year price revisions. ERP plays a strong role in defining maximum public price ceilings—particularly relevant when generics are introduced. **Generic Pricing & Adjustments** Generics and biosimilars are mandated to enter the reimbursable market at substantial discounts to originators—initial deductions of 20–70%, based on volume. After each three-year review, originator prices may be further reduced, and generics/biosimilars prices are adjusted accordingly. The use of generics is incentivized with a co-payment mechanism, forcing patients to pay higher out of pocket contributions if the originator price exceeds a certain threshold versus the prices of generics.	enter the List of Specialities (LS, the reimbursement market) **Access risk arises** if prices or revenues fall below commercial thresholds; often, small-volume medicines may become unprofitable, being no longer commercialized in Switzerland.	
The UK[7,23,67,108,109]	**ERP/IRP:** The UK does not use ERP or IRP for off-patent medicines. Prices are set through market competition, especially for generics. ERP only applies to patented,	Generally, NHS savings and supply have been maintained with ongoing	Industry bodies (e.g., Medicines UK, OHE, LSE) are lobbying to exempt branded generics and biosimilars from

	Key Policies	Impact of Policies	Interventions
	branded medicines. **IRP** is used indirectly via the Drug Tariff (Category M and other Tariff categories) for reimbursement prices among generics and to regulate pharmacy margins. **Category M adjustments** are used to bring the reimbursement price **closer to actual market prices** to avoid swings. Accordingly, every quarter, The UK's Department of Health and Social Care collects pricing and volume data from manufacturers and wholesalers. sets **reimbursement prices** for these medicines on a quarterly basis. The goal is to reflect the **average market purchase price** (based on data collected from manufacturers and wholesalers). Based on this, they adjust the reimbursement prices of Category M drugs **up or down** to ensure fair reimbursement to pharmacies and budget neutrality and cost control for the NHS. These adjustments affect **only reimbursement prices**, not retail or wholesale prices. **Clawback:** Implemented via the **VPAS (Voluntary Pricing and Access Scheme).** It includes branded generics and biosimilars in	policy adaptations, with concerns related to sustainability. **Profitability Pressure**: Low prices and high rebate rates have led to **thin margins**, discouraging manufacturers. **Category M** includes **generic medicines** that are **readily available** from multiple suppliers Many **off-patent (generic)** medicines fall under Category M. **Frequent price reductions** (to reflect falling market prices) can **reduce profitability** for suppliers. **Shortages**: The UK has faced **persistent shortages**, especially in antibiotics and epilepsy drugs. Price cuts have been linked to supply disruptions	VPAS to avoid double-taxation and preserve competition. Proposals include revised tariff structures, more dynamic Category M adjustments, and potentially separating branded generics out of the VPAS structure.

	Key Policies	Impact of Policies	Interventions
	repayable rebates when NHS spending growth exceeds agreed limits. The rebate rate has been rising (expected >23,7%, possibly over 30% from 2024), threatening supplier sustainability. **Tendering:** Tendering used selectively, mostly at regional or hospital level, not systematic national tendering for off-patent **Other Policies:** • Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG): Applies to branded off-patent drugs, includes rebate mechanisms. • Price Concessions: Temporary price increases granted when supply issues arise.		

IV. POLICY RECOMMENDATIONS

The main findings section demonstrates **several examples where tight, eroded prices lead to fragility and supply surges in the market for off-patent medicines**, namely antibiotics. EU policy now treats a subset of medicines – including many antibiotics – as "critical," with a Union list, a European Medicines Agency Coordination Mandate, and a new Critical Medicines Alliance to craft structural solutions for supply security that include market-shaping and procurement/pricing approaches and underline the magnitude of the issue[110].

In crafting the policies recommendations, we have considered some **policy goals** that can be achieved, summarized as:

a. Ensure **minimum viable economics model** for reliable and stable supply of off-patent medicines.

b. **Preserve competition (≥3 suppliers) and supply diversity** rather than price races to the bottom.

c. **Stay budget-sustainable**, to maintain the sustainability of health budgets, while guaranteeing access to patients. And,

d. **Align with stewardship**. For the case of antibiotics, it should be noted that the policy options must be in alignment with the EU Council AMR Recommendation (2023)[111] that imposes a target of reducing antibiotic consumption by 20% by 2030.

Policy options and recommendations to strengthen off-patent medicines availability, have been grouped under **4 categories** [3]:

(1) **Price system reviews** at country level aiming to keep critical off-patent medicines viable and with a suitable number of suppliers.

(2) **Administrative and regulatory levers**, which focus on (i) reducing or removing administrative burdens/fees needed for regulatory permission to put and maintain these medicines on the market and (ii) modifying or removing market authorisation "sunset clauses".

