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ORIGINAL RESEARCH ARTICLE

Pricing and Reimbursement of Patent-Protected Medicines: Challenges and Lessons from South-Eastern Europe

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Abstract

Background Efficiency and transparency of pricing and reimbursement (P&R) rules and procedures as well as their implementation in South-eastern Europe (SEE) lag substantially behind Western European practice. Nevertheless, P&R systems in SEE are rarely critically assessed, warranting a detailed and wider-encompassing exploration.

Objective Our study provides a comparative assessment of P&R processes for patent-protected medicines in ten SEE countries—EU member states: Croatia, Slovenia, Hungary, Romania and Bulgaria; and non-EU countries: Albania, Montenegro, Serbia, North Maceodina, Bosnia and Herzegovina. P&R systems are compared and evaluated through a research framework that focuses on: (1) public financing of patent-protected medicines, (2) definition of benefit packages, (3) requirements for the submission of reimbursement dossiers, (4) assessment and appraisal processes, (5) reimbursement decision making, (6) processes that occur post reimbursement, and (7) pricing. The study aims to contribute to the discussion on improving the efficiency and quality of P&R of patent-protected medicines in the region.

Methods We conducted a non-systematic literature review of published literature, as well as policy briefs and reports on healthcare systems in the SEE region along with legal documents framing the P&R procedures in local languages. The information gathered from these various sources was then discussed and clarified through structured telephone interviews with relevant national experts from each SEE country, mainly current and former senior officials and/or executives of the funding and assessment/ appraisal bodies (total of 20 interviews conducted in late 2019).

Results Capacity building through sharing knowledge and information on successful reforms across borders is an opportunity for SEE countries to further develop their P&R policies and increase (equitable) access to patent-protected medicines (especially expensive medicines), increasing affordability and containing costs. Simple yet robust and systematic decision-making frameworks that rely on international health technology assessment (HTA) procedures and are based on the pursuit of transparency seem to be the most cost-effective approach to strengthening P&R systems in SEE.

Conclusions Further reforms aiming to develop transparent and robust national decision-making frameworks (including oversight) and build institutional HTA-related and decision-making capacity are awaited in most of SEE countries, especially the non-EU members. In non-EU SEE countries, these efforts could increase access to patent-protected medicines, which is—at the moment—very limited. The EU-member SEE countries operate more developed P&R systems but could further benefit from developing their procedures, oversight and value-for-money assessment toolbox and capacity, hence further improving the transparency and efficiency of procedures that regulate access to patent-protected medicines.

1 Introduction

The wealth of nations and their respective level of healthcare spending have a profound impact on the availability of patent-protected medicines. While Western European states sustain comparatively generous pharmaceutical benefit packages that contribute to relatively comprehensive and timely access to patent-protected medicines for their citizens, less affluent South-eastern European countries (SEE) face substantial challenges in keeping pace with financing patent-protected (usually expensive) medicines [1]. This gap in access has been well documented [2–4]. Furthermore, the comparative lack of funding can also contribute to delays in payments for pharmaceuticals and to the accumulation of government debts towards the pharmaceutical industry

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Key Points for Decision Makers

All stages of pricing and reimbursement processes in South-east Europe would benefit from having clearly defined rules, procedures and processes.

Simple yet robust and systematic decision-making frameworks (including, e.g., guidelines, scorecards, assessment checklists, consensus building methodologies, etc.) that rely on international health technology assessment procedures and are based on the pursuit of transparency seem to be the most cost-effective approach in strengthening the pricing and reimbursement systems in South-east Europe.

Pricing of medicines should be undertaken based on clear and transparent rules within regulated cycles.

that have, in some SEE countries, lead to occasional drug shortages even of products listed on positive drug lists [5, 6] that should be readily available to citizens. However, in addition to wealth and the level of healthcare spending, various other contributing factors such as differences in prices [7–10] and utilization [11, 12] also affect access to patent-protected therapies. The quality and efficiency of pricing and reimbursement (P&R) processes is another important determinant of access to patent-protected therapies [1] as these processes determine which products will be financed from limited public budgets (and which will not be made available to patients) and at what prices.

This study comparatively evaluates key P&R processes for patent-protected medicines in ten SEE countries: non-EU member states—Albania, North Macedonia, Bosnia and Herzegovina, Serbia, Montenegro, and EU member states—Croatia, Slovenia, Hungary, Romania and Bulgaria.[1] The study reflects regulation and practice valid up to July 2020. The purpose of the study is twofold:

1) It aims to provide a concise comparative overview of the procedures and rules governing the P&R of patent-protected medicines in the region. Adding to the existing literature (e.g., [13–15]), the study is unique in the literature in terms of the sizable number of SEE countries it encompasses and the depth of information and decision-making contexts it aims to categorize. Previous studies either focused on P&R policies in one particular SEE country (e.g., Vogler 2011, for Croatia [16]) while comparative studies mostly focused on EU member states [17, 18] or focused on particular elements of P&R such as HTA [19]) or Managed Entry Agreements [20]. However, the quality, efficiency and transparency of P&R rules and procedures as well as their implementation in SEE lag substantially behind western European practice and cannot be critically assessed through a prism of a single aspect of P&R but warrant more detailed and wider-encompassing exploration.
2) The study seeks to contribute to the discussion on improving the outcomes of P&R by comparing and studying the successes and failures of contemporary national P&R processes. While P&R rules and procedures and the challenges in their implementation differ widely between these countries (as they differ over time [21, 22]), they also share notable similarities. The countries of the SEE region underwent great social, political, economic, and cultural transformations in the past decades (for healthcare see [23], creating P&R systems of varying degrees of transparency, efficiency and traceability. We aim to derive lessons for healthcare policymakers trying to improve the quality and outcomes of P&R decision-making in the SEE region and hence contribute to reducing hurdles to equal, generous and timely access to new patent-protected medicines for all citizens.

