https://doi.org/10.31925/farmacia.2026.1.25 **ORIGINAL ARTICLE**

SUPPLY CHAIN VULNERABILITY AND REGULATORY GAPS: AN EVALUATION OF DRUG SHORTAGES IN THE ROMANIAN PHARMACEUTICAL MARKET (2008-2024)

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Abstract

Most studies on medicine shortages have primarily focused on the prevalence and characteristics of affected products. This study assesses supply discontinuities in Romania, with emphasis on supply trends, regulatory frameworks, pricing policies, and their impact on patient access to treatment. The analysis is based on data from the National Catalogue of Human Medicines (CANAMED) and shortage notifications reported by the National Agency for Medicines and Medical Devices. Medicines were classified according to pharmaceutical form, route of administration, and ATC therapeutic class. Temporary and permanent shortages, marketing authorizations, and special needs authorizations were examined as indicators of systemic and regulatory responses to supply imbalances. Between 2017 and 2024, the number of reported shortages increased substantially, with permanent discontinuities accounting for 57.6% of all cases. Special-needs authorizations increased markedly during the COVID-19 pandemic, while oral and parenteral formulations dominated the market. In contrast, alternative dosage forms maintained a limited and stable share. These findings highlight widespread shortages of medicines in Romania and emphasize the need for integrated national and European strategies to strengthen the pharmaceutical system's resilience and ensure equitable access to essential medicines.

Rezumat

Majoritatea studiilor privind lipsa medicamentelor s-au concentrat asupra prevalenței și caracteristicilor produselor. Acest studiu evaluează discontinuitățile în aprovizionarea cu medicamente în România, cu accent pe tendințele de aprovizionare, cadrul de reglementare, politicile de preț și impactul asupra accesului pacienților la tratament. Analiza se bazează pe datele din Catalogul Național al Medicamentelor de Uz Uman (CANAMED) și pe notificările de discontinuitate raportate de Agenția Națională a Medicamentului și a Dispozitivelor Medicale. Produsele au fost clasificate după forma farmaceutică, calea de administrare și clasa terapeutică ATC. Notificările temporare și permanente, autorizațiile de punere pe piață și autorizațiile pentru nevoi speciale au fost analizate ca indicatori ai răspunsului sistemic. Între 2017 și 2024, numărul discontinuităților a crescut semnificativ, cele permanente reprezentând 57,6% din total. Numărul autorizațiilor pentru nevoi speciale emise a crescut în perioada pandemiei, iar formele orale și parenterale au dominat piața. Rezultatele subliniază necesitatea unei abordări integrate pentru consolidarea rezilienței sistemului farmaceutic și asigurarea accesului echitabil la medicamente esențiale.

Keywords: drug shortages, medicine shortages, availability, Romania, public health

Introduction

Despite its critical importance for the functioning of health systems (1), there is no globally unified definition for the phenomenon of drug discontinuity (or shortage) (2). Different stakeholders (regulatory authorities, international organizations, pharmaceutical professionals, patients) use different criteria and terms to describe the same realities: temporary or permanent drug shortages, stock-outs, and unavailability of a specific dosage form or strength (3). This fragmented conceptual framework complicates systematic assessment, yet the negative consequences are clear (4,5). For patients, discontinuations can mean delayed or no access to treatment. For health professionals, they create situations in which therapeutic decisions must be made under pressure and without suitable alternatives (6). For public authorities, medicine shortages become a systemic vulnerability, with direct effects on public health and public confidence in the health system's ability to deliver quality care (7).

The globalization of the pharmaceutical industry, while leading to more efficient production and distribution, has also created a critical dependence on several strategic pillars of the supply chain, particularly in the production of active pharmaceutical

ingredients (APIs) and raw materials (4,5,8). Countries such as China and India have become important suppliers to the global pharmaceutical market. In this context, any geopolitical or economic disruption in these regions creates the risk that rapid reflection can lead to problems with the availability of medicines internationally (1,8). Concentrating production in potentially vulnerable areas transforms the lack of a drug from an isolated problem into a public health crisis on a wide geopolitical scale (9). Disruptions in the supply of medicines are no longer an exceptional situation in Europe (10-12); they have become more problematic, particularly during the COVID-19 pandemic, which has exacerbated existing vulnerabilities in supply chains and demonstrated their profound impact on public health as well as on economic and social balances (13). Overdependence on specific external sources of production (14), logistical difficulties, and inadequacies in some national regulatory and strategic planning policies (15).

The adoption of Regulation (EU) 2022/123 of the European Parliament and of the Council was a groundbreaking step, marking the transition from reaction to prevention concerning discontinuity in the supply of medicines across the European Union (EU) (10). It enlarges the role of the European Medicines Agency (EMA), which becomes responsible for monitoring, coordinating, and managing availability crises, including through tools such as the development of a list of critical medicines at the European level, notification obligations on the part of pharmaceutical industry stakeholders, and a Medicines Standing Steering Group (MSSG) (12). Supply constraints in Europe are caused by a fluctuating matrix of factors that vary significantly between countries (16). These factors incorporate the national legislative framework, the pharmaceutical market's maturation, pricing, and reimbursement policies, local manufacturing resources, distribution structure, external factors such as international market volatility or geopolitical tensions (17).

The situation regarding the availability of medicines in Romania is directly influenced by the legislative framework governing pricing policy and the tax mechanisms applied to the pharmaceutical industry. According to the Romanian legislation, the prices of prescription drugs (Rx) are subject to prior approval by the Ministry of Health and cannot exceed the lowest price for that drug in a basket of 12 EU comparison countries (18). This "lowest European price" mechanism has placed Romania among the countries with the lowest drug prices in the Union (19). Simultaneously, beginning in 2009, the government introduced an additional clawback tax (20), which pharmaceutical companies perceive as highly burdensome (21). Although these measures aim to ensure the sustainability of public spending on medicines (19), they have placed considerable economic pressure on manufacturers and distributors and are frequently cited as significant factors contributing to discontinuities and product withdrawals from the Romanian market (19-21).

Given these particularities, the present study aimed to investigate the dynamic evolution and characteristics of medicinal product shortages on the Romanian market, as well as to probe the extent to which pricing policies could have influenced patients' access to medicines. The analysis compared the evolution of discontinuities reported between 2008 (20) and 2024 (18) to capture both the situation before the introduction of these measures (2008) and their effects over time to date.

Materials and Methods

Background and objectives of the study

This study examined discontinuities in the supply of medicines in Romania, utilizing official, publicly available data collected from 2008 to 2024. This interval was selected based on the introduction of the clawback tax in 2009 (20) and the adoption of the Ministry of Health Order No. 368/2017 (18), which still regulates the methodology for approving prices for prescription-only medicines. Extending the analysis to 2024, the period preceding the introduction of these measures, can provide a longitudinal perspective on the cumulative impact of public policies on the availability of drug treatments. The main objective of the research is to assess, through quantitative analysis, the relationship between national pharmaceutical policies, particularly those related to pricing and authorization, and the phenomenon of discontinuity in the supply of medicines. Thus, the study is structured in three directions: (1) analysis of the composition of the pharmaceutical market in Romania, focusing on the authorized and commercialized pharmaceutical forms and their evolution over time; (2) assessment of the dynamics of marketing authorizations and special needs authorizations, as indicators of the capacity of the regulatory system to react to supply imbalances; and (3) analysis of discontinuation notifications and their associated statistical patterns, according to the characteristics of the affected products (pharmaceutical form, route of administration, prescription status, ATC code and price range).

Data sources and documents used

Official, publicly available datasets from relevant national and European authorities in the field of medicines regulation were used.

The National Catalogue of Prices of Medicinal Products for Human Use Authorized for Marketing in Romania (CANAMED), published by the Ministry of Health (22), was the primary source for assessing pharmaceutical forms and prices. CANAMED includes all prescription (Rx) medicines with a

nationally approved price. For the period 2008-2024, the data was collected from different sources: the Ministry of Health Official Platform (for the period 2008-2014); Annexes to the ministerial orders on drug prices: Order no. 251/13.03.2017 (23), Order no. 1468/2018 (24) (valid for 2019), Order no. 443/23.02.2022 (25); CANAMED registers for the years 2023 and 2024, downloaded from the official platform of the Romanian College of Pharmacists (consolidated versions published by the authorities) (26); additionally, official data from Romania's Official Journal which updated CANAMED prices by ministerial orders, was incorporated. All these documents are officially issued and published in the Official Journal or on government platforms, and are used as references by industry, distributors, and pharmacies.