(3) **Supply chain resilience**, including (i) product mapping and stockpiling to improve short-term availability in specific sections of the supply chain but which may have negative impact on cost; and (ii) manufacturing capacity strengthening to dynamically and proactively improve supply in the long-term and promote international partnerships.

(3) **Strategic purchasing**, to mitigate commercial unattractiveness by reducing costs or increasing revenues for MAHs; which focus on (i) tendering contracts that stipulate multiple suppliers favouring diversified supply chains. (ii) joint tenders through multiple buyer (such as multiple countries) collaboration, mainly for low volume medicines where individual markets might be less attractive. (iii) basing critical low value, low volume off-patent medicines payments on contractually agreed annual revenues that may be independent of ('delinked' from) sales volume.

It is possible to reconcile the goal of cost efficiency for health systems with the need for suppliers to sustain the availability of off-patent medicines at accessible prices. Older off-patent medicines have an **important place in treatment**, as they provide cost-effective alternatives to new preparations. For antibiotics, which are at the core of our study, they can secure effectivity of new preparations and avoidance of AMR for end-treatment. Since most off-patent medicines have long been on the market and their prices have already been pushed to low levels, ongoing efforts to monitor and control further price reductions may no longer be necessary, nor relevant. Instead, **a more forward-looking model that reflects the importance of ensuring long-term access to these medicines and continuous market availability** may be more appropriate[112]. Prolonged periods of low financial returns have led many manufacturers to exit the market, leaving behind a limited number of suppliers who lack motivation to enhance the production and availability of older, off-patent medicines with declining or negative viability.

While addressing the economic challenges in this segment is complex, doing so could yield **long-term sustainability benefits across the supply chain** – for instance, by creating revenue streams that support manufacturing improvements, viable supply models and attract additional suppliers.

We have also identified some pillars regarding policies for which some measures to monitor market performance and supply security, can be defined and prepared with the contribution of all stakeholders in the market in each country and, possibly, at European level. Some possible measures are listed below:

- **Supply resilience:** # of suppliers per molecule/strength; share of tenders with ≥3 winners; average lead times; shortage notifications trend (EMA and/or national catalogues), accuracy of forecasting by health entities [110].
- **Market viability:** Entry/exit rates; realized vs indexed ex-factory prices for eligible products[7].
- **Patient impact:** Therapeutic substitutions made; backorders filled; days of stock at wholesalers. [113].

The following recommendations have been mostly thought through to be applied to critical medicines. A foundational step would be for each country to identify which specific off-patent medicines that should be considered "critical", based on transparent criteria such as unmet clinical needs, shortage vulnerability, and public health significance, with mechanisms for regular review and updating, has some countries have already done for antibiotics.

Pricing Systems Reviews

Key pricing interventions that are viable and deserve discussion on the above mentioned four goals can be (not limited to):

Policy Intervention	Description and Conditions
Minimum price and automatic indexation to input-cost proxies[7]-	Currently, the manufacturers are unable to reflect increasing cost of goods in their market prices, as highlighted in this report. Allowing the application of indexation systems is a way to recognize the value of keeping critical products in the market.

Policy Intervention	Description and Conditions
	• An automatic indexation mechanism enables periodic, formula-based price adjustments for a designated list of critical off-patent medicines, anchored to objective economic indicators such as inflation, API producer price indices, industrial energy costs, and wage benchmarks. This approach helps prevent real-price erosion that can lead to market exits, while reducing reliance on ad hoc emergency price interventions. • To safeguard public budgets, indexation can be limited to a critical medicines' subset defined at country level, but considering also the EU critical list of medicines, with annual or biannual adjustment caps. A practical starting point would involve annual recalibration using a transparent index basket—such as the EU industrial energy index, API PPI proxies, and labour cost indices—with clearly defined floors, ceilings, and no retroactive application. Defining minimum prices at sustainable price levels can also be considered. The concept has been endorsed by Medicines for Europe as a leading policy option to support supply sustainability and pricing predictability for essential off-patent medicines.
Tiered pricing linked to market structure[7,69]	A **tiered pricing model** provides a flexible and market-responsive mechanism for safeguarding supply continuity. This approach defines **reference price bands** that dynamically adjust based on the degree of market competition—**expanding** when the number of active suppliers falls below a critical threshold (e.g., fewer than three) and **contracting** as competitive intensity increases.