2 Methods

To allow for comparative assessment, the study uses a research framework that focuses on the most relevant components of the P&R systems, as outlined in Table 1.

To gather information on the different components of the P&R systems in each SEE country, we first conducted a non-systematic literature review. It encompassed published, peer-reviewed literature, as well as policy briefs and reports on healthcare systems in the SEE region together with respective official internet references of health insurance funds, agencies and ministries. The review also included legal documents (laws, bylaws, ministerial orders, etc.) that regulate the P&R procedures in local languages. Next, this vast amount of information gathered from various sources was then discussed and further clarified through structured interviews with relevant national experts from each SEE county. Two leading authors (LV and AB) each telephone-interviewed one stakeholder from each participating country,[2] mainly current and former senior officials and/or executives of the funding and assessment/ appraisal bodies

[1] Slovenia and Hungary joined the EU in 2004, Bulgaria and Romania in 2007, Croatia in 2013.

[2] Twenty local experts in total from ten SEE countries.

Table 1 Research framework

Component	Topics covered
1. Public financing of patent-protected medicines	Budgeting procedure for medicines, predictability of funds available for medicines in future years, practice and handling of savings or overspends
2. Defining the pharmaceutical benefit package	Lists of reimbursed medicines and restrictions, professional formularies/guidelines
3. Requirements for company submissions	Submitters, clinical and health economic evidence required, guidelines, data availability, variations in quality, cost of submissions
4. Assessment and appraisal processes	Standard operating procedure (SOP), clarity and transparency, deadlines, bodies in charge, checklists, consensus building methodologies, criteria, prioritization, grievance redress
5. Reimbursement decision-making	SOP, clarity and transparency, deadlines, bodies in charge, consensus building methodologies, criteria, accountability, prioritization, negotiations, handling risk, grievance redress
6. Pricing	Scope of pricing regulation, international price comparisons, internal price referencing, VAT rates
7. Post reimbursement processes	Clinical and health economic assessment, patient registers, delisting

[interviews were conducted late 2019; see Table 1 in the Online Supplementary Material (OSM))] The aim was to clarify and discuss each step of the P&R process in detail, as well as to reflect on both official rules and regulation and their implementation in practice, drawing on interviewees' own experience from currently serving or having in the past served at various technical, policy or commercial posts. This approach was taken to fill in the gaps in published research that critically evaluates P&R policy and decision making in most of the SEE countries covered by this study. To allow for a comprehensive comparison and to ensure that all topics were equally addressed in all countries (i.e., using the same approach and level of detail), interviews were conducted using a structured questionnaire (OSM, Tables 2a–5b) containing a set of prepared questions. The answers to each point are provided in detail in the tables in the OSM.

Following the stakeholder interviews, leading authors compared the answers and comments obtained from the interviewees, ensuring that all P&R attributes were clarified and well understood.[3] When interviewers encountered discrepancies either among the responses of the stakeholders within a particular country or their responses and the available literature, further stakeholders' clarifications were requested. The process of clarifying any discrepancy through follow-up with stakeholders was deemed crucial to ensure reliability of information and objectivity since the available literature often covered only a portion of the information required to evaluate the P&R policy in ten countries.

Finally, all interviewees reviewed the findings and conclusions regarding their own countries and those listed as co-authors also extensively contributed to the comparative assessment of the P&R policies in the region. Comparative assessment helped identify the common issues as well as specific policies that present a step forward in the development of P&R in the region (we label those "good practices") as well as the lessons learned. The findings of this paper, built through a participatory approach, therefore represent the professional consensus of its authors and cover the P&R rules up to July 2020. Comparative assessment is presented in detail as a part of the OSM.

Although the study encompassed ten SEE countries, we present the results of 11 healthcare systems because Bosnia and Herzegovina sustain two separate entities.[4]

3 Results

While detailed information on individual countries is available in the OSM, the Results section aims to provide an overview of common issues identified by the comparative assessment in the SEE region.

3.1 Public Financing of Patent-Protected Medicines

Our findings indicate that the leading issues related to public financing of patent-protected medicines in SEE (equally in the EU member and non-EU member states) fall under poor budgeting practices. First, budgeting seems stretched between the health sectors' desires to list patent-protected (cost-) effective drugs available to patients in Western Europe and the Ministry of Finances' top-down budgeting processes focused on trimming government expenditure,

[3] Due to their significant input in clarifying the particulars of each P&R process and the related "grey area", the majority of the interviewed experts are also included as co-authors in this final report.

[4] Bosnia and Herzegovina consist of two entities – the Federation of Bosnia and Herzegovina or FBiH, and the Republika Srpska or RepS. Both govern their own separate P&R policies and processes (along with their own health insurance systems, healthcare providers, etc.).