The annual activity reports published by NAMMDR (formerly NAMMD) for the period 2017-2023 (27-33) were the primary source of information on the number of marketing authorizations (MAs) issued through national and MRP/DCP procedures; the number of marketing authorizations withdrawn voluntarily or by administrative decision; the number of special needs authorizations (SNAs) issued annually; discontinuation notifications received from MA holders, classified by the nature of the discontinuation (permanent, temporary, other reasons). For the discontinuation notifications, the summary report published by NAMMDR on the situation of discontinuations in Romania for the 2017-2024 period was used.

For the analysis of marketing authorizations issued through the centralized procedure at the European Union level, the European Medicines Agency's annual reports for 2019-2023 were used. The data collected included only products authorized in the mentioned interval, according to the procedure regulated by Regulation (EC) No 726/2004 (34) and Directive 2001/83/EC (35). The information was retrieved from the official EMA platform, *Statistics and Annual Reports* section (36).

Data classification and selection

The data used in this study were subject to selection, cleaning, and categorization. Only records from official, publicly verified sources that satisfied the minimum standards of completeness and consistency were included.

To assess the available pharmaceutical forms, the data provided in CANAMED in the section corresponding to the pharmaceutical form of each registration were grouped according to Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (37), based on the routes of administration (oral, parenteral, inhalation, topical, *etc*.), this grouping is illustrated in Tables I and II.

Table I

Classification of pharmaceutical forms from data contained in CANAMED registers - Category A

Parenteral dosage forms	Oral dosage forms	Topical dosage forms	Inhalation formulations
Solutions	Tablets Orodispersible tablets	Cream	Aerosols
Suspensions	Film-coated tablets	Gel	Inhalation formulations
Emulsions	Sugar-coated tablets Capsules controlled-release capsules/tablets Sublingual tablets Oral solution Oral suspension (syrup)	Topical solution	Nebulized formulations
		Ointment Transdermal therapeutic systems (transdermal patches) Dermal patches	

Table II

Classification of pharmaceutical forms from data contained in CANAMED registers - Category B

Vaginal formulations	Rectal preparations	Transdermal formulations	Medical gases	Others
Ovules Vaginal capsules Vaginal tablets Vaginal gel Vaginal cream Vaginal solution	Suppositories Rectal solution Rectal foam Rectal suspension Rectal ointment	Transdermal gel Transdermal patch Transdermal spray	Medical carbon dioxide Medical oxygen Medical nitrous oxide Medical nitric oxide	Organ preservation solutions Hemostatic matrix Powder and solvent for intravesical administration Intestinal gel Radiopharmaceutical kits Medicinal gases Intrauterine Device (IUD)

Registrations with incomplete, inconsistent, or missing information or missing tracked identifiers (international non-proprietary name, pharmaceutical form, route of administration, ATC code, price, prescription status) were excluded. Duplicates were also removed after cleansing the datasets by sorting, filtering, and matching using unique codes and trade names.

Discontinuation notifications collected from NAMMDR reports were classified into the following categories based on the information in the notifications: temporary discontinuation (explicitly stated as such); permanent discontinuation (definitive discontinuation, voluntary withdrawal, or administrative suspension); and other situations: commercial withdrawals, MA suspensions, and quantity limitations. Notifications categorized as 'MA suspension', 'withdrawal', or 'limited quantities' have been reclassified as permanent discontinuations due to their impact on product affordability.

Included pharmaceutical products were categorized as follows: (1) pharmaceutical form, products were grouped according to dosage form (oral, parenteral, inhalation, topical, rectal, vaginal, transdermal, medicinal gases, others), according to the CANAMED nomenclature; (2) route of administration, derived from the pharmaceutical form; (3) therapeutic class, ATC classification (level 1), according to the WHO scheme for the classification of medicinal products; (4) legal status, each product noted as prescription (Rx) or over-the-counter (OTC), according to the information in CANAMED; (5) price, maximum wholesale distribution price (excluding VAT) was used to categorize products into two categories for analysis: below 100 RON and above 100 RON. The 100 RON threshold was chosen to assess the vulnerability of products in the lower price segments.

The years 2008, 2009, 2015, 2018, 2020, 2023, and 2024 were selected for analysis of pharmaceutical form and market dynamics, due to the introduction of the clawback tax in 2009 and Order No. 368/2017.

Analysis of the regulation on the authorization of medicinal products

The assessment of regulatory dynamics was conducted by analysing marketing authorisations (MA/SNA) issued, withdrawn, or granted under derogation (special needs) in Romania from 2017 to 2023, and by integrating centralized European Union-level data for 2019-2023. At this stage, we aimed to identify temporal trends in authorization activity, focusing on possible correlations between legislative changes, health crises such as the COVID-19 pandemic, and pharmaceutical market behavior.

Marketing authorizations in Romania

Data on marketing authorizations issued in Romania were extracted from the annual activity reports of the National Agency for Medicines and Medical Devices in Romania (ANMDMR/NAMMDR), available for each year of the period under analysis. These authorizations were classified by authorization procedure type, in accordance with Directive 2001/83/EC. Under the national procedure, used for medicinal products authorized exclusively in Romania, the authorization is fully managed by the NAMMDR, in accordance with Law 95/2006 on health reform and Directive 2001/83/EC. Through the Mutual Recognition Procedure (MRP), which applies when a medicinal product is already authorized in one EU Member State (reference State), and the applicant wishes to extend the authorization to other Member States (concerned States), including Romania, the NAMMDR recognizes the decision of the reference State, with the possibility to express justified objections. Under the decentralized procedure (DCP), used for simultaneous authorization in several Member States, in the absence of a pre-existing authorization, Romania can act either as Reference Member State (RMS) or as Concerned Member State (CMS).

The data collected have been aggregated annually to show the evolution of the volume of MAs issued through each procedure, with separate reporting for authorizations granted through the national procedure and those granted through the MRP/DCP.

Marketing authorizations issued through the centralized procedure (EMA)

The number of authorizations issued by the European Medicines Agency (EMA) through the centralized procedure has also been analysed. This procedure is governed by Regulation (EC) No 726/2004. It is compulsory for certain classes of medicinal products (*e.g.*, specific sophisticated biotechnology products, advanced therapies, orphan medicinal products) and optional for others. Under the centralized procedure, the European Commission issues a single decision that is automatically valid in all EU Member States, including Romania. However, for national regulatory purposes (pharmacovigilance, distribution, reimbursement), the medicinal product appears in the NAMMDR records in a form analogous to that of national authorization.

Special Needs Authorizations (SNA)

This study also assessed the special needs authorizations (SNA) issued in Romania under Art. 703 of Law No. 95/2006 on healthcare reform (38). These authorizations permit the controlled use of medicinal products that do not have a valid marketing authorization in Romania, under exceptional circumstances and based on clinical justification. They are granted, as a rule, at the request of a hospital, a specialist doctor, or an authorized importer, for the treatment of patients

with specific indications for which there is no therapeutic alternative available locally (39).

Data on the total number of SNAs granted annually were extracted from the NAMMDR reports, section "The activity of NAMMDR Committees - Market Authorization Committee" (27-33). They have been centralized and analysed over the 2017-2023 period, with a focus on the variations in 2021 and 2022, particularly in the context of the COVID-19 pandemic.

Withdrawals of marketing authorizations

In parallel with the analysis of the issued authorizations, an assessment of the number of authorizations withdrawn from the national portfolio for the period 2017-2023 was conducted. These withdrawals may be initiated voluntarily by MA holders following commercial or strategic decisions, or they may be imposed by the Authority by reasoned decision (*e.g.*, non-compliances in quality, missing renewal dossier, *etc*.) (35,38). Data were obtained from the NAMMDR annual reports, aggregated annually, and compared with the number of MAs issued in the same period to assess the net dynamics of the authorized market.

Analysis of discontinuity in the supply of medicines

The analysis of discontinuations in the supply of medicines was conducted using official data from the NAMMDR on notifications of discontinuation received from marketing authorization holders for the period 2017-2024. This analysis aimed to characterize discontinuation patterns, identify associated factors, and quantify the impact on various therapeutic and commercial segments of the pharmaceutical market.

The primary data on supply interruptions were extracted from the public report entitled "Drug discontinuity notifications", published by NAMMDR, which aggregates the notifications submitted in accordance with the legal obligations imposed by national and European legislation (including Law no. 95/2006 and the provisions of Directive 2001/83/EC) (35,38). Each notification includes information on the trade name of the medicinal product, the INN, the pharmaceutical form, the strength, the MA holder, and the type of discontinuation. Information on the ATC code, route of administration, and legal/prescription statutes was supplemented using content available on the official NAMMDR Medicinal Product Index platform. All records from 2017 to 2024 were centralized in one dataset. Incomplete records (without specification of discontinuation type or administration pathway) were excluded from the analysis. Duplicates identified based on the combination of INN + pharmaceutical form + strength + discontinuation type + year were removed to avoid over-reporting.