Policy Intervention	Description and Conditions
	Although historically applied to drive prices downward, tiered pricing can serve as a **pragmatic alternative to fixed price ceilings**, particularly in markets at risk of supplier withdrawal. If carefully calibrated, tiered pricing allows to reconcile the goals of incentivizing competition and maintaining access to critical off-patent medicines —an essential consideration for **thin markets** such as some **off-patent medicines**, where production economics are increasingly fragile and supply risks are escalating. By aligning reimbursement levels with market dynamics, European countries could adopt a variable pricing model that **prevents prices from being driven unrealistically low in contexts of limited competition**, thereby supporting continued supply. According to the Medicines for Europe study on generic medicine pricing models, tiered pricing was identified as the most effective strategy for simultaneously preserving competitiveness and ensuring long-term sustainability. That has been the policy in Canada where the price for generics is set in a tiered model that considers the number of suppliers. The more suppliers the lower the price[7,69]. Although implementation may require dedicated infrastructure and regulatory adaptation, the anticipated benefits—namely improved supply continuity, reduced risk of shortages, and enhanced market stability—justify the investment.
Exemption (or attenuation) of ERP/IRP for off-	External Reference Pricing (ERP) is widely recognised as poorly suited to off-patent pharmaceutical markets, where it may inadvertently distort competition and exacerbate supply

Policy Intervention	Description and Conditions
patent medicines, especially the critical ones	fragility. To mitigate cross-country price convergence and downward spirals, policymakers could consider modifying ERP linkages—for example, by introducing wider price corridors, excluding statistical outliers, or extending update cycles to reduce volatility. The European Critical Medicines Alliance (CMA) has called for coordinated EU-level action, including the granting of Service of General Economic Interest (SGEI) status to safeguard the availability of critical medicines—particularly off-patent medicines—, which could target pricing exemptions, as its continued supply is essential to public health resilience[16].
Volume-delinked reimbursement approach and revenue guarantee for *existing* (off-patent) medicines at risk	Revenue guarantees can provide a predictable baseline revenue to sustain supply of clinically essential, low-volume/low-margin medicines while preserving stewardship (no volume-linked bonuses). As described in detail in section 3A, Sweden has piloted the revenue guarantee model for a select set of antibiotics and now working to expand the tested model to include some selected off-patent antibiotics. Volume de-linked revenue guarantees as a policy option have been in the agenda of Nordic Collaboration[82] along with being under consideration by the EC, as proposal on EU-coordinated subscription payment mechanisms encouraging wide member state participation, for both new and existing antimicrobials. Pilot implementations can be designed for very small volume of existing off-patent medicines with guaranteed annual revenue.

Policy Intervention	Description and Conditions
Targeted, time-limited price uplifts for shortage mitigation	**A temporary, narrowly scoped reimbursement/ex-factory price increase** when there is a risk of shortage due to too few suppliers. These increases should remain in place until healthy market competition is restored, at which point prices will self-regulate through competitive dynamics. The uplift can be in the form of a capped percentage uplift, such as "up to X% above last regulated price for the affected INN/presentation during the activation window" as in Germany case or a cost indexed reopener. Eligibility can be limited to off-patent medicines on the EU Union List of Critical Medicines (or a national subset of it) and to specific presentations (e.g., paediatric suspensions, IV injectables) with recurrent vulnerability. This approach could give rapid economic relief to manufacturers of off-patent medicines when costs spike. In the EU, some Member States have adopted such flexibilities, as in the case of Germany (ALBVVG)[114] which provides targeted price leeway and supply-security criteria, including API sourcing in tenders. This approach is also consistent with the Commission's shortages Communication emphasizing market-shaping and security-of-supply measures[110]. Uplifts can be exercised in a time-limited (e.g., 6-12 months) way to avoid prolonged market distortions. Periodic uplift reviews based on market recovery and supply stabilization indicators can be made[3]. Triggers such as risk ratings, supply alerts, etc. can be defined and based on the critical levels of these triggers. A **hard sunset** (e.g., max 12 months) and an **automatic rollback** to baseline pricing once security of supply returns to normal can be introduced. It should be noted that **production planning timelines are long**, and even

Policy Intervention	Description and Conditions
	extraordinary incentives should give companies **mid -term predictability.**
De-linkage from originator's price for generics	In most countries generic medicines prices are linked with the originator's price by a predefined percentage. This model has the potential to cause a race to the bottom, as every time the originator lowers the price, all the generic prices change, becoming unviable for some medicines. Possible solutions could be[7,69]: **Partial de-linkage:** the originator's price is fixed at one point in time and used as the permanent reference, so later price changes do not affect generics. **Competition maturity de-linkage:** generics stay linked to the originator's current price until enough competitors enter the market; once maturity is reached, the link to the originator's price is removed. **The discount over the reference price should consider the complexity of the generics entering the market, its production costs and its importance for public health.**
Limit paybacks, clawbacks and extraordinary price measures for off-patent medicines	A policy could be implemented where off-patent medicines in general, or below a certain price and/or belonging to a critical medicines list, could be **exempt from any type of payback, clawback or other cost-cutting related measures**, as Italy has recently approved and the UK does for generic medicines.

Administrative and Regulatory Burdens

Administrative and regulatory burdens become especially significant when the market volumes or/and prices are low, which is the case in several European countries.