Table 2 Good practice examples in public financing of patent-protected medicines

Good practice examples in fiscal issues	Countries
Dedicated funding envelopes or payments for expensive medicines improving access and equity of access to patent protected products	FBIH and RepS, HR, HU, Sl
MEA implementation leading to improved expenditure forecasting and control and resulting in easier reimbursement of patent-protected products	AL, BG, HR, HU, ME, RO, RS, Sl
Centralised hospital tendering or other generic pricing mechanisms improving expenditure efficiency through lowering prices of generics, creating fiscal space for patent-protected products	AL, HR, HU, ME, RS
Market payback mechanisms improving overall expenditure control, resulting in easier reimbursement of patent-protected products	BG, HU, RO

HR Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *ME* Montenegro, *HU* Hungary, *AL* Albania, *FBiH* Federation of Bosnia and Herzegovina, *RepS* Republika Srpska, *NMK* North Macedonia

which often take little account of actual healthcare needs. Second, it seems that health insurance funds (the payers) generally have a low analytic capacity and lack the resources for horizon-scanning activities, leading to simplistic and inaccurate expenditure forecasts that fail to account even for the growth in the current benefit packages expenditure, let alone for the future reimbursement of new patent-protected medicines.

Another important issue related to the funding of patent-protected medicines in several SEE countries is mixing the health-related and economic policy objectives, resulting in many instances with overpayment of generics and inadequate fiscal space for patent-protected (cost-)effective therapies. Domestic generic companies are often seen as generating employment while companies that focus on patent-protected products, with limited local presence in the SEE region, are considered to be foreign and exporting profits. Poor awareness of patent-protected medicines' health benefits among policymakers and the public could be contributing to low public prioritisation of access to patent-protected products, seen primarily as "expenditure".

In addition, health sub-budgets (hospitals, rehabilitation, long-term care, etc.) function typically as separate siloes. Even if the added medical value of a patent-protected medicine is recognized by the experts at payer organizations and if its listing would result in savings in other health sub-budgets, these cannot be realised (or adequately taken into account in policymaking) as there is typically no rebalancing between the separate sub-budgets.

Specific good practice examples in the domain of public financing that are already implemented are listed in Table 2 and include, among others, Managed Entry Agreements (MEAs) that distribute the risk of overconsumption, centralised hospital tendering, which decreases the prices of multisource products, and market payback mechanisms, which ensure the repayments over legislated limits.

3.2 Definition of Benefit Packages

In SEE countries, official national strategic documents to guide pharmaceutical policies are rare[5] and there is little explicit prioritization in the definition of benefit packages. Most countries have brand name-based lists that perpetuate the branded generics market model in which generic companies aggressively market their particular generic's brand rather than compete on prices. While lists of reimbursed medicines define the benefit packages that should be available to all citizens, selected patients in some SEE countries also have access to non-listed medicines through hospital or separate Ministry of Health (MoH) budgets on a case-by-case basis.[6]

Access is further hindered by inadequate basic health insurance coverage in some SEE countries. Only about 40–45% of the population in Albania has a valid health insurance, and only 20% in the mountain regions [24, 25]. Romania and Bulgaria (EU members) also fall short of universal coverage by 10–15% [26, 27]. Healthcare system organization can also impact access to patent-protected medicines, as in Bosnia and Herzegovina, which operates a very complex, decentralized P&R system with a number of payers with different purchasing powers [28]. Due to the lack of centralized control over pharmaceutical funding, the citizens of different regions face substantial variability in access to and co-payment levels [29].

Scarce, infrequently updated domestic therapeutic guidelines and their poor implementation as well as poor enforcement of prescribing restrictions are identified as potentially

[5] Bulgaria, Republic of Srpska and North Macedonia have or have recently created strategic documents dealing with drug policies.

[6] For example, in FBiH, North Macedonia, Albania and Serbia patients access patent-protected medicines through dedicated MoH "project funds" so that the de facto reimbursement of these medicines (as a rule, expensive patent-protected medicines) bypasses the usual P&R procedures and relies to a great extent on the political will of decision-makers. Given that the funds are very limited (especially for expensive hospital medicines), patients are often informally prior-

Table 3 Good practice examples in defining benefit packages

Good practice examples in defining benefit packages	Countries
INN-based list promoting prescribing of low-cost generics	NMK
Strict enforcement of prescribing restrictions benefiting rational prescribing habits	BG, HR, HU, RepS, RS, Sl
Clearly designated strategic priorities in access to patent-protected medicines	RS
Frequent updating of lists with patent protected products due to efficient HIF administration (more than once annually)	HU, Sl
Efforts in developing professional guidelines to improve quality of care	BG, FBiH, HU, RS

INN International Nonproprietary Name, *HR* Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *ME* Montenegro, *HU* Hungary, *AL* Albania, *FBiH* Federation of Bosnia and Herzegovina, *RepS* Republika Srpska, *NMK* North Macedonia

leading to irrational prescribing in some jurisdictions, exhausting the limited funds. Generally, lists of reimbursed medicines are infrequently updated in most SEE countries (often annually) due to low administrative efficiency as P&R processes very often take longer than the 6-month EU Transparency directive prescribed period [30].

Good practices with respect to defining benefit packages (Table 3) include frequent updating of lists with patent-protected products due to efficient HIF administration (more than once annually, as in Hungary and Slovenia). Some SEE countries strictly enforce prescribing restrictions contributing to increasingly rational prescribing habits and increasingly invest in developing professional guidelines to improve quality of care.