Notifications of discontinuation were classified according to the criteria used by the NAMMDR, into the following categories: (1) temporary discontinuation (situations where the APP holder has informed the Authority of a fixed duration of unavailability with the intention to resume marketing); (2) permanent discontinuation (interruptions without a timeframe for resumption, usually associated with commercial decisions, withdrawal of the APP, voluntary suspension or administrative decisions); (3) other reasons (notifications indicating limited quantities available, temporary suspension or withdrawal on technical grounds without explicit details on duration). Notifications in the categories 'withdrawal', 'suspension', and 'limited quantities' have also been reclassified as permanent discontinuations, given the impossibility of guaranteeing the resumption of supply within a predictable timeframe.

For each valid record, additional attributes relevant for further analysis were added: route of administration, therapeutic class (ATC classification at level 1) according to the WHO system to assess the distribution of discontinuations among the main therapeutic areas, legal status, and price (wholesale distribution price, obtained from CANAMED or, in its absence, estimated from previous versions). Based on price, drugs were categorized into two segments: below 100 RON and above 100 RON, the threshold used to assess the relationship between commercial value and discontinuity probability. The wholesale price data were linked to the drug shortage registry by matching them to the CANAMED books for each reporting year in which the shortage was recorded. To account for differences in size between the two categories, incidence rates adjusted to the base rate were averaged for the period 2022-2024, which corresponded to the interval for which detailed data on market composition were available. The adjusted incidence was calculated as the ratio of the number of reported shortages to the total number of authorized products in each category. The analysis used descriptive statistics and proportional comparisons to assess the relative vulnerability of Rx drugs compared to OTC drugs.

In order to assess the relative size of discontinuations, the following indicators were calculated for each year: absolute number of annual notifications (total and by type of discontinuation); proportion of reported notifications out of the total number of Rx medicines marketed in that year, obtained by reference to the annual CANAMED database; distribution of discontinuations by route of administration and ATC class; ratio of permanent and temporary discontinuations by price, legal status and pharmaceutical form.

Statistical analysis and data visualization

Statistical analysis was performed to assess associations between the relevant categorical variables (type of discontinuation, route of

administration, year of reporting, price segment) and to estimate the likelihood of permanent discontinuation, based on the characteristics of the pharmaceutical product. Data processing was performed with Microsoft Excel (Microsoft Office Professional Plus 2019, Microsoft Corporation, Redmond, WA, USA) (40,41) and JASP (version 0.95.4; JASP Team, 2025) on a Windows-based system (42).

The dataset was structured in long format, with one record per product per year per notification. Independent variables were recoded and labelled to improve interpretability and ensure consistent modelling. The oral route of administration was used as the reference in all comparative analyses, given its numerical representativeness (n = 422 notifications) and clinical relevance. For continuous variables, such as price, a two-category binarization (below 100 RON and ≥100 RON) was applied using a predetermined threshold to enable testing of differences between commercial segments. Absolute and relative frequencies were calculated for all categories of variables (discontinuity type, route of administration, ATC, legal status, price). The evolution of the number of discontinuities over time was plotted by year to highlight trends. The proportion of reported discontinuations among the total number of Rx drugs marketed annually was calculated and expressed as a percentage, serving as an indicator of relative severity.

A Chi-square test was used to assess the association between year and type of discontinuity (permanent vs. temporary). Results are presented as frequencies and percentages, together with χ^2 and p-values.

Results and Discussion

Structural Characteristics of the Romanian Pharmaceutical Market

The structural context for understanding drug shortages in Romania can be illustrated using the parameters of the regulated market and represented visually by a supply chain model. This visual model encompasses the path of a medicine, from the supply of active pharmaceutical ingredients (API) to the stages of authorization and regulatory approval, pricing mechanisms, and distribution routes, culminating in patient access. It also highlights the roles of regulatory institutions (NAMMDR - National Agency for Medicines and Medical Devices of Romania; Ministry of Health; NHIH - National Health Insurance House) in ensuring the availability of medicines and in responding to supply discontinuation (Figure 1).

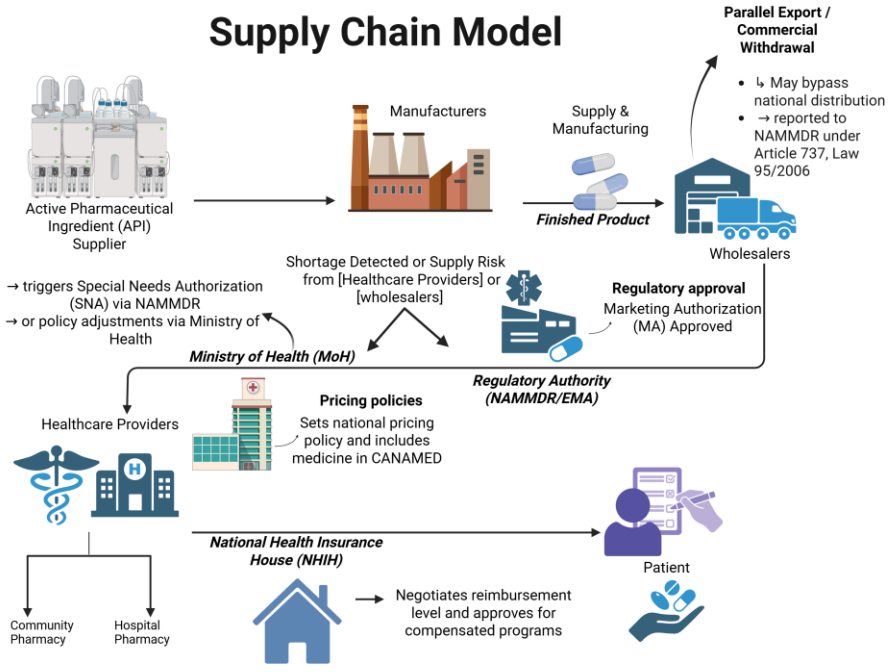

Figure 1.
Visual overview of the medicine supply chain in Romania, including manufacturers, regulators, wholesalers, reimbursement authorities, and healthcare providers. Key points of regulatory intervention and policy responses to shortages are highlighted. Graphic created using Biorender (https://www.biorender.com)

The composition of the pharmaceutical market, from the perspective of formula availability and the resilience of the prescription drug supply in Romania, is described in what follows.

Oral formulations consistently represented the most prevalent category throughout the analysis period, with 3,149 products in 2008 and 3,195 in 2009. The peak was observed in 2015, reaching 4,155 products, followed by a gradual decline and stabilization between 2018 and 2024, with annual counts ranging from 3,662 to 3,915.

Parenteral dosage forms were the second-largest category. Their availability increased from 1,161 products in 2008 to 1,179 in 2009, reaching 1,515 in both 2015 and 2018. A steady upward trend was noted thereafter, with 1,919 products in 2020, 1,921 in 2023, and 2,058 in 2024.

Inhalation formulations remained marginally represented, with product counts progressing from 54 (2008) and 56 (2009) to 63 (2015), 77 (2018), 76 (2020), 79 (2023), and 88 (2024). Topical formulations showed moderate variability, ranging from 248 to 312 products. Specific yearly values included: 296 (2008), 287 (2009), 284 (2015), 296 (2018), 312 (2020), 248 (2023), and 250 (2024).

Transdermal preparations were consistently limited in number, fluctuating between 20 and 39 products: 27 (2008), 28 (2009), 39 (2015), 33 (2018), 31 (2020), 20 (2023), and 21 (2024).

Vaginal formulations remained relatively stable at low levels, with a gradual increase from 27 (2008) to 47 (2024). Intermediate values included: 28 (2009), 31 (2015), 33 (2018), 34 (2020), and 45 (2023).

Rectal formulations ranged from 34 to 48 products over the years, with the following distribution: 48 (2008), 41 (2009), 44 (2015), 34 (2018), 35 (2020), 38 (2023), and 37 (2024).

Medicinal gases were first documented in 2020, with 90 products; this number increased to 105 in 2023 and 106 in 2024. The 'Others' category comprised a small and fluctuating number of products: 9 (2008), 12 (2009), 12 (2015), 15 (2018), 24 (2020), 32 (2023), and 19 (2024) (Figures 2 and 3).