Policy Intervention	Description and Conditions
Removing disproportionate financial disincentives to marketing off-patent medicines	Lowering barriers to market entry and re-entry could help restore and sustain off-patent medicines supply. Current practices, such as imposing penalties for shortages and fees for re-registration, add financial risk and discourage manufacturers from participating. To improve market resilience, policy adjustments could include: • proportional penalty frameworks, • removal of re-filing fees, reducing or waiving annual maintenance fees and adapting sunset clause requirements, as Norway has been implementing and Sweden is preparing to implement, for key off-patent antibiotics. • expedited approval for new manufacturers (especially those with diverse API sources)
Informed decision making for the impact of environmental regulations	Thorough regulatory impact assessment studies that take market segments, medicine price sensitivity, and public health impact into consideration would make a good basis for the regulatory transitions that are costly to the private sector. For low-priced essential off-patent medicines, applying proportionate or exception rules to fees, such as urban waste fees based on volume,

Policy Intervention	Description and Conditions
	can prevent disproportionate financial pressure causing withdrawal. It is also important to maintain collaborative stakeholder dialogues where an open channel for information and perspective sharing is secured between pharma manufacturers, environmental experts, and public health stakeholders to co-develop practicable environmental standards that safeguard both patient access and ecosystem protection. The collaborative nature of decision making contributes to the quality of the overall regulation. Risk-Based Prioritization of Environmental Measures: Regulatory bodies might prioritize measures targeting substances or processes with the highest environmental risk, potentially relaxing or delaying controls on lower-risk areas where cost-impact is severe for critical low-priced medicines. This would lead to a better planned transition.
Easier Transition for Environmental Liabilities	Pharmaceuticals have been affected by several environment regulations, which while very important, further erode the margins in low priced off-patent medicines. One of the last ones is the Extended producer responsibility (EPR) for pharmaceuticals to fund post human/patient use treatment for micro-pollutants in urban wastewater has been introduced by the EC in Directive 2024/3019, which is currently being discussed, as its model will disproportionately hurt low margin off-patent medicines.

Policy Intervention	Description and Conditions
	Manufacturers of off-patent medicines operate on thin margins, so EPR levies, manufacturing upgrades, or forced substitutions can render them non-viable unless policy calibrates by essentiality, hazard and market fragility. • **Subsidies or Financial Incentives for Green Transition:** Offering targeted subsidies, tax breaks, or grants specifically for switching to eco-friendlier substances or cleaner production technologies alleviates the upfront investment burden. This encourages sustainable manufacturing without forcing price increases that jeopardize market presence. • **Flexible Regulatory Timelines and Transitional Support:** Governments can implement phased approaches or transitional periods for compliance with new environmental requirements. This reduces immediate cost shock and gives companies time to adapt production processes or reformulate products without abrupt market exits. • **Procurement reforms:** Rewarding companies for investments in reducing their impact on the environment, proving a level playing field with companies that are competing on cost bases only.
Introduction of Core Pack Size	There is no harmonized pack size for off-patent medicines across EU member states, as many were registered nationally. Different countries have different package size requirements often driven by national treatment guidelines, reimbursement rules, and other clinical rules such as antimicrobial stewardship policies. This

Policy Intervention	Description and Conditions
	results in a fragmented market where pharma companies must manufacture and stock multiple pack sizes for the same product across countries. Different packages sizes also make it harder to bring medicines from one country to another in the case of shortages. Each pack size change or addition requires regulatory approval, stability testing, and potentially new packaging lines. This adds complexity and costs to production, making it expensive to keep low-price medicines on the market when multiple pack sizes must be maintained. More stock keeping units at low prices mean shorter runs, more artwork, translation, serialisation variants, higher write-off risk, and less flexibility to re-allocate stock during shocks. Regulators and industry both point to multi-country/multilingual packs as a practical shortage-mitigation tool, however current labelling space and language rules can constrain their use. Nordic Collaboration has considered common packaging and electronic package leaflets for antibiotics[115]. Reducing variants of stock keeping units improves forecasting, distribution, allows shared-packages by multiple countries, and reduces the risk of shortages. Harmonized pack sizes can save resources on regulatory filings and associated delays. As harmonized pack size enables easier supply to multiple countries with the same packaged product, improving economies of scale and maintaining profitability even for low-priced medicines would be more feasible. Additionally, standard sizes can be