3.3 Requesting Company Submissions

In all SEE countries, apart from Bosnia and Herzegovina, decisions on medicines' reimbursement are taken at the national level. Marketing authorisation holders (MAHs) are required to submit application dossiers to MoHs or HIFs or other relevant authorities (i.e., National Council on Prices and Reimbursement of Medicinal Products in Bulgaria) when requesting their products to be included in the positive lists of reimbursed medicines.

In the non-EU member states, submission guidelines prescribe few methodological details. This can cause ambiguity with respect to the content and detail of the applications. EU member states, on the other hand, publish more detailed instructions. Budget Impact Analysis (BIA) is requested in all countries except in Albania, FBiH and Romania, which require simplistic cost comparisons to already reimbursed therapies. All countries except Romania, Croatia (not mandatory), Albania, FBIH and North Macedonia request Cost-effectiveness/utility analyses (CEA/CUA) as well. However, the quality (varying from country to country, and dossier to dossier) of the submitted health economic (HE) analyses in SEE is not necessarily in line with the quality standards prescribed in Western Europe. The prepared CEA/CUA analyses (even if international models are used) are heavily influenced by the low availability and reliability of local epidemiological and cost data throughout SEE. However, interviewees from several countries stressed that substantial variations in the quality of submitted dossiers have little bearing on the outcome of the assessment process, partly due to payers' inability to scrutinize submitted CEA/CUA evidence. Overall, HE analyses required in reimbursement dossiers in SEE countries can best be described as simplistic, relying on payer perspectives, and disregarding any societal costs and benefits. Locally developed health economic models are typically simplistic and need to be submitted in electronic format only in a subset of countries, supporting the notion of inadequate levels of (methodological) scrutiny dedicated by the payers. Alternatively, companies submit centrally developed "core" models that may or may not be adequately tailored to reflect local clinical circumstances, raising various validity issues.

Finally, most countries mandate the involvement of local experts (typically physicians or "key opinion leaders") in the submission process. It could be argued, however, that there is little need to mandate the involvement of local experts as companies bare the ultimate responsibility for all aspects of the submitted dossiers and should be allowed to involve experts of their own choosing. While all countries charge companies modest submission fees, none (except Hungary to an extent) systematically use the collected funds to improve their assessment process, for example through outsourcing methodological assessment or for building in-house assessment capacity.

Good practices in the domain of requesting company submissions (Table 4) include the creation and a clear presentation of detailed submission guidelines (publicly available) to inform submitters on what is expected and how evidence should be supplied, requiring a cost-effectiveness analysis to inform the assessment process and allowing companies to submit scientific evidence with no involvement of domestic

Footnote 6 (continued)

itized on the bases of age (children), time of request (first-come first-served) and geographical representation. Informal criteria may also play a role.

Table 4 Good practice examples in requesting company submissions

Good practice examples in requesting company submissions	Countries
Requiring companies to submit health economic models in electronic format so that these could be inspected	BG, HR, HU, RepS, RS, Sl
Allowing companies to submit scientific evidence with no involvement of domestic experts as authors as companies are responsible for the products and the science behind them	FBiH, HU, RO, Sl
Making detailed submission guidelines publicly available to inform submitters on what is expected and how evidence should be supplied	BG, HR, HU, RO, Sl
CEA formally required to inform the assessment process	BG, HU, ME, RepS, RS, Sl

CEA cost-effectiveness analysis, *HR* Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *ME* Montenegro, *HU* Hungary, *AL* Albania, *FBiH* Federation of Bosnia and Herzegovina, *RepS* Republika Srpska, *NMK* North Macedonia

experts as authors as companies are responsible for the science behind them (as in, e.g., Hungary, Slovenia).

3.4 Assessment/Appraisal Process

Following the MAH request for inclusion in the positive list of reimbursed medicines, experts (gathered together in "Medicine committees") evaluate the submitted dossiers and the enclosed evidence. Their recommendations are envisaged as a steppingstone in the shaping of final reimbursement decisions. The assessment and the appraisal process are not clearly separated in SEE countries and are in fact interlinked with reimbursement decision-making (which should be based on assessment and appraisal, but in fact influences it).

In the non-EU member states, appointment of Committee members is generally undertaken at the discretion of high-level decision-makers (most often politicians who in some settings even preside over the committees). Potential conflicts of interest do not seem to be well addressed even though most countries do have formal policies in place. For instance, the Committee members (typically medical doctors) habitually have close ties to pharmaceutical companies but disclose these ties at their own initiative. Although formal criteria for dossier appraisal officially exist in all countries, they tend to be vague and are not well elaborated (or not uniformly applied), leading to no formal prioritization mechanisms and a lack of traceability in assessment/appraisal process. Formally, Committee recommendations should be formed primarily based on assessing the relative therapeutic benefit, budget impact considerations and ethical reflections such as severity of disease. However, the process is nowhere supported by consensus-building methodologies such as MCDA [31, 32] or Delphi [33], and the reimbursement recommendations are not published or elaborated on, exacerbating the lack of trackability. No grievance redress mechanisms exist to challenge the Committees' recommendations. Regional and international reimbursement decisions exist in all countries, but in Serbia are consulted only informally.