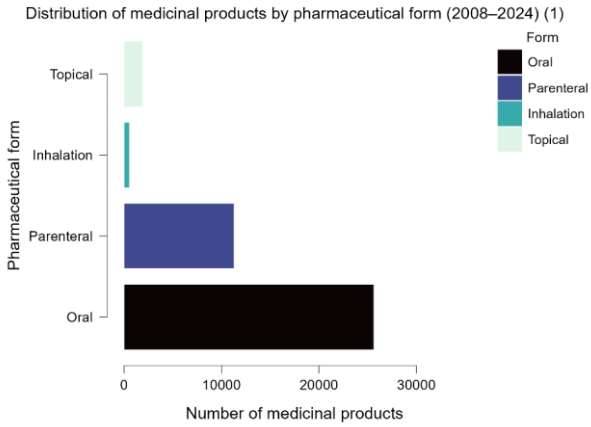

Figure 2.
Distribution of pharmaceutical forms of medicinal products listed in CANAMED across selected time points (2008, 2009, 2015, 2018, 2019, 2020, 2023, 2024). Oral, parenteral, inhalation, and topical products

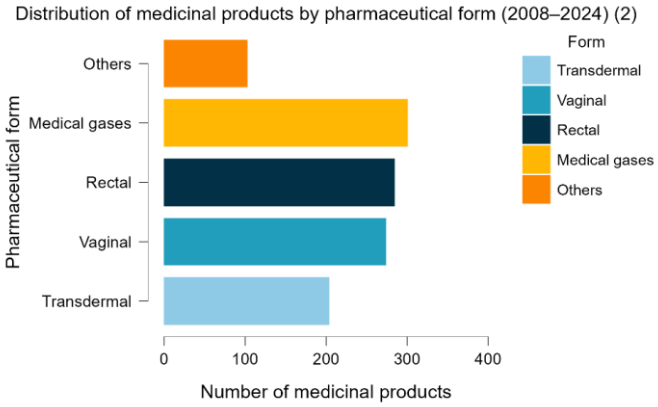

Figure 3.
Distribution of pharmaceutical forms of medicinal products listed in CANAMED across selected time points (2008, 2009, 2015, 2018, 2019, 2020, 2023, 2024). Medicinal products for transdermal, vaginal, and rectal administration, medical gases, and others

The aforementioned data on the availability of pharmaceutical forms suggest that the Romanian pharmaceutical supply system is highly dependent on oral and parenteral dosage forms, which dominate the national market. This is in line with what is known about the pharmaceutical market: the oral route is the most frequently used method for administering medicines (43), followed by parenteral and topical products. However, this comes with a significant downside: swallowing difficulties, whether confirmed or perceived, can make oral medication administration challenging for some patients (44). This is particularly an issue for patients with dysphagia and for the larger oral dosage forms, specifically with sizes larger than 11 mm (44,45). Although other routes of administration can help overcome swallowing difficulties, the limited availability and minimal growth in alternative forms, such as inhalation, topical, or intrauterine formulations, may hinder patient-centered therapeutic options.

Another idea worth highlighting is that certain sterile injectable forms require manufacturing processes with high technological standards, including controlled environments, extensive validations, and strict compliance with GMP requirements for sterile products. In addition, the global production of injectables is concentrated in a few facilities, making them susceptible to disruptions in the supply of raw materials, sterile packaging materials, and critical consumables (*e.g.*, filters, vials). Inhalation forms also involve a high degree of complexity, including specialized devices, pressure-filling equipment, and dose uniformity validations. Production of these devices is often outsourced and fragmented, which magnifies the impact of disruptions in global supply chains on their availability. References indicate that Romania is not the only country experiencing a shortage of these pharmaceutical formulations; for instance, an analysis of FDA data covering the 2018 to 2023 interval showed that injectable medications constituted more than half of all shortages (46), and another study found that in the United States, three-quarters of shortages impact parenteral products (47). In a Belgian hospital, a study also reported that parenteral shortages were three times more frequent than oral shortages (48). The situation is even more critical in the case of the neonatal field, where a study found that over 86% of shortages involved parenteral dosage forms (49).

According to EMA literature and regulatory reviews, recall and discontinuation rates are higher for dosage forms associated with advanced technologies or high fixed manufacturing costs, especially in the absence of reimbursement price adjustments (50,51). In a market such as Romania, where economic incentives to maintain these products are limited, discontinuity is a predictable consequence of underestimating real production and distribution costs.

Regulatory Dynamics from the Perspective of Marketing Authorization

Marketing authorizations issued in Romania between 2017 and 2023 varied considerably, peaking at 3,140 in 2019 (902 national, 668 MRP/DCP, 1,570 other types). From an initial total of 1,828 in 2017 (260 national, 654 MRP/DCP), authorizations dropped to 1,680 in 2018 (182 national, 658 MRP/DCP). Following the 2019 peak, numbers declined steadily: 1,486 in 2020 (250 national, 493 MRP/DCP), then 1,202 in 2021 and 1,196 in 2022 (both with only 46 national authorizations). The period's lowest point occurred in 2023 with just 858 authorizations (33 national, 396 MRP/DCP) (Figure 4).

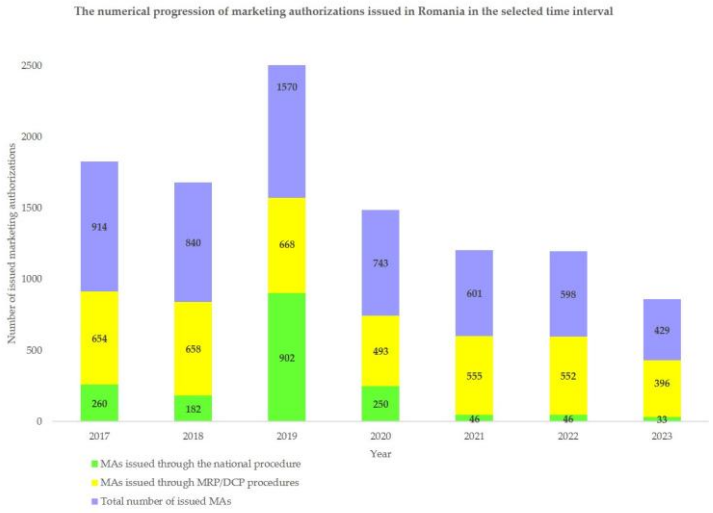

Figure 4.
The numerical progression of marketing authorizations issued in Romania in the selected time interval

The marketing authorizations issued in Romania and presented in this analysis include all categories of medicines, regardless of the legal basis for the authorization application, as provided for in Directive 2001/83/EC (35).

After 2019, there was a steady decline in the number of marketing authorizations (MA) granted in Romania, both through the national procedure and through the mutual recognition procedure (MRP) and decentralized procedure (DCP). In 2023, the number of MAs obtained through the independent national procedure reached a historical minimum (n = 33), sharply decreasing compared to 2019. This trend may indicate a decline in commercial interest among authorization holders in the Romanian market. The main explanation lies in the cumulative impact of the minimum pricing policy (the lowest European reference price) and the clawback tax mechanism, which reduces the market's financial attractiveness, especially for generics, biosimilars, or low-margin molecules (52). In the absence of stable and predictable reimbursement conditions, Romania is perceived as an unprofitable market with high operational risk. Decisions to launch or maintain products on the market are strongly influenced by the degree of predictability and profitability. In small or poorly capitalized markets, such as Romania, the combination of rigid pricing policies and additional taxation (clawback rates exceeding 20%) may encourage market exit, even for products authorized at the European level (19,21).

In contrast to the analysis of the number of marketing authorizations (MA) granted, this analysis presents the picture of MA withdrawals recorded in Romania between 2017 and 2023. Both significant decreases and increases characterized their evolution, with particularly high peaks in the middle years of the study period. Starting at 712 withdrawals in 2017, the number dropped to a low of 589 in 2018 before surging to 902 in 2019. After a slight decline to 818 in 2020, withdrawals peaked dramatically at 1,474 in 2021—the highest recorded level. Despite a decrease to 1,334 in 2022, numbers remained elevated. However, 2023 marked a sharp reversal with only 503 withdrawals, the lowest in the entire seven-year period (Figure 5).

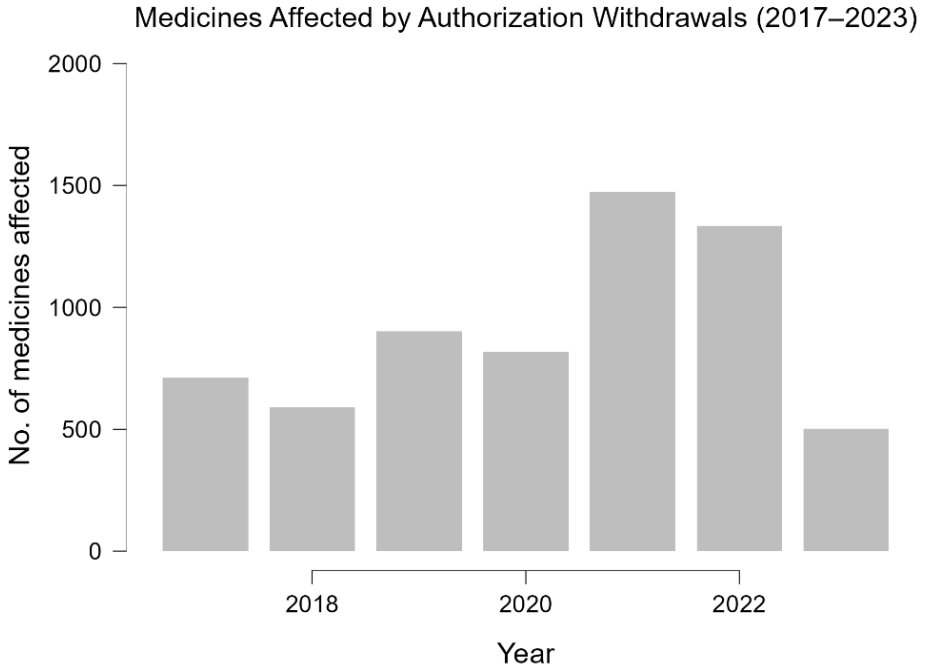

Figure 5.
Trend in the number of medicines affected by marketing authorization withdrawal decisions in Romania (2017-2023)

A possible explanation is the pharmaceutical market's adaptation to post-pandemic conditions, or a potential resumption of commercial interest in the Romanian market, amid the relative stabilization of logistics flows and the revaluation of portfolios at the European level.

