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OSLO MEDICINES INITIATIVE
Solidarity Transparency Sustainability

World Health Organization
European Region

POLICY INSTRUMENTS (NON-PRICE) FOR MEDICAL INNOVATION

OSLO MEDICINES INITIATIVE TECHNICAL REPORT

Jorge Mestre-Ferrandiz, Brendan Shaw, Chirantan Chatterjee, Jin Ding, Preeti Singh and Michael M. Hopkins

Oslo Medicines Initiative

Established in 2020, the Oslo Medicines Initiative (OMI) is a collaboration between the WHO Regional Office for Europe, the Norwegian Ministry of Health and Care Services and the Norwegian Medicines Agency. The OMI aims to provide a neutral platform for the public and private sectors to jointly outline a vision for equitable and sustainable access to and affordability of effective, novel and high-priced medicines.

In line with the Regional Office's European Programme of Work 2020–2025 – "United Action for Better Health", equitable and sustainable access to quality medicines is critical for universal health coverage and for achieving the Sustainable Development Goals. The OMI provides a strong focus on equity and on leaving no one behind, and is underpinned by three pillars: solidarity, transparency and sustainability.

The OMI has commissioned a series of technical reports to summarize relevant evidence and provide policy considerations as a basis for discussion to inform its work. These reports are also in line with the implementation of World Health Assembly resolutions – in particular, resolution WHA72.8 on improving the transparency of markets for medicines, vaccines and other health products.

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Abstract

Innovation policy instruments are policy interventions with a specific mechanism of action that influences the innovation process. This Oslo Medicines Initiative technical report presents a broad range of such instruments available to national policy-makers in support of innovation for new medicines (excluding those focused on price, which are covered elsewhere in the report series). This report explores various types of policy instruments, based on reviews of the literature on policies for innovation in the medical and other sectors. For each type identified, the report explores the mechanisms of action, the effects these have and where they occur, and the extent to which these instruments have been implemented globally. It also sets out considerations for their effective implementation. The report demonstrates that the long-established push/pull (supply/demand) framing that dominates discourse around medical innovation can be broadened, providing policy-makers with instruments to supplement push/pull approaches, by emphasizing the role of communication, collaboration and coordination in supporting the emergence of medicines to address societal needs.

Keywords

INNOVATION, POLICY INSTRUMENT, ACCESS TO MEDICINE, PHARMACEUTICAL POLICIES

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Abbreviations

ATMP	advanced therapy medicinal product
DRG	diagnosis-related group
IPR	intellectual property rights
OMI	Oslo Medicines Initiative
PPP	public–private partnership
R&D	research and development

Executive summary

Background

It is very challenging to bring new medicines through research and development (R&D) and on to the market to address the needs of patients. Societies expect medicines to be safe and effective. Yet it generally takes between 6 and 12 years for drugs to complete the scientific and regulatory procedures that seek to ensure that this is the case, with high costs and uncertain outcomes. Additionally, debate continues around whether the resulting medicines address areas with the highest unmet need and serious public health issues, or whether they tend to focus on areas already established to provide lucrative markets. There is also a paucity of evidence on how to best use public policy to ensure alignment of R&D outputs with unmet societal needs. This report reviews a broad range of policy instruments that are available and could support a more sustainable approach to developing innovative medicines.

Objectives and approach

Research publications that explore the possible policies to support the discovery, development and use of new medicines are numerous and increasing in number. This Oslo Medicines Initiative (OMI) technical report makes a contribution by presenting a synthesis of those policy instruments available to national policy-makers. It does so by drawing on reports and articles focusing specifically on medical innovation, as well as on innovation in other sectors.

An innovation policy instrument is a policy intervention with a specific mechanism of action that influences the innovation process. The aim of this report is to identify relevant policy instruments, how they work, the constituencies they target and the extent to which they have been implemented. It also sets out considerations for effective implementation of policy instruments in various contexts.

Findings and policy considerations

The report's findings indicate that the literature on policies for medical innovation often uses the bifurcating "push/pull" distinction (distinguishing between supply-oriented and demand-oriented policies). This is a more simplistic categorization than that found in the wider literature on innovation policy in other sectors, where at least three useful approaches for framing policies are identified – each providing a trifurcated categorization. This report advances a "3×3" approach to classifying policy instruments, which can be demonstrated by the answers selected for each of the following three questions.