In the EU member states, HIF Committees for medicines or national HTA institutions (in Bulgaria, Hungary and Romania) assess the submitted dossiers. Committee members are also most often appointed at the discretion of political leaders or HIF management, typically with full-time employment elsewhere so their involvement in the appraisal process is not extensive or long term, undermining institutional experience and decision-making rigor.[7] Although conflicts of interest are addressed and resolved relatively more effectively than in non-EU members, there is room for improvement. International assessment practice is in principle consulted, by requesting already published evidence from other EU member states, NICE reports or reports from other national HTA agencies. However, the criteria for appraisal of the entire content of submitted dossiers are also not structured, for instance through check lists, except in Romania and Hungary [34], and in principle vary from very general (e.g., therapeutic value and ethical aspects in Croatia) to more elaborate and specific (e.g., soft CEA thresholds in Hungary and Slovenia). Overall, it can be argued that the prioritization between submissions is undertaken arbitrarily and can result in over-relying on budget impact. Procedures are almost exclusively concealed from the public and Committees' recommendations remain unpublished or insufficiently elaborated.[8] As in non-EU member states, the submitters informally consult Committee members.

[7] Committee members are rarely full-time employees of the institution in charge of appraisal (e.g., in Croatia, one HIF committee member is a full-time employee of HIF) and serve only for relatively short periods of time during which they continue performing their full-time duties in hospital clinics and other (healthcare) institutions, resulting in poor development of in-house institutional experience.

[8] There are notable exceptions. In this case, the Slovenian Health Insurance Fund's Committee for Medicines publishes the minutes of its committee sessions on the HIF's website. These contain detailed recommendations on all submitted medicines. Recommendations are also delivered to companies. Recommendations are well elaborated, primarily focusing on clinical benefit versus requested prices compared to already-listed medicines and cost-effectiveness considerations. Companies can submit additional arguments and evidence if not satisfied with committee recommendations.

Table 5 Good practice examples in assessment/appraisal processes

Good practice examples in assessment/appraisal processes	Countries
Process in part or in totality implemented by educated and full-time employed staff	BG, HU, RO, Sl
Experts from outside the committees included in the process to improve the competence of recommendations	BG, HU, RO
The methodology of the required health economic analyses can be adequately scrutinised and evaluated by the persons in charge	HU, RO
Critical appraisal checklist publicly available	BG, HU, RO
Published well-elaborated committee recommendations	RO, Sl
Clear and effective grievance redress mechanism for submitters	RO, Sl
Explicit assessment criteria and consensus building methodology (MCDA) used to define recommendations	RO
Formally requiring consulting international practice	BG, HZ, FBiH, RO
Prioritisation between submissions made explicit through publicly declared priorities and/ or at the minimum defined fiscal space for reimbursement of patent-protected medicines	HR, FBiH, RO, RS

HR Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *ME* Montenegro, *HU* Hungary, *AL* Albania, *FBiH* Federation of Bosnia and Herzegovina, *RepS* Republika Srpska, *NMK* North Macedonia

Assessment/appraisal processes are not periodically analysed or improved. No consensus-building methodologies are used to form final recommendations, while a formal grievance redress mechanism exists only in Romania and Slovenia.

Good practice policy and practice examples in assessment/appraisal of company submissions that are already implemented are presented in Table 5. EU member states excel in the domain of assessment/appraisal by, for example, employing full-time educated staff, publishing critical appraisal checklists and elaborating on committee opinions. In Hungary and Romania, the assessment/appraisal processes are implemented by educated full-time staff and the methodology of the required HE analyses can be adequately scrutinised and evaluated by the persons in charge, assisted by publicly available critical appraisal checklists. In Slovenia[9] and Romania, committee recommendations are published, with a clear and effective grievance redress mechanism in place.

3.5 Reimbursement Decision-Making

In the non-EU member states, governments formally decide on reimbursement.[10] Reimbursement decisions are based on the same criteria as assessment/appraisal recommendations and are officially made at the proposal of the MoH or HIF. Prioritisation between alternative funding options is undertaken at the level of recommendations. Decisions are not published or elaborated and there are no internal control mechanisms for dealing with inconsistencies therein. The legislated deadlines for the reimbursement decisions are generally not adhered to.

In the EU member states, governments or HIF management boards (in Slovenia the Director general) are responsible for making reimbursement decisions that are largely based on assessment/appraisal recommendations. Prioritisation among funding alternatives is also reflected in the recommendations. In Croatia only negative decisions are published and briefly elaborated. Only Slovenia publishes well-elaborated recommendations with clear argumentation as to why a medicine should or should not be included in reimbursement. Mechanisms to deal with inconsistency or variability in decisions are not in place in any of the EU member states. The deadlines for reimbursement decisions are typically not adhered to.

Overall, the "ownership" of final reimbursement decisions in the SEE region can best be described as diluted. As with other stages of P&R, actual reimbursement decisions seem to be, in most jurisdictions, forged in unsystematic and unstructured processes that often lack transparency and argumentation. Quality management tools are not used to evaluate decisions. Potential grievances can be redressed only on procedural or administrative grounds. The process of reimbursement decision-making itself could be tainted with ineffective dealing with conflicts of interest and it seems to informally influence the appraisal stage even though they should be strictly separated. Decisions are often made in the absence of (practical) prioritization guidelines or criteria guiding prioritization between competing products. This contributes to our conclusion that the accountability is generally low in all SEE jurisdictions, further supported by the fact that the elaborations of reimbursement decisions are

[9] The Slovenian Health Insurance Fund's Committee for Medicines publishes the minutes of its committee sessions on the HIF's website. These contain detailed recommendations on all submitted medicines. Recommendations are also delivered to companies. Recommendations are well elaborated, primarily focusing on clinical benefit versus requested prices compared to already-listed medicines and cost-effectiveness considerations. Companies can submit additional arguments and evidence if not satisfied with committee recommendations.