This downward trend should be interpreted with caution. In the immediate post-COVID period, structural measures have been introduced at the European level to increase the resilience of pharmaceutical systems, such as the development of national and European essential medicines lists, the restriction of parallel exports for deficient products,

and the strengthening of notification obligations for the risk of discontinuity (53,54). These interventions, together with ad hoc measures taken by the Romanian authorities, may have contributed to a temporary reduction in withdrawals.

In the post-pandemic period, it has been shown that the reorganization of supply chains, the diversification of production sources, and the adjustment of companies' commercial strategies have led to a partial stabilization of markets previously considered unattractive (55,56). Romania could indirectly benefit from these changes, particularly if recent initiatives to digitize the permitting process and increase regulatory transparency are further strengthened. However, lower withdrawals do not address the root causes of the shortage. Without sustainable interventions in pricing policy, a review of the clawback mechanism, and strengthening access to essential medicines, the risk of a reversal of the trend remains high.

For marketing authorizations issued by the European Medicines Agency (EMA) through the centralized procedure, the analysis of the 2019-2023 period reveals a different trend from that observed at the national level. Regardless of the legal basis for the authorization application, the authorizations are issued through the centralized procedure according to Regulation (EC) No 726/2004 (34), which are the focus of this analysis, encompass all categories of medicinal products that Directive 2001/83/EC regulates (35). Thus, in 2019, 66 authorizations were granted, representing the lowest number in the analyzed interval. In 2020, authorizations rose significantly to 97, the highest recorded during the study period. Subsequently, the number of authorizations gradually decreased: 92 in 2021, 89 in 2022, and 77 in 2023, indicating a downward trend towards the end of the analyzed period (Figure 6).

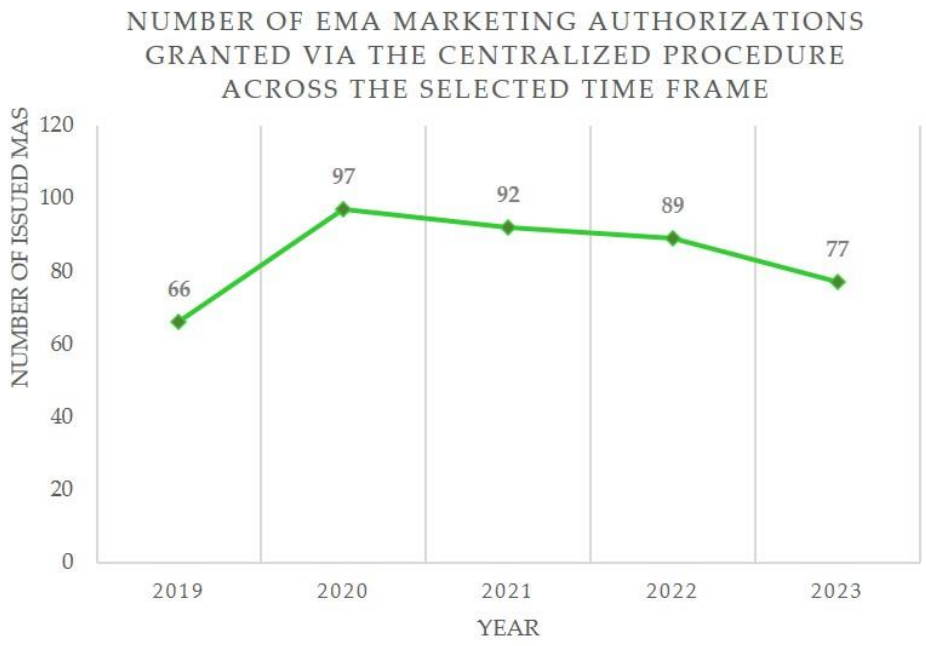

Figure 6.
Evolution of the number of marketing authorizations issued by EMA through the centralized procedure in the selected time interval

Special needs authorizations (SNAs) issued by NAMMDR in Romania from 2017 to 2023, as a direct and specific regulatory response to medicinal product shortages, showed an oscillating pattern with notable peaks in 2021-2022. Starting at 74 authorizations in 2017, the number dropped to its lowest point of 62 in 2018, then gradually recovered to 72 in 2019 and 80 in 2020. A sharp increase followed in 2021 with 127 authorizations—more than double the 2018 figure—and peaked at 132 in 2022, the highest recorded during this period. However, 2023 saw a significant decline to 76 authorizations, returning to levels similar to those at the start of the period (Figure 7).

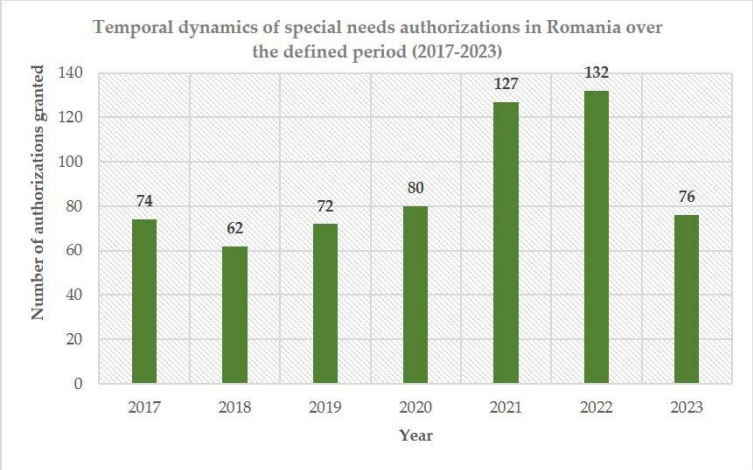

Figure 7.
The evolution of the number of special needs authorizations issued in Romania in the selected time interval

Special needs authorizations, based on Art. 703 of Law No. 95/2006 on healthcare reform (38), allow the controlled use of medicinal products without a valid marketing authorization in the Member State (39). Their increasing frequency could indicate a lack of resilience of the supply system and difficulties in ensuring continuity of access to essential medicines through conventional procedures (57). The peak observed in that period coincided with the COVID-19 epidemic and apparently reflects the regulatory response to the logistic pressures associated with that complex regulatory and social landscape (58). A study reported that in the United States, there was an increase in drug shortages at the beginning of 2020, followed by a decline in shortages after May 2020 (53). There could have been a delay in Romania, both in the increase in shortages and in the regulatory response of the Romanian authorities, as granting special-needs authorizations still takes time, despite the authorities' efforts to speed up the process. The decline of their number in 2023 could suggest a normalization of supply or an administrative tightening of exception criteria.

3.3. Drug Shortages in Romania: Patterns and Determinants

An analysis of drug shortages reported in Romania between 2017 and 2024 reveals a clear upward trend, characterized by notable yearly fluctuations and a sharp intensification in the final years of the period. In 2017, 41 drug shortages were reported, followed by a decline to 27 in 2018 - the lowest figure recorded during the study interval. From 2019 onward, the situation shifted, with 59 cases reported, indicating a marked increase. This trend briefly reversed in 2020, when shortages dropped to 45, before rising again in the following years: 76 cases in 2021 and 67 in 2022. The phenomenon then accelerated significantly, reaching 113 reported discontinuities in 2023 - almost double the previous year's figure. The escalation became particularly pronounced in 2024, with 234 reported cases, representing the highest value in the entire timeframe and a striking surge compared to earlier years (Figure 8).