1. What is the aim that the policy instrument is aligned to achieve?
    a. Spurring invention
    b. A holistic approach to building and maintaining innovation systems
    c. Missions that address societal challenges
2. What is the governance mode of the innovation policy instrument?
    a. Regulation to mandate particular forms of action
    b. Economic measures to provide incentives
    c. Voluntary measures to communicate information
3. Which constituencies does the policy instrument target?
    a. Supply side (push) – such as firms
    b. Demand side (pull) – such as health-care systems
    c. Coordination at the system level – such as intermediaries between firms and health-care systems

A key message of this analysis is that policy-makers have the opportunity to move beyond the simple push/pull (supply/demand) framing of policy interventions that has been prevalent in discourse around medical innovation by placing more emphasis on communication, collaboration and coordination to support push/pull processes, and to support most fully those medical innovations that address societal needs.

This report identifies 18 broad families of policy instrument to support medical innovation (limited to those that are non-price-related), each based on a common mechanism of action (influencing a specific part of the innovation system). These are:

1. public R&D grant funding;
2. advice and facilitation of clinical development;
3. expedited regulatory pathways;
4. intellectual property rights (IPR) – patents;
5. IPR extensions via patents and market/data exclusivity;
6. patent pools and patent buyouts;
7. tradable vouchers;
8. financial guarantees for development and manufacturing;
9. prizes to reward medicine developers reaching milestones in the innovation process;
10. R&D tax incentives to subsidize R&D costs;
11. loans and loan guarantees;
12. access to risk capital financing mechanisms;
13. fees/taxes for medicine developers to incentivize them to use their capabilities to develop specific medicines;
14. collaborations and partnerships with the public sector;
15. open knowledge principles around sharing of data, ideas and research outputs;
16. general health service infrastructure, services and funding;
17. diagnosis-related group carve-outs for medicines dispensed in hospital;
18. limited indemnification from liability claims for medicine developers.

As a starting point, the 18 families were categorized using the 3×3 approach, to ascertain their focus, and to identify potential gaps in the types of policy instruments specific to medical innovation. Three observations were made, based on this analysis.

- Policy instruments that aim to spur invention (that is, they are product-specific) are much more common in the literature on medical innovation than those focusing on either innovation systems or missions to address specific societal challenges.
- Policy instruments are most commonly governed by regulatory and economic modes, rather than voluntary and communications-based approaches to influence change.
- The literature on medical innovation mainly focuses on instruments that act on the supply side, with few targeting the demand side specifically, although more such possibilities are discussed in the literature on innovation in other industrial sectors.

Some of the 18 policy instrument families address a specific stage in the product life-cycle (or stage of development), while others are relevant for developers of medicines regardless of the stages of the process they are engaged in. The review found a relatively even distribution across all stages considered.

The review assessed the relative usage of the 18 policy instrument families, and found that most policy instruments identified have not been widely implemented internationally. Even where implementation has taken place, published evaluations and impact assessments are often lacking.

A range of implementation issues were identified from tailored reviews of literature on each individual policy instrument family, suggesting common challenges, such as the expense of interventions, and ensuring that they lead to the desired innovations and represent value for money. Moreover, individual instruments may not be sufficient on their own, or may require specific policy capabilities to design and implement effectively.

Different families of policy instruments described in this report often share the direct effects they have for medicine developers (such as reducing uncertainty, costs or time to market). Instruments with similar effects can be combined to reinforce these, while those with different effects can be combined to provide more comprehensive support.

When considering the above, it seems that there is room for much more application of known policy instruments across countries and therapeutic fields. There also appears to be considerably more scope for systematic implementation of policy instruments to provide more coordinated policy for medical innovation. This may take the form of disease-specific missions (such as targeting antimicrobial resistance) or industrial strategies (for example, to support the development and use of particular technological capabilities). These involve complex, expensive and long-term commitments, however, with non-trivial questions around what kinds of governance arrangements may be required for successful outcomes.