[10] Except in the Republic of Srpska (Bosnia and Herzegovina) where the HIF's management board is in charge.

Table 6 Good practice examples in reimbursement decision-making

Good practice examples in reimbursement decision-making	Countries
Strict observation of committee recommendations in decision-making	SI, RS
Efforts to clearly designate mandates and criteria for negotiations on risk sharing through managed entry agreements	BG, HR, HU, RO, RS, RS, Sl
Clear ownership of decisions by appropriate bodies even if methodology is unclear	HU, RO, RS

HR Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *HU* Hungary

Table 7 Good practice examples in pricing of patent-protected medicines

Good practice examples in pricing of patent-protected medicines	Countries
No VAT or reduced VAT rates on medicines	AL, HR, HU, RO, RS
Clear and transparent internal price referencing rules implemented in regulated deadlines	BG, HU, Sl

HR Croatia, *Sl* Slovenia, *BG* Bulgaria, *RO* Romania, *RS* Serbia, *HU* Hungary, *AL* Albania

mostly not published. There seems to be barely any evaluation or oversight of the entire decision-making process, including the negotiations with pharmaceutical companies and MEAs, thus further reducing accountability of the persons and institutions participating in the processes.

However, there are examples of good practices and policies in the domain of reimbursement decision-making, mainly in the EU member states (Table 6), and these refer to a clearer ownership of decisions by appropriate bodies (even if methodology is not always unclear) and strict abiding by the committee recommendations in decision-making.

3.6 Pricing of Patent-Protected Medicines

Countries in the SEE region have thus far been partly unsuccessful in implementing entirely clear and transparent pricing rules undertaken according to their respective national regulation. Timely implementation of pricing calculations seems to be a particular challenge for most, with substantial delays and occasionally skipped pricing cycles being the norm.

Typically, both EU member and non-EU member SEE states rely excessively on international price comparisons, which is problematic in the light of widespread international implementation of MEAs that conceal real net prices. On the other hand, therapeutic referencing is undertaken either at the International Nonproprietary Name (INN) level 5 (molecule) or, less often, in wider groups at ATC 4 level that can also impact patent-protected medicines, but the processes are most often not explicitly regulated in detail in terms of which products are to be referenced. High VAT on medicines in most countries redirects resources, collected for healthcare through salary contributions, to the state treasury.

In the EU member states, financial MEAs have become very popular over the last decade [20, 35] as a tool to either agree confidential discounts or share the risk of expenditure over projected targets, which can also translate to lower prices if expenditure surpasses the agreed thresholds. In a few cases, even outcomes-based MEAs are being used. The non-EU member states have only recently started or are preparing to start implementing such financial arrangements, but caution is advised (e.g., [20]). For instance, inadequate regulatory frameworks that guide price negotiations and MEAs (as well as institutional inexperience) may have in some instance contributed to varying prices for comparable products as well as distorted markets by establishing long-term fixed prices for individual products that prohibit price competition among emerging competitors over time.

Good practices in pricing patent-protected medicines that are already implemented in the SEE region are outlined in Table 7.

3.7 Post-Reimbursement Activities

After the final decision on reimbursement and pricing, it seems that the post-listing follow-up of medicines in the SEE region remains underdeveloped. Countries do not engage in systematic and comprehensive HE assessment or evaluation of effectiveness and other clinical or non-clinical benefits. Real-world evidence collection is a matter of discussion, but little initiative has so far been noted in the SEE region. Examples of efforts to improve the evidence on real-world use and effectiveness of expensive products can be found in Croatia, Slovenia and Hungary. In 2018, Bulgaria was the first to publish a regulation that aims to establish a system for monitoring the clinical effectiveness of some expensive

Table 8 Good practice examples in post-reimbursement activities

Good practice examples	Countries
Real-world eidence considered in payment for a single patent-protected medicine for hepatitis C under outcomes-based MEAs	HR, HU, RO, RS

HR Croatia, *HU* Hungary, *RO* Romania, *RS* Serbia

products. Good practice policy or practice includes real-world evidence considered in payment for a single patent-protected medicine for hepatitis C under outcomes-based MEAs (Table 8).

4 Discussion

Our study adds to the existing literature that has comparatively assessed pricing criteria, HTA implementation and reimbursement requirements in the region of East and Central Europe in the past (e.g., [13–15]). In the Discussion section we identify lessons learned for further improving pharmaceutical policy in the SEE region. It draws on issues identified in the Results section as well as on the examples of specific policies and practices that have already been implemented in some of the countries, which can perhaps inspire and direct positive reforms in others. Both the recommendations and the identified good practice examples have been consensually developed by the authors based on the comprehensive comparative assessment of by-country policies and practices.