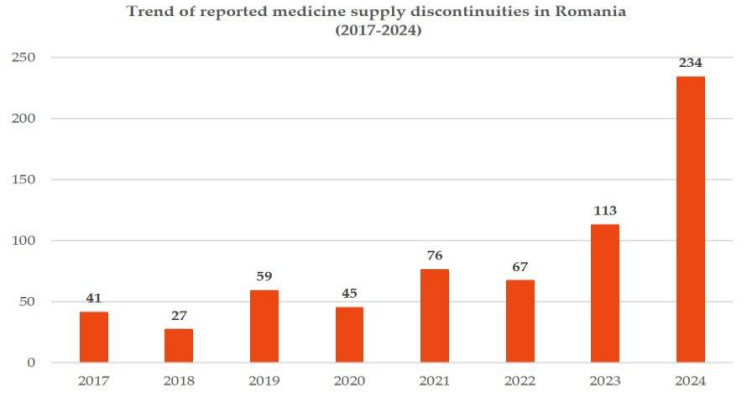

Figure 8.
Trend of reported medicine supply discontinuities in Romania (2017-2024)

Evolution does not follow a linear trend, but the general direction is upward. This trend may indicate a persistent imbalance in the pharmaceutical supply chain, suggesting reduced capacity to prevent or mitigate supply bottlenecks. From an operational perspective, the phenomenon can be associated with the effects of the pandemic crisis, which highlighted the limits of local production, the high dependence on non-EU raw materials, and the absence of effective mechanisms for anticipatory intervention (59). At the European level, comparable increases in the frequency of outbreaks have been reported for the period 2020-2023, particularly in Italy, France, and Belgium (5,48,60). The EMA and HMA reports in the post-pandemic period also describe a shift in approach, whereby drug shortages are treated as a persistent systemic risk rather than a transitory phenomenon (54). However, the effectiveness of these instruments at the national level remains limited in the absence of a strengthened institutional infrastructure and adaptable pricing policies (61).

The distribution of shortage notifications reported to the Romanian National Agency for Medicines and Medical Devices (NAMMDR) for the period 2017-2024 shows important shares for both permanent and temporary supply interruptions. Of the 662 shortage notifications recorded, 54% were permanent (356) and 41% were temporary (272). The remaining notifications were far less common: 3% (19) involved suspended marketing authorizations, 1% (5) were authorization withdrawals, 1% (8) concerned limited quantities, and less than 1% (2) fell into other categories. To better reflect the actual impact on the availability of medicines, notifications of suspended or withdrawn marketing authorizations were reclassified as permanent discontinuities because of their long-term or indefinite unavailability. After this adjustment, permanent shortages accounted for 57% (381) of notifications, while temporary shortages represented 42% (281). This distribution, which reflects the proportion of different types of discontinuities, is outlined in Figure 9.

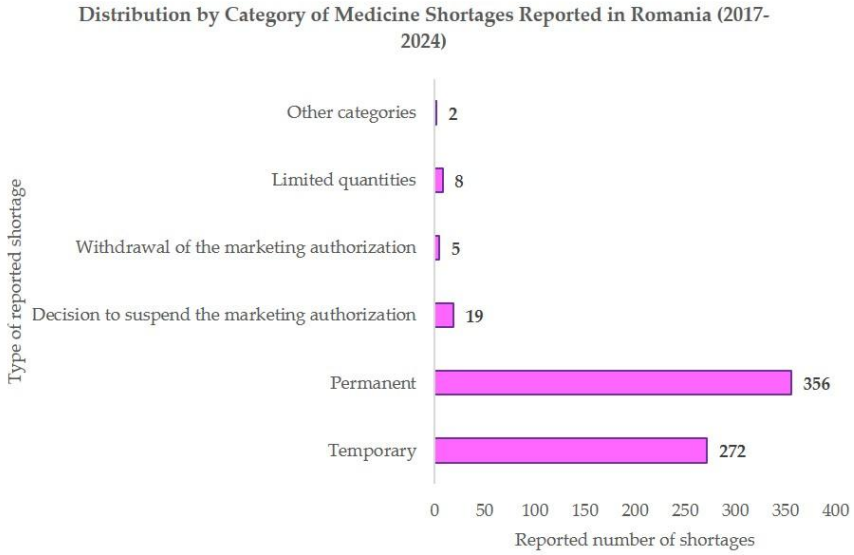

Figure 9.
Distribution by category of medicine shortages reported in Romania (2017-2024)

The ratio of discontinuity notifications shown in the figures above indicates a structural problem rather than a transitory phenomenon. The high share of permanent discontinuations suggests that predominantly economic and regulatory mechanisms are at play, rather than temporary production or distribution disruptions. This type of withdrawal is characteristic of markets with low profitability, especially for low-priced and low-volume generic medicines (62). The scientific literature describes the "low-price trap" phenomenon, observed in countries with strict cost-control policies, including Romania (21). The European minimum price obligation and the application of the regressive clawback tax generate financial pressure on marketing authorization holders (19). Voluntary withdrawal is thus becoming a rational economic option for manufacturers, especially for medicines with very low profit margins (21).

A Chi-square test assessing the distribution of discontinuity types (permanent vs. temporary) across years revealed a significant association ($\chi^2 = 40.39$; $df = 7$; $p < 0.000001$), indicating year-on-year variation in discontinuity types as summarized in Table III.

Table III

Statistical analysis to investigate variation in discontinuities between 2017 and 2024

Year	Permanent (n, %)	Temporary (n, %)	Total (n, %)	χ^2	p-value
2017	6 (14.6%)	35 (85.4%)	41 (100.0%)		
2018	16 (59.3%)	11 (40.7%)	27 (100.0%)		
2019	38 (64.4%)	21 (35.6%)	59 (100.0%)		
2020	26 (57.8%)	19 (42.2%)	45 (100.0%)		
2021	56 (73.7%)	20 (26.3%)	76 (100.0%)	40.39	0.0000011
2022	40 (59.7%)	27 (40.3%)	67 (100.0%)		
2023	66 (58.4%)	47 (41.6%)	113 (100.0%)		
2024	133 (56.8%)	101 (43.2%)	234 (100.0%)		
Total	381 (57.6%)	281 (42.4%)	662 (100.0%)		

The analysis of standardized residuals indicated that 2017, 2019, and 2021 were the main contributors to the overall χ^2 statistic. In 2017, permanent discontinuities were significantly underrepresented relative to expected values, reflecting the early phase of reporting, whereas in 2021, coinciding with the COVID-19 pandemic, they were significantly overrepresented. These findings confirm a statistically robust temporal heterogeneity in discontinuity patterns and suggest that external systemic shocks may influence the persistence of medicine shortages. The increasing proportion of permanent discontinuities may also reflect cumulative pressures on supply chain resilience.

The disaggregation of the drugs reported as being in short supply, classified by therapeutic area according to the ATC system (level 1), shows a heterogeneous distribution of discontinuities, with a tendency to cluster in specific therapeutic classes. Most reports concerned drugs in the nervous system class, followed by those in the cardiovascular system category, which together accounted for the majority of cases identified. Medicinal products for the digestive and metabolic systems, as well as those for the respiratory system, also had many discontinuities. Other therapeutic areas, such as antineoplastic and immunomodulatory drugs, as well as systemic anti-infectives, also contributed to the total number of notifications, albeit to a lesser extent compared to the dominant groups. The remaining classes, including the genitourinary system, hormone products, dermatologicals, and miscellaneous categories, had relatively few reports. This distribution underscores that shortages have hit therapeutic classes central to managing both prevalent chronic conditions and acute, high-burden diseases (Figure 10).

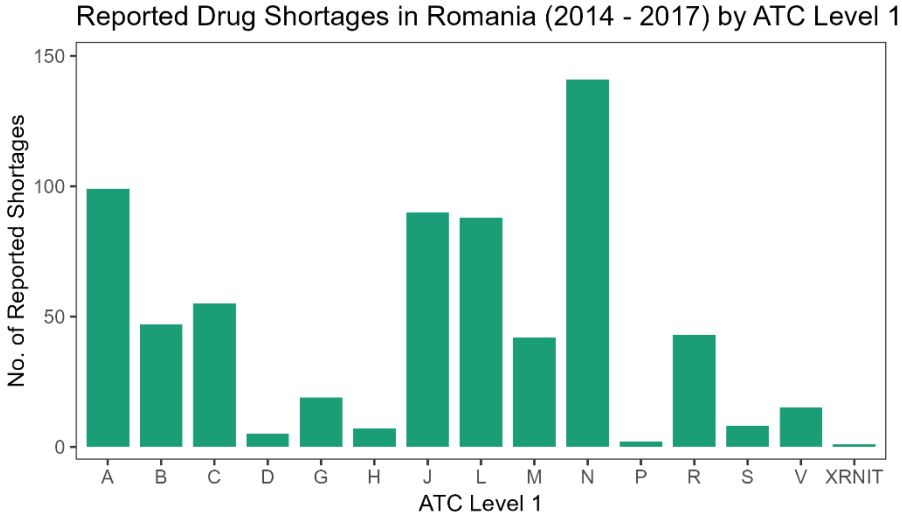

Figure 10.