Policy Intervention	Description and Conditions
	optimized for minimum packaging waste, aligning with stringent EU environmental policies. One example towards harmonization of packaging is PHAS/PLATINEA Nordic mapping & roadmap (2024) that recommends moving toward common needs/treatment-based harmonisation of packaging across Denmark, Finland, Norway and Sweden for key antibiotics; the policy study notes that harmonising information and pack sizes is difficult *as long as* each country maintains different guideline-driven pack sizes, i.e., guideline convergence is a prerequisite. Nordic medicines agencies launched a pilot to use English-language "common Nordic packages" across Denmark, Finland, Iceland, Norway and Sweden to simplify production/distribution and improve availability[116,117]. Some action items for harmonization could include: • **Enabling "core pack-size":** Use national guideline groups (or an EU working stream) to define standard total-dose ranges and encouraging MAHs to register matching packs across markets. • **Creating a Core Pack-Size Table Cross-Referenced to National Guidelines:** The table would list standard pack sizes (e.g., number of pills/capsules or course duration) for common outpatient indications (e.g., community-acquired pneumonia, urinary tract infections). The table would reference differences in national guidelines and provide mapping or exceptions where needed, allowing some country-specific flexibility. Collaboration between the European Medicines

Policy Intervention	Description and Conditions
	Agency (EMA), public health authorities, clinical guideline committees, and industry would be key to align on definitions and implementation. • **Fee-light variations for MAHs adding those core pack sizes to off-patent medicines** (esp. those on the Union list of critical medicines) could be defined.

Procurement Related Interventions

Strategic procurement frameworks, by considering other factors but price, can play a pivotal role in incentivising manufacturers to sustain supply and invest in buffer production capacity. By adjusting contract conditions, governments can actively shape supply chain behaviour and promote long-term resilience. Some procurement-related policy approaches can include:

Policy Intervention	Description and Conditions
Replacing single winner modality with a multi-winner award modality	One practical approach highlighted in the literature to promote more sustainable competition in the off-patent medicines market is the allocation of tender contracts to multiple suppliers with each successful tenderer securing a sufficiently large market share to ensure financial viability and supply continuity. This prevents reliance on a single provider for a given market or group of markets over time, thereby reducing the risk of supply interruptions. It also facilitates broader distribution of market share, which can incentivise more suppliers to remain active in the market[112]. A more sophisticated approach could be diversification of API manufacturers, to create a safeguard against supply chain

	disruptions stemming from issues with any single API source. This approach helps avoid single point of failure, spreading the risks, keeping multiple suppliers streams active, promoting diversity and supply security[65]. As sophisticated as it is, successful implementation of this model depends on enhanced visibility and understanding of API sourcing practices and create or improve incentives for API production in Europe, if needed.
Better forecasting for tender volume	Realistic volume forecasts to include in the tender calls with minimum purchase guarantees and 6+ months lead time between award and first delivery could help manufacturers plan better and take less risks, thus enabling them to respond the tenders with more favourable bids[118].
Contract lengths	Contract lengths play a key role in management of the risk and financials. A contract duration of 24–48 months with annual re-openers (mini-competition confined to incumbents/new entrants) would serve to keep the competitive tension while making sure the supply is not destabilized[119].
Changing the award criteria (shifting to MEAT)	Health systems often pursue cost savings by awarding tenders based solely on price, a practice that compresses profit margins and has led some manufacturers to withdraw their medicines from the market, as we have seen in the case of antibiotics. This approach can result in supply vulnerabilities and the emergence of de facto monopolies, ultimately diminishing the purchasing leverage of procurers and undermining the intended cost efficiencies. To foster sustainable competition and long-term value, both industry and buyers share an interest in adopting strategic procurement models that incorporate broader selection criteria. One such approach is the use of the Most Economically

Advantageous Tender (MEAT), which enables contracting authorities to evaluate bids based not only on price but also on qualitative, technical, and supply sustainability considerations. For instance, requiring the inclusion of two distinct API sources in registration documentation could help mitigate market concentration and enhance supply resilience. When moving away from lowest price as the single criterion, **security-of-supply** and **sustainability** criteria could be included in the assessment criteria. One **example** is assigning weighs for constrained INNs[65]:

Criterion	Weight	Components
Price	60-70%	
Security of supply and resilient supply chains	20-30%	**Supply redundancy**: number of **qualified Finished Dosage Form (FDF)** sites and **independent API** sources; geographic diversification; audited **Business Continuity Plan/surge** capacity. **Service reliability**: on-time delivery rate; back-order history; **lead times**; **safety stock** commitments. **Transparency**: supply-chain mapping and early-warning processes.

	Environmental/AMR (illustrative sub-criteria)	5–10%	Evidence of **clean manufacturing** and effluent control aligned to recognised industry standards and EU sustainability aims (use as award—not exclusion—criteria to keep competition).
Rejection of "abnormally low" offers	Applying Article 69 logic from 2014/24/EU which implies that contracting authorities must request explanations from bidders if a tender appears abnormally low in relation to the works, supplies, or services; if an offer implies non-compliance (e.g., unrealistic cost base), it should be rejected. This could prevent low bids that damage the market and public in the medium-long run more than the profit from the lowest price.		
Indexation for pricing clauses	Automatic indexation approach that was mentioned in pricing section can be reflected on procurement processes where input-cost proxies could be used for indexation. In order to prevent supply exits when costs spike, indexation to objective inputs (e.g., electricity/natural gas indices; API/solvent benchmarks) and reopener triggers (such as changes in input basket; regulatory fees) could be used as effective tools.		