4.1 Lessons for Improving Public Financing of Patent-Protected Medicines

Budgets for medicines need to be defined at levels that are publicly affordable and sustainable, but much could be done to improve the way in which they are planned. Countries could invest more effort in expenditure forecasts to better define fiscal space for the inclusion of new patent-protected products. HIFs could be made more flexible to accommodate options for redistribution of funds across different sub-budgets. Last, but not least, having in mind the differences in wealth between Eastern and Western Europe, if SEE countries want to reduce the gap in access to patent-protected medicines compared to Western European countries, they should consider increasing their public expenditure on medicines within publicly bearable limits.

Specific policies and practices examples (i.e., good practices) in the domain of public financing that are already implemented and that may be taken as a step forward in the development of P&R in SEE are listed in Table 2 and include, among others, Managed Entry Agreements (MEAs), centralised hospital tendering and market payback mechanisms. These measures, although not without drawbacks or downsides, can still be very effective in preventing unnecessary spending [38].

4.2 Lessons for Improving Defining the Pharmaceutical Benefit Package

Defining pharmaceutical benefit packages could be made more strategic, for instance through clear determination of priority areas and avoiding parallel decision-making processes (e.g., [39]). All patients with the same condition should be entitled to the same benefit levels, without exceptions. Countries could invest more effort and resources in defining clinical guidelines that reflect actual circumstance and monitoring their implementation. Administrative reimbursement procedures could be made more efficient to allow for more frequent updating of positive drug lists. Good practice policies that are already implemented (Table 3) include the INN-based lists that promote prescribing and dispensing of low-cost generics and efforts in enforcement of prescribing restrictions targeted towards rational prescribing [40].

4.3 Lessons for Improving the Submission Process

Well-structured and elaborated submission processes can lead to improved policymaking through higher quality dossiers and more diligence and responsibility both from submitters and decision-making bodies. Detailed and structured submission guidelines should contribute to the quality of the information presented for review, ensuring that the dossiers are prepared in line with requested methodologies. Requests for formal HE conducted by adhering to the local context and models submitted in electronic format imply a higher quality of submissions, which could potentially lead to more informed and transparent reimbursement decisions. Improvements of local data collection practices are also suggested. Good practice policies that are already implemented (Table 4) include, among others, the provision of detailed submission guidelines and not mandating companies to hire

local experts. EU member states[11] excel among the SEE countries with respect to the level of detail in their submission guidelines.

4.4 Lessons for Improving the Assessment/Appraisal Process

The assessment process could improve in quality if conducted by relevant well-educated and non-politically appointed experts who could devote sufficient time to evaluation and who could base their assessment on the relevant evidence within the scope of expert knowledge. Experts may benefit from more structured appraisal processes as well as formal checklists (or similar tools guiding the appraisal process) and formal consensus-building methodologies, while the public and the submitters may benefit from well-elaborated published opinions and decisions with the possibility of grievance redressing. Assigning assessment processes to institutions and in-house experts rather than appointed committees would result in specialisation, dedication of time and effort, and developing institutional memory.

Due to the lack of financial resources, low institutional capacities and few experts in the HE field, at this time, it seems unwise to suggest that all SEE P&R systems should be strengthened by developing extensive and sophisticated HTA processes that would guide P&R decision-making for patent-protected medicines. For those countries in which the development of sophisticated process is simply not realistic, defining simpler yet robust and systematic decision-making frameworks (including guidelines, scorecards, assessment checklists, consensus-building methodologies, etc.) that rely on international HTA procedures and are based on the pursuit of transparency [41] seems to be a more cost-effective approach [42]. These simple but robust and systematic decision-making frameworks should be developed in parallel with building institutional capacity in the domain of HE and the professionalisation of public healthcare administration. A balance between relying on international HTA procedures while still being relevant to the local context would be desirable since the transferability of methods and results always needs to be considered [43].

Good practice policy and practice examples in assessment/appraisal of company submissions that are already implemented are outlined in Table 5 and include employing full-time educated staff, publishing critical appraisal checklists and well-elaborated committee opinions, mostly in EU member states.

4.5 Lessons for Improving Reimbursement Decision-Making

"Ownership" of final reimbursement decisions in the SEE region should be more clearly designated. As with other stages of P&R, actual reimbursement decision-making would benefit from systematic and structured processes in which HIF management boards or even governments make decisions based on committee recommendations, relying on clearly defined rules, procedures and processes.

The process of reimbursement decision-making itself can be improved by more effective dealing with conflicts of interest. Processes that prevent decision-makers from influencing appraisal bodies should be put into place. Reimbursement decisions should be informed by clear and well-developed (practical) prioritization guidelines or criteria. Deadlines for reimbursement decisions, although clearly defined in most jurisdictions, should be adhered to, and potential grievances should be redressed not only on procedural grounds but also on the grounds of the decision itself and its determinants.

Good policy and practice examples in decision making that are already implemented include strict observation of committee recommendations in decision-making, efforts to standardise and regulate MEA negotiating processes and clear ownership of decisions in some countries (Table 6). In Slovenia, recommendations of the medicines committee are strictly followed through. Slovenia has taken the biggest step towards allowing public insight into the decision-making process, publishing extensive minutes of HIF management board meetings (and committee recommendations) on-line. In Hungary, there is a clear ownership of decisions by appropriate bodies even if the decision-making criteria and methodology remain vague [44]. Reimbursement decisions for most patent-protected medicines are clearly owned by the State Secretary of Health, even though these do not always follow a transparent methodology and do not necessarily correspond to the results of the Hungarian state-of-the-art assessment process [44]. Romania has the clearest criteria on which reimbursement recommendations are based (scorecard); however, the criteria for reimbursement decisions and the financial conditions at which medicines are provided to the population remain open to interpretation.