The frameworks presented in this report can help decision-makers to identify gaps in policy support for medicine developers and the policy instruments that could be used to address them. Additional considerations are needed to determine which policy instruments should be used in a particular context, and how they can be configured, implemented and combined in order to address local needs.

For example, large-scale financial commitment and monitoring may be required to ensure appropriate use of funds and, with this, human capacity/resources. While large commitments may be affordable and acceptable in some countries, this may not be feasible in others. Moreover, local evidence is needed to determine the appropriate course of action for a particular context, including the ongoing review of performance to ensure that a policy instrument is performing as expected. Indeed, the intended goals of policy implementation may differ between contexts and over time, as motivations for countries choosing to support medical innovation also differ. Some will wish to support job creation, attract foreign direct investment or encourage innovative capabilities that may lead to increased exports or improved health care. Others may focus on improved cost–effectiveness of health-care spending or more affordable access to medicines. There may be trade-offs in meeting these goals, as one policy configuration may not be able to address them all. Tensions between policy goals should be acknowledged and ideally addressed prior to policy launch. Risk mitigation approaches could be considered to ensure that one goal is not undermined by another and, ideally, to help select complementary rather than divergent policy goals.

As policy priorities differ, the report emphasizes that policies are often best used in combinations that are highly context-specific, but there is often no clear guidance for the public sector on how to select policy combinations. The lack of evaluation data on the impact of policies – alone and in combination – hinders the potential to make generalized recommendations about the applicability of policies for specific contexts. Policy experimentation and evaluation have important roles to play in creating a more sustainable market for medical innovation.

1

Introduction

1.1 Purpose

It is very challenging to bring new medicines through research and development (R&D) and on to the market to address the needs of patients. Drugs introduced to the human body enter a complex biological system where they may bring benefits and harms. Societies expect medicines to be safe and effective, but it generally takes between 6 and 12 years for drugs to complete the scientific and regulatory procedures that seek to ensure this is the case *(1)*. Moreover, most candidate medicines fail to progress through clinical trials, because they do not work, have unacceptable side-effects, or because commercially attractive returns appear less likely than previously hoped by developers. As a result, the clinical approval success rate for new medicines has been estimated to be between (approximately) 10% and 30%, but with wide variation across studies and therapy areas *(1)*. Moreover, payoffs from products that reach the market are uncertain, and are delivered over the medium to long term – if at all – and after many years of incurring R&D costs. Although particular innovative medicines can be extremely profitable, growing costs and diminishing chances of success have spurred debate about whether there is a productivity crisis in the pharmaceutical industry as a whole. Part of the discussion around the industry's reduced productivity in the 1990s and early 2000s was based on an increase in the R&D costs of new molecular entities, triggered mainly by increasing attrition rates and the duration of clinical trials *(2)*. This spurred concerns that the model for developing new medicines was becoming unaffordable *(3)*. More recent studies suggest that the decline in productivity has not persisted *(4,5)*, although it may be too early to know for sure.

In addition, debate continues around whether R&D and resulting medicines address areas with the highest unmet need and the most serious public health problems, or instead target more lucrative areas where needs may already be covered. Barrenho et al. *(6)* provide an analysis of the relationship between disease burden and pharmaceutical innovation (measured as the number of successful compounds that effectively passed the approval and licensing requirements between 1990 and 2010), and find a mismatch: there are still disease areas around the world for which morbidity and mortality remain unaddressed. Yet there is a paucity of evidence on how to best ensure alignment of R&D outputs with unmet societal needs.

Further concerns have been raised by researchers, patients groups and policy-makers expressing dissatisfaction with the pharmaceutical industry's pricing policies, including for rare diseases – see *(7–9)* as examples. The high price of cancer drugs has also raised concerns over affordability and access *(9–11)*. This is in contrast with other instances where the expectation of a low economic return has, in part, reduced the incentives to invest in developing new treatments, even where there is progress in scientific understanding and an underserved medical need. Examples include medicines for neglected infectious tropical diseases, antibiotics and vaccines.

Given these challenges, public policy has a vital role to support, guide, and perhaps even steer the direction of medical innovation, in order to address societal needs for new medicines. This role needs to be included in any consideration of corporate social governance/social contracts *(12)*.