V. CONCLUSIONS

In disease areas with the highest public health impact, **off-patent medicines are typically the first treatment option**. As a result, **the effectiveness of public health** initiatives in enhancing population health **relies heavily on ensuring access to and proper use of these lower-cost medicines.**

This study has highlighted that the **viability** of off-patent antibiotics, as a case study for off-patent medicines, **is critical but many times undervalued** putting them under a significant strain in Europe. Historical price reductions, while delivering important savings to health systems, have progressively eroded the economic viability of many critical molecules. Our analysis shows that between 2020 and 2024, **prices for the most widely used off-patent antibiotics in 16 countries fell on average by more than 10%, while production costs, labour costs, and energy prices rose substantially.** This divergence between declining prices and increasing costs has placed off-patent antibiotics that already have a thin margin, at the brink of commercial unsustainability. The result has been widespread market withdrawals, recurrent shortages, and a dangerous reliance on a small number of suppliers. The results observed for antibiotics, are believed to be similar for other off-patent medicines, because the unsustainability root causes are the same.

The policy mechanisms traditionally employed in Europe, such as external and internal reference pricing, tendering, and clawback schemes—have achieved their cost-containment objectives but at the expense of long-term supply resilience. Also, these policies might create dependency risks on one or very few suppliers. Evidence across multiple country case studies confirms that these measures, when applied indiscriminately, create perverse incentives for manufacturers, discourage investment in European production, and ultimately threaten patient access. At the same time, broader cost drivers, including regulatory complexity, environmental compliance, and rising logistical expenses, disproportionately affect low-margin off-patent medicines, intensifying their vulnerability.

The European policy debate has increasingly recognised that critical off-patent medicines, particularly antibiotics, cannot be solely subject to cost minimisation. Rather, they constitute strategic public health assets whose availability is essential to preserving the

effectiveness of health systems and preventing the further spread of antimicrobial resistance. **Innovative policy responses, such as revenue guarantees, volume-delinked reimbursement models, multi-winner tenders, tiered pricing and exemption of critical off-patent medicines from rigid reference pricing**, offer promising avenues to reconcile cost efficiency with supply sustainability. Some countries, notably Sweden and the United Kingdom, have pioneered revenue guarantees, and their early results underscore the feasibility of balancing financial incentives with stewardship objectives.

Ensuring the long-term sustainability of off-patent medicines requires a shift from short-term cost containment towards a resilience-oriented approach at both national and European levels. This entails integrating pricing reforms, strategic procurement frameworks, and regulatory adaptations into a coherent policy mix that safeguards both affordability and availability. Moreover, the development of EU-wide mechanisms, such as the Critical Medicines Act and coordinated procurement strategies, may provide the necessary legal and institutional framework to align national actions with shared European objectives.

In conclusion, **the sustainability crisis facing off-patent medicines is neither accidental nor inevitable.** It is the outcome of accumulated structural imbalances between policy goals and market realities. **By adopting forward-looking, evidence-based interventions that support viable economics for manufacturers, preserve supplier diversity, and strengthen supply security, Europe can protect access to essential off-patent medicines and ensure that these critical treatments remain available for future generations.** The lessons from this study extend beyond antibiotics and can be applied to other off-patent medicines which are critical for public health in Europe.

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ANNEX 1 – METHODOLOGY ADDITIONAL INFORMATION

The study is based on a retrospective observational design using secondary data collected between March and June 2025. To identify the appropriate secondary data and literature, structured searches were conducted using Google, B-On, and institutional portals. The following keywords and Boolean operators were used: ("mature antibiotics" OR "antibiotic pricing" OR “off patent medicines”) AND ("price evolution" OR "price trends") AND ("Europe" OR "European Union") AND ("macroeconomic indicators" OR "input costs" OR "electricity prices" OR "labour costs" OR “production index”) AND ("health expenditure" OR "policy impact" OR "access to medicines" OR “pharmaceutical cost drivers”).

The main data sources included medicines price evolution data, retrieved from IQVIA MIDAS, focusing on average unit prices per counting units of off-patent antibiotics across 16 European countries (Belgium, Germany, Estonia, Ireland, Spain, Croatia, Italy, Austria, Poland, Portugal, Finland, Sweden, Norway, Switzerland, Hungary, UK).