Reported drug shortages in Romania (2017-2024), stratified ATC Classification, Level 1.

These therapeutic areas correspond to the treatment of high-prevalence chronic diseases, for which continuity of access to medicines is particularly important (63). The convergence of shortages in frequently used therapeutic segments is not coincidental; it illustrates a systemic vulnerability in ensuring the continuity of chronic treatments. Medications used for pathologies such as hypertension, diabetes mellitus, epilepsy, or dyslipidaemias require constant, long-term

administration without interruption (16). Withdrawal, even for short periods, may lead to clinical decompensation or acute complications with increased mortality potential. For example, interruption of antihypertensive or antiepileptic treatment is associated with an increased risk of stroke, recurrent seizures, and unplanned hospitalizations (64). In the case of antidiabetic drugs, shortages can lead to acute metabolic imbalances, ketoacidosis, or severe hyperglycaemia (65). These effects are magnified in elderly patients or patients with multiple comorbidities, where therapeutic discontinuation worsens the underlying disease and generates additional costs for the health system (66). However, shortages disproportionately affect medicines for chronic diseases. These products are generally low-priced, face strong generic competition, and are frequently subject to parallel exports or selective commercial withdrawals. Thus, ensuring therapeutic continuity in chronic diseases is necessary for patient safety, and the loss of access to these treatments is a public health issue (67).

From another perspective, the distribution of medicine shortages reported in Romania between 2017 and 2024, categorized by regulatory status, reveals a contrast between prescription-only (Rx) and over-the-counter (OTC) products. Of all shortage notifications, 606 involved prescription medicines, compared to just 56 for OTC products. This pronounced disparity suggests that shortages have overwhelmingly affected prescription medications, which are typically used to treat conditions requiring close medical supervision and ongoing management. It also reflects the base rates for the categories, as OTC products represent a minority of all authorized products. OTC products accounted for only a marginal fraction, approximately 8% of all reported cases. Qualitative categorization shows that out of 56 OTC medicines reported as experiencing discontinuity during the analyzed period, 39 had temporary interruptions while 17 were permanently discontinued. We analyzed market data to determine the percentage of over-the-counter (OTC) drugs among all drugs. Adjusting for the base rate and restricting the analysis to the period 2022 - 2024, which corresponds to the availability of detailed data on market composition, 40 over-the-counter (OTC) products and 374 prescription (Rx) drugs were reported to be discontinued. According to market data for the period July 2022-June 2025, 927 OTC products and 4,300 Rx drugs were available on the Romanian pharmaceutical market. These figures correspond to shortage incidence rates of approximately 4.3% for OTC and 8.7% for prescription drugs. Although the difference is less pronounced than in the unadjusted analysis (2017-2024), Rx drugs remain approximately twice as susceptible to shortages. Figure 11 provides a visual summary of this distribution.

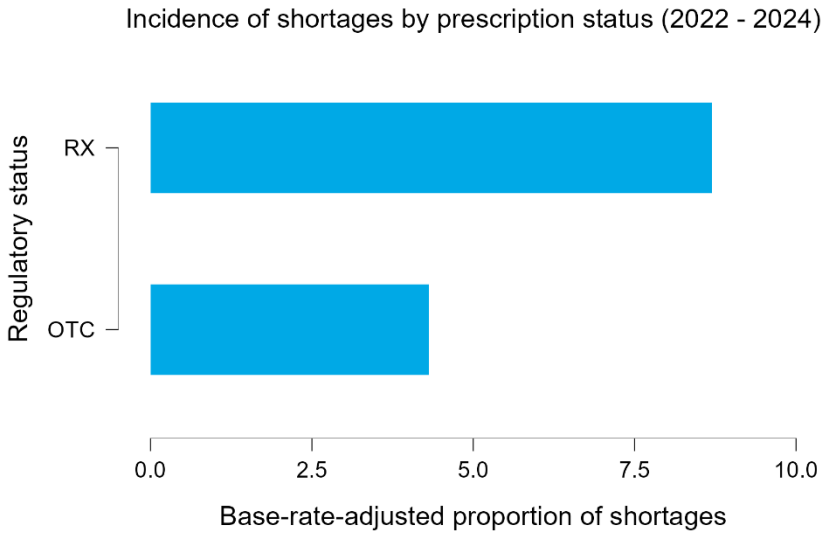

Figure 11.
Base-rate-adjusted incidence of reported drug shortages by prescription status (2022-2024)

This distribution highlights a structural asymmetry, whereby medicines essential for treating patients with chronic diseases are more likely to be discontinued. The impact is significant, as most prescription medicines are part of therapeutic regimens for severe acute diseases or chronic conditions that require continuous treatment and monitoring. In addition, the Rx category includes many medicines of vital therapeutic interest (VTMs), the lack of which may lead to treatment

interruptions with effects on morbidity and mortality (68).

Recently, the differences between Rx and OTC medicines have been highlighted. Rx medicines are subject to strong regulatory pressure through mechanisms such as reimbursement, price controls, public procurement, or distribution restrictions. In contrast, OTC products operate within a more liberal framework, driven primarily by market demand and less stringent regulation. Discontinuities in the Rx segment can thus also be interpreted as the effect of cost-containment policies disproportionately applied to prescription drugs, especially generics (69).

Proceeding to consider only the shortage of prescription drugs (Rx) marketed in Romania, an overview of the proportion of shortages relative to their total number shows a consistent and progressive increase from 2018 to 2024. Starting at 0.40% in 2018, the rate initially suggested a limited extent of the problem relative to the overall market. However, a gradual amplification began in 2020, with the share of discontinuities rising to 0.59%. The trend accelerated significantly in the following years, tripling the 2018 figure to reach 1.65% in 2023. This dynamic culminated in 2024, when the proportion peaked at 3.41%. Overall, the data show a clear shift in magnitude, moving from modest shortages in the early years to significantly more concerning levels in recent years (Figure 12).

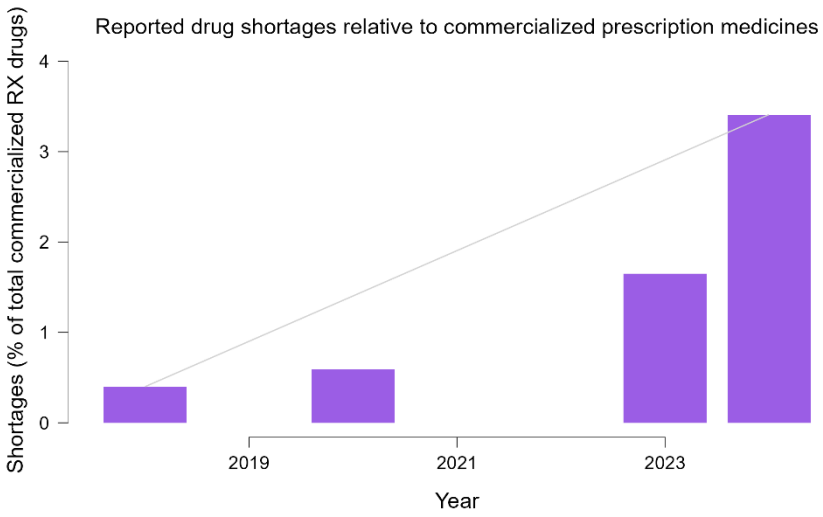

Figure 12.
Trend in the proportion of reported drug shortages relative to commercialized prescription-only medicines in Romania (2018, 2020, 2023, 2024)

Probing a potential pricing influence on the dynamics of medicines shortages in Romania, we found a notable difference between categories of medicines priced below and above the RON 100 (20 EUR) threshold in the appraisal of pharmaceutical products reported as being in short supply in Romania between 2017 and 2024, as conducted from the perspective of wholesale prices. In total, 339 products with a distribution price below RON 100 were reported as being in short supply, compared to 260 products with a price above RON 100. This repartition shows that shortages were more frequently associated with medicines in the lower price segment, suggesting that it was precisely the lower-value products, often essential in routine treatments, that were most vulnerable to discontinuities. On the other hand, higher-priced medicines were reported in smaller but still significant numbers, confirming that the shortage phenomenon affected both affordable products and some in the higher price range. Therefore, the price distribution highlights the widespread nature of the shortages, which were not limited to a particular segment but affected medicines across the entire price range, with an emphasis on the category priced below RON 100 (Figure 13).