[11] Hungary has taken the greatest steps towards developing the HTA framework. In 2002, the Hungarian Ministry of Health released its first guidelines for conducting health economic analyses in the SEE region. The Hungarian Health Economics Association, now ISPOR Hungary chapter, was established in 2003. The association publishes methodological articles in the field of health economics, most notably the Hungarian Pharmacoeconomic Guideline that was first published in 2003 and was revised in 2013 and 2016. The guideline gives an in-depth description of the requirements on conducting HTA analysis in Hungary. It also sets an explicit cost-effectiveness threshold at three times the annual GDP per capita. Furthermore, it highlights that HTA analyses should be adapted to the Hungarian settings and should follow the Hungarian Pharmacoeconomic Guideline as much as possible.

4.6 Lessons for Improving Pricing Decision-Making

Pricing medicines should be undertaken based on clear and transparent rules within regulated cycles. While MEA terms are confidential in all countries, SEE countries should be aware that the international price comparisons they rely on do not consider what the referenced countries are actually paying for medicines [45].

4.7 Lessons for Improving Post-Reimbursement Practice

Real-world evidence of the effectiveness and cost-effectiveness of medicines, as a foundation for value-based pricing schemes, remains a hotly debated topic in SEE, as well as among the authors. Two opposing views predominate. Some feel that public funds would be better spent if MAHs were paid according to outcomes rather than inputs (products). This seems to be a slowly developing trend in primary- and hospital-care financing in some SEE countries. With this approach, development of patient registries is advocated as a prerequisite for implementing value-based pricing. Others recognise the argument but feel that this is impractical as it requires substantial investments and time, and that the issue can be resolved either more cost-effectively through MEA negotiations based on available evidence collected through clinical studies that would take these uncertainties into account or through more simple approaches that rely on simplistic traditional reporting mechanisms. In addition, allocating "guilt" for potential non-achievement of health outcomes in individual patients between the products themselves and how they are used as well as how other components of clinical care contribute to the results remain a concern. Real-world evidence is, in some jurisdictions, used as a payment criterion for the patent-protected medicine for hepatitis C, under outcomes-based MEAs.

4.8 Limitations

Our study had several limitations. We did not consider the differences in pharmaceutical policy frameworks that existed between all SEE countries in the past but only looked at the present. Moreover, it was not always clear whether observed policies are a short-term solution (for instance, a reaction to recession-related budgetary constraint) or whether the policy was part of a planned long-term change to the system. Major policy changes, such as improvements in reference pricing, may take several years to implement since they involve a multitude of stakeholders with opposing agendas. Finally, the specific policies and practices we labelled "good practices" could in certain circumstances have unintended negative consequences not only on the P&R system but also in a wider context, such as the access to and prices of medicines, as with external price referencing or MEAs (e.g., [1]). In other words, although conventionally perceived as beneficial for healthcare systems, policies such as MEAs or external price referencing can have unintended negative effects as well. Although this discussion on the trade-offs between positive and negative consequences of particular P&R policies remains out of the scope of the current study, policymakers should be aware of both the positive as well as the negative sides and consequences of introducing a particular policy in their healthcare system.

4.9 Conclusions

Capacity building through sharing knowledge and information on successful reforms across borders is an important opportunity for SEE countries to further develop their range of P&R policies with the aim of increasing (equitable) access to patent-protected medicines (especially new expensive medicines), increasing affordability, and containing costs. Within the EU member states, with established initiatives such as EUNetHTA [36] and a multitude of other cross-country collaborations [46], this sort of cooperation should not be difficult to initiate even though controversial expert positions still exist regarding the Regulation of the European Parliament and of the Council on HTA and its efficiency and appropriateness [37].

Investing and engaging in international cooperation is even more important given the financial constraints and low institutional capacities (including experts in Health Economics) in most (if not all) SEE countries. Some countries, such as Hungary, have advanced their HTA capacity and continue to develop it. However, suggesting that all SEE P&R systems should be strengthened primarily by developing extensive, sophisticated and expensive HTA processes to guide P&R decision-making for patent-protected medicines seems unrealistic and unnecessary. For the majority of SEE countries, especially non-EU member states, defining simple, transparent and robust decision-making frameworks that rely on international HTA procedures are a more cost-effective approach. These simple but robust decision-making frameworks should be developed in parallel with building institutional capacity in the domain of HE and the professionalization of public healthcare administration more generally. Professional healthcare administration is also a prerequisite for more efficient post-reimbursement practices such as frequent updating of positive drug lists, internal and external price referencing, and outcomes monitoring. Much of this, including the cooperation between the (non-)EU member states, remains a matter of priorities and political will.

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Declarations

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Authors' contributions Luka Vončina and Ana Bobinac made substantial contributions to the conception or design of the work, and the acquisition, analysis and interpretation of data. Luka Vončina, Tea Strbad, Jurij Fürst, Maria Dimitrova, Maria Kamusheva, Megi Vila, Ileana Mardare, Kristina Hristova, Andras Harsanyi, Dragana Atanasijević, Igor Banović and Ana Bobinac participated in drafting the paper or revised it critically for important intellectual content as well as approved the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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