Macroeconomic and production indicators to the same countries were obtained from multiple institutional sources, namely: Eurostat (HICP, PPI, LCI, non-households electricity prices, non-households natural gas prices); European Central Bank (ECB) (GBP/EUR exchange rates); as well as National statistical offices, including: Office for National Statistics (ONS) – UK, Department for Energy Security and Net Zero (DESNZ) – UK, Federal Statistical Office (FSO) of Switzerland and FSO of Germany, Statistik Austria, Statbel (Belgium), Statistics Estonia, Statistics Finland, Croatian Bureau of Statistics (CBS), Hungarian Central Statistical Office (HCSO), Central Statistics Office (CSO) – Ireland, ISTAT (Italy), Statistics Norway, Statistics Poland (GUS), Statistics Portugal (INE-PT), Instituto Nacional de Estadística (INE-ES), and Statistics Sweden.

The selection of indicators was based on relevance to pharmaceutical cost dynamics and included: Consumer Price Indices (HICP), Labor Cost Indices, Electricity Prices (non-household), Producer Price Indices, and Import Prices in Industry (e.g., aluminum, packaging). Data was normalized when necessary (e.g., adjusting prices using ECB exchange rates).

A comparative analysis was conducted to explore the relationship between economic context and the pricing of off patent antibiotics: a country-level time-series data (2020/2024) was

analyzed to assess changes over time in key macroeconomic indicators alongside antibiotic price evolution.

Economic indicators definitions

	Data Definition
HICPs All Items (annual rate of change)	Measures inflation based on the prices of a representative basket of goods and services purchased by households, allowing comparison across EU countries.
HICPs Food and non-alcoholic beverages (annual rate of change)	Tracks consumer price changes specifically for food and non-alcoholic beverages, as part of the broader HICP, reflecting their impact on overall inflation.
Industrial Producer Price Index (PPI)	Measures price changes from the point of view of the producers/manufacturers of a product. The PPI reflects basic prices, which exclude VAT and similar deductible taxes directly linked to turnover. All price-determining characteristics of the products are considered, including quantity of units sold, transport provided, rebates, service conditions, guarantee conditions and destination.
Industrial Labor Cost Index (except construction)	Shows the evolution of total costs on an hourly basis of employing labor, including wages and salaries as well as non-wage costs (e.g., social contributions).
Electricity prices for non-household consumers - all taxes and levies included (€ per kW/h)	This indicator reflects the average electricity prices paid by non-household consumers, expressed in euro per kilowatt-hour (€ per kWh), including all taxes, fees, and levies.
Natural gas prices for non-household consumers - all taxes and levies included (€ per kW/h)	This indicator reflects the average price (per kilowatt-hour) paid by non-household users for natural gas, excluding all recoverable taxes and levies.
Producer Price Index (PPI) for corrugated paper and	Measures price changes from the point of view of the producers/manufacturers of a product. The PPI for corrugated paper and

	Data Definition
paperboard and of containers of paper and paperboard	paperboard and of containers of paper and paperboard reflects basic prices for these materials, which exclude VAT and similar deductible taxes directly linked to turnover. All price-determining characteristics of the products are considered, including quantity of units sold, transport provided, rebates, service conditions, guarantee conditions and destination.
Producer Price Index (PPI) Aluminum	Measures price changes from the point of view of the producers/manufacturers of a product. The PPI for aluminum reflects basic prices for these materials, which exclude VAT and similar deductible taxes directly linked to turnover. All price-determining characteristics of the products are considered, including quantity of units sold, transport provided, rebates, service conditions, guarantee conditions and destination.

ANNEX 2 – EUROPEAN PRICING POLICIES

In several parts of Europe, countries regulate medicine prices, except for the UK and Denmark which apply free pricing. Germany and the Netherlands adopt a mixed approach, combining elements of free pricing with measures such as tendering, mandatory discounts, preferential policies, and reference pricing. Internal reference pricing is widely used in Europe to regulate the generic medicines market by setting a reimbursement threshold for groups of interchangeable medicines. Reimbursable medicines are typically subject to price controls, while over-the-counter medicines are generally freely priced. In most countries, price controls target reimbursable medicines totally or partially funded by national health systems or insurers. Only a few countries regulate all medicines regardless of reimbursement status. In contrast, countries like Denmark, Germany, and the UK apply free pricing to off-patent reimbursable medicines, though Germany and Denmark maintain certain long-standing price control tools for generics[7].

External reference pricing (ERP)[7]	**External reference pricing (ERP)** involves comparing medicine prices across countries to establish a benchmark for setting or negotiating prices domestically. It typically applies to **reimbursable medicines**, while non-reimbursable medicines are usually freely priced, despite some markets can still apply ERP on non-reimbursement products (like Austria, Norway and Portugal). Pricing is either determined solely by authorities or negotiated with manufacturers. ERP aims to ensure prices are aligned with those in comparable markets, preventing countries from paying more than their peers. The selection of reference countries is a key step, often based on factors such as geography, income levels, market size, availability of medicines, or the country of origin. The size of these reference baskets varies widely — from as few as 3-4 countries (e.g., France, Portugal, Croatia, Cyprus) to over 20 (e.g., Austria, Italy, Poland). Some countries also require at least half of the basket to include countries with established prices to ease the process.