A comparison of the evolution of the base rate with the discontinuity rate for medicines priced at ≤100 RON (approximately 20 EUR) and >100 RON, respectively, between 2018 and 2024, reveals distinct dynamics between the two segments. For medicines priced at ≤100 RON (Figure 14), the base rate fell steadily from 67.6% in 2018 to 52.2% in 2023, then rose slightly to 54.6% in 2024, indicating a gradual reduction in the share of low-cost products in the total CANAMED book. In contrast, the discontinuity rate increased from 0.34% in 2018 to 3.57% in 2024, more than tenfold over the period analyzed. For drugs priced above RON 100 (Figure 15), the base rate showed an inverse trend - a progressive increase from 32.3% in 2018 to 47.8% in 2023, followed by a slight decrease to 45.4% in

2024. In this case, the discontinuity rate increased from 0.54% in 2018 to 3.07% in 2024, remaining slightly lower than the values observed for the under RON 100 category. In practice, this comparative analysis shows that, although inexpensive medicines remained predominant in the market, the rate of discontinuity growth in this segment was more pronounced, proportionally exceeding the evolution observed for higher-priced products.

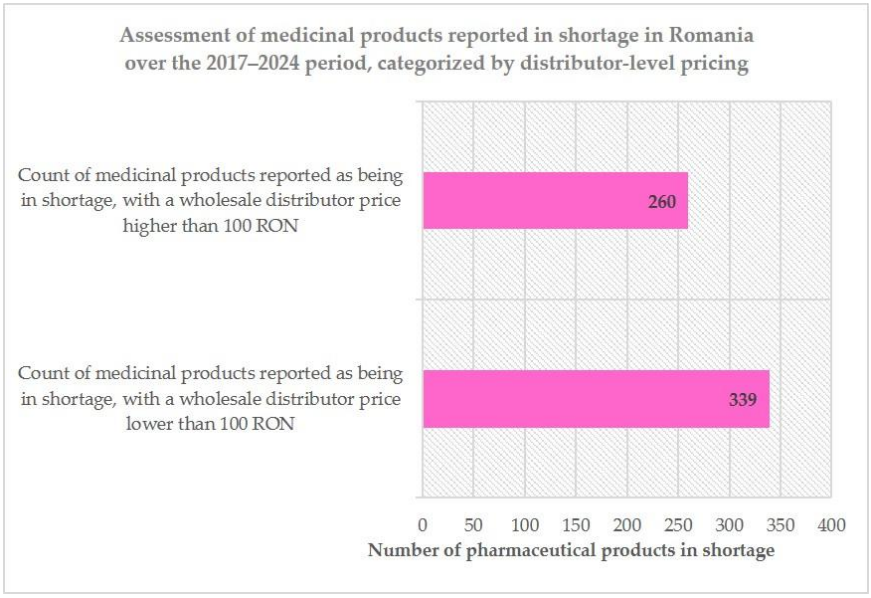

Figure 13.
Assessment of medicinal products reported in shortage in Romania over the 2017-2024 period, categorized by wholesale price

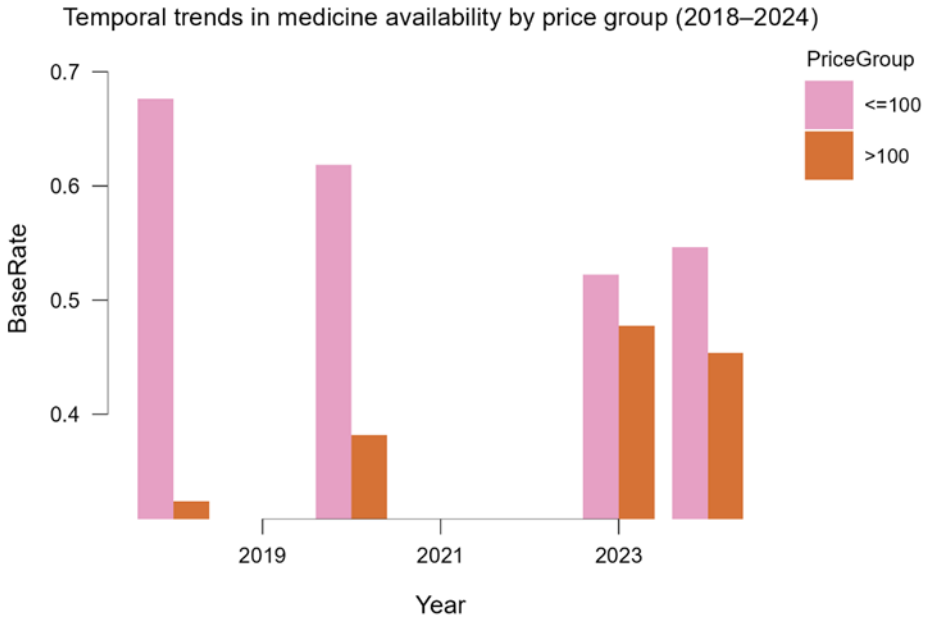

Figure 14.
Temporal trends in medicine availability by price group (2018 - 2024)

The analysis of discontinuations by commercial value shows that medicines priced below 100 RON are significantly more frequently subject to discontinuation notifications than those priced above 100 RON. Thus, a correlation has been established between low price and product vulnerability to market withdrawal or lack of supply. The base rate-adjusted analysis shows that variations in the frequency of discontinuities cannot be attributed to a base rate fallacy related to the price segments. Between 2018 and 2020, medicines priced above RON 100 had slightly higher discontinuity rates,

indicating a proportional impact on products with higher commercial value. However, after 2020, the trend reversed: drugs priced ≤100 RON gradually became more exposed, reaching a discontinuity rate of 3.57% in 2024, compared to 3.07% for the higher category. This reversal, confirmed by the adjustment to the base rate, suggests that recent discontinuity phenomena are increasingly concentrated on low-priced products, often essential medicines, generics, or those used in chronic treatments (70). Economic pressures on manufacturers and distributors, low profit margins, and rigid price regulations may explain this vulnerability (71). Consequently, the results support the hypothesis that the low-priced drug segment is structurally more exposed to the risk of withdrawal or temporary absence from the market, even when its higher share in the total product portfolio is taken into account (63).

The benchmark RON 100 (approximately EUR 20) was selected as the reference value for classifying products by price level, taking into account several economic and methodological considerations. Firstly, this value provides a balanced delimitation of the Romanian pharmaceutical market, being close to the median point of the price distribution reported in CANAMED. Market structure analysis revealed that between 2018 and 2024, medicines priced at ≤100 RON accounted for 52%-68% of all listed products, indicating that this threshold serves as a natural boundary between low- and high-priced products. Additionally, from the perspective of pharmaceutical market dynamics (72), the RON 100 threshold highlights differences in commercial behavior and profitability across price segments. Thus, the reason for selecting the threshold of 100 RON (approximately 20 EUR) is justified both by statistical considerations, as a natural separation point in price distribution, and by economic and social reasons, representing a relevant level for analyzing accessibility and supply vulnerabilities in the Romanian pharmaceutical market (73).

From an industry perspective, low-priced products, especially generics, often operate with minimal profit margins, making them sensitive to increases in production, distribution, or regulatory costs, such as additional taxes, logistics costs, or currency fluctuations. Under a strict price cap policy and the uniform application of the clawback tax, maintaining these products often becomes economically unsustainable. The literature describes several relevant mechanisms in this context. The phenomenon of "pricing erosion" refers to the ongoing decline in prices driven by intense competition among generics, without fully accounting for the real costs of production. "Shadow inventory" refers to products that remain authorized but are not actually available in stock or in distribution due to a lack of profitability. In addition, competitive pressures in the generics segment lead manufacturers to prioritize large and profitable markets at the expense of perceived marginal ones, such as Romania, where prices are administratively set and rigidly maintained (19,21,52).

This economic reality creates a vicious circle: low-cost products, often prescribed as first-line therapies, are the first to be at risk of discontinuation, even though it is precisely these products that should be protected in order to guarantee fair access to treatment. In these circumstances, shortages are not just the result of a lack of stock, but the predictable consequence of the systematic undervaluation of the commercial value of essential medicines (74).

Conclusions

The current data-driven study provides a comprehensive depiction of the discontinuity phenomenon affecting Romania's pharmaceutical market. The findings demonstrate increasing vulnerability in national supply chains, reflected in a growing number of reported product discontinuations and a narrowing of available treatment options. The limited availability and concentration of specific pharmaceutical forms raise concerns about treatment adherence and therapeutic effectiveness. The prevalence of permanent discontinuations across various routes of administration highlights the need to address systemic and economic barriers that contribute to supply instability. These challenges require a broader, long-term strategy that goes beyond short-term remediation, focusing instead on enhancing resilience through improved monitoring, strengthened European regulatory collaboration, and reform of pricing and reimbursement frameworks. Special Needs Authorizations and centralized approvals granted by the European Medicines Agency are important instruments for ensuring patient access during critical supply disruptions, particularly during global health crises such as the COVID-19 pandemic. Looking ahead, future efforts must strike a balance among regulatory stringency, economic viability, and therapeutic diversity to secure a national pharmaceutical supply that is both adaptable and robust in the face of internal and external disruptions.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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