	Price comparisons are made at standard points along the distribution chain, from manufacturer to retailer. The method for calculating the final price varies: some countries adopt the lowest price, while others use averages or adjusted figures considering factors like market size or currency. Price revisions may occur annually or more frequently.
Internal Reference Pricing (IRP)[7]	**Internal Reference Pricing (IRP)**[6] compares the prices of therapeutically equivalent and interchangeable medicines within a country. Interchangeability is typically determined using the **Anatomical Therapeutic Chemical (ATC) Classification System**, with most countries applying **ATC-5** (same active ingredient), though some allow broader groupings (ATC-4). IRP aims to limit public payer costs by controlling prices within groups of similar medicines, reducing price variation among comparable products. It is most effective when paired with policies promoting the use of generics and biosimilars. Reference prices are typically set based on factors such as active substance, dosage, administration route, and packaging, with price comparisons made at common distribution points. Calculation methods vary: Countries may use the lowest price, average price, average of the lowest prices, or apply a percentage reduction (price-capping) from the originator price. Price updates occur at intervals ranging from biweekly to annually.
Control of Public Spending (payback, clawback,	**Payback and clawback policies** are designed to control public pharmaceutical spending by requiring manufacturers or pharmacies to refund part of their revenue when expenditure exceeds set budgets. These budgets may be defined globally, segmented by sector, or linked to expenditure growth rates. The calculation bases vary across countries and may include factors such as market share, revenue, or growth.

[6] Some countries use the acronym IRP to refer to International Reference Price. In our study we use ERP – External Reference Price.

rebates, and discounts)[7]	**Payback mechanisms** typically oblige manufacturers to return revenue if public pharmaceutical spending surpasses a predetermined ceiling. In some cases, such as Hungary, paybacks are automatic regardless of spending levels. In Greece, there is no cap on the amount manufacturers must repay. **Clawback mechanisms** often apply to pharmacies, capturing discounts on dispensing fees or medicine purchases to redirect these funds to public payers. Countries like Romania and the Netherlands apply differentiated payback rules for generics, with periods ranging from two months to a year. **Price cuts:** A price cut refers to the significant reduction in the cost of a drug after its patent protection expires. Once a drug's patent expires, other manufacturers can produce generic versions, which are chemically identical but sold at lower prices. Multiple generic manufacturers enter the market, driving prices down – sometimes by 80–90% within the first year. In some countries, governments enforce automatic price reductions for off-patent drugs to reflect their lower production costs and increased availability. **Price freeze:** A **price freeze** is a policy tool used to **maintain the current price** of off-patent medicines for a set period, preventing any increases. It's typically applied by governments or health authorities to control pharmaceutical spending and ensure affordability. Once a medicine loses patent protection, generics enter the market and prices usually drop. A price freeze locks in that lower price to avoid future hikes. By freezing prices, it creates a level playing field for generic and off-patent brands, promoting market competition. Especially in publicly funded healthcare systems like most of Europe, it prevents originator companies from raising prices on off-patent brands to maintain revenue and helps contain costs and forecast expenditures more reliably. **Extraordinary contributions,** a type of payback based on net sales, as seen in Portugal, complement these measures. **Extraordinary contributions** refer to **mandatory contributions that MAH are required to make at**

	certain percentage levels, depending on the type of medicine. This is set annually in the government budget.
Tendering[7]	**Tendering** is a formal, competitive procurement process used to purchase medicines or vaccines, where offers are evaluated based on criteria such as price, quality, and value for money. **Negotiations** involve discussions with suppliers to finalize contract terms, often resulting in further price reductions through discounts or rebates. The main goal of tendering is to stimulate competition among suppliers. In some countries, such as **Poland**, negotiations are also used to agree on specific aspects like price, quality, risk, and payment terms, or to resolve outstanding issues. Tendering and negotiation may be applied independently, together, or alongside other pricing policies.

About New Angle

New Angle was founded by specialists across health, finance, automotive, public sector and industry, bringing many years of consulting expertise to highly complex and demanding environments, operating out of Portugal and Angola. Our interdisciplinary team combines deep domain knowledge with strategic insight to deliver creative, integrated, and high-impact solutions. New Angle's Health Unit is a center of excellence in strategy, market access, and research. We support health stakeholders across Portugal, Angola, Central Asia, and other African regions, driving meaningful impact through region-adapted, evidence-based approaches.

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For Further Information, contact:

Margarida Bajanca
Partner
margarida.bajanca@newangle.pt

Teresa Rodeia Marques
Associate Partner Healthcare
teresa.rodeiamarques@newangle.pt