Different forms of medical innovation exist, including organizational, diagnostic, procedural, pharmaceutical, vaccine, device and platform technology innovations. In accordance with the remit of the Oslo Medicines Initiative (OMI), this technical report focuses on new medicines (which includes products defined as "therapeutics", "pharmaceuticals", "drugs" and "vaccines"). The term "medical innovation" is consistently used here in keeping with the terminology in much of the literature on relevant policy instruments.

This technical report explores possible public policy instruments to support medical innovations that might meet the needs of the market – while understanding that needs will vary locally. In particular, the overall objective of this report is to identify and categorize innovation policy instruments (with the exception of those specifically focusing on price, which are covered elsewhere in the OMI technical report series *(13,14)* to encourage the development of new medicines; to assess the extent to which these have been implemented internationally; to highlight evidence of their impact; and to identify any anticipated design issues.[1] The report is intended to be a conversation starter for relevant policy- and decision-makers on the range of policy instruments available, beyond those just focusing on price, to drive innovation in the form of new medicines. Diverse policy instruments are presented, and it is anticipated that combinations of these could be in use currently in all countries, or could be adopted. No "one-size-fits-all" solution is presented for countries exploring how to support medical innovation that is affordable to users, however. Local circumstances and priorities – including the evolution of domestic industry or wider scientific capacity, market size, economic status, prevailing public health concerns and local political commitment to innovation – determine how policy instruments are configured and which combination of instruments may be most appropriate at a particular point in time or for a particular country or organization.

Importantly, this report concludes that much of the current debate around innovation policy instruments for medicines has been limited for too long to instruments that create push or pull incentives (those focused either on supply- or demand-side stakeholders, respectively). This is not a new observation – for example, a similar point was made by Tidd in 2006 *(15)*. Some have suggested further classification of policies into different types (see, for example, Renwick et al. *(16)*). Yet this remains in large part a significant limitation of the literature and the debate on medical innovation.

Reaching beyond this, the literature review of broader innovation policy provided here highlights other options – in particular, greater exploration of instruments that encourage more communication, collaboration and coordination between the range of stakeholders engaged in innovation, together with push/pull policies.

1 Generics and the off-patent market are outside the scope of this report.

1.2 Approach

The approach used for this report was to undertake a series of literature searches and reviews in order to present a diverse and inclusive list of policy instruments relevant to the support of medical innovation – that is, to avoid focusing only on those options discussed in a particular region or strand of the literature.

In section 2, the first literature review summarizes a well-established, peer-reviewed literature on the topic of innovation policy, discussing policy instrument types and the use of policy mixes (irrespective of industrial sector) (see Annex 1). This provides a wider context for the study of policy instruments used in medical innovation, potentially allowing identification of gaps where instruments used in other sectors may not have been applied.

In section 3, two further literature types are brought together and summarized – the peer-reviewed and grey literature on policy instruments used to support medical innovation, capturing relevant lessons from numerous specialist nongovernmental organizations, including philanthropic foundations and charities, as well as international organizations. These searches aim to identify the existence of different "families" of policy instrument, which are related through a common mechanism of action. In order to find a broad range of instruments, the main sources used were those that themselves have sought to present a range of relevant policy instruments. In an additional step, separate mini-literature reviews were undertaken for each family (18 in total) to explore a common set of questions. The mini-reviews for the 18 policy instrument families are provided in web-annex.

Section 4 provides ways forward for policy-makers, with some key messages. In particular, the ways in which policy instruments can be configured (with implications for their effectiveness) is discussed. The importance of reviewing the policy instrument mix and evaluating instrument performance is emphasized.

The discussions presented in section 3 and section 4 are based on synthesis and analysis of the findings of the literature reviews and the summaries of the policy instrument families.

2

Innovation policy instruments in context

2.1 Background

Policy instruments to support medical innovation can be understood by positioning them within a wider "innovation systems" framework.[2] This section provides context for the following analysis of policy instruments for medical innovation by introducing key concepts, theories and frameworks drawn from economics and the interdisciplinary field of innovation studies. The details of the literature review and the papers included can be found in Annex 1.

Definitions provided by Borrás and Edquist *(17)* serve as the starting-point for understanding key terms used in this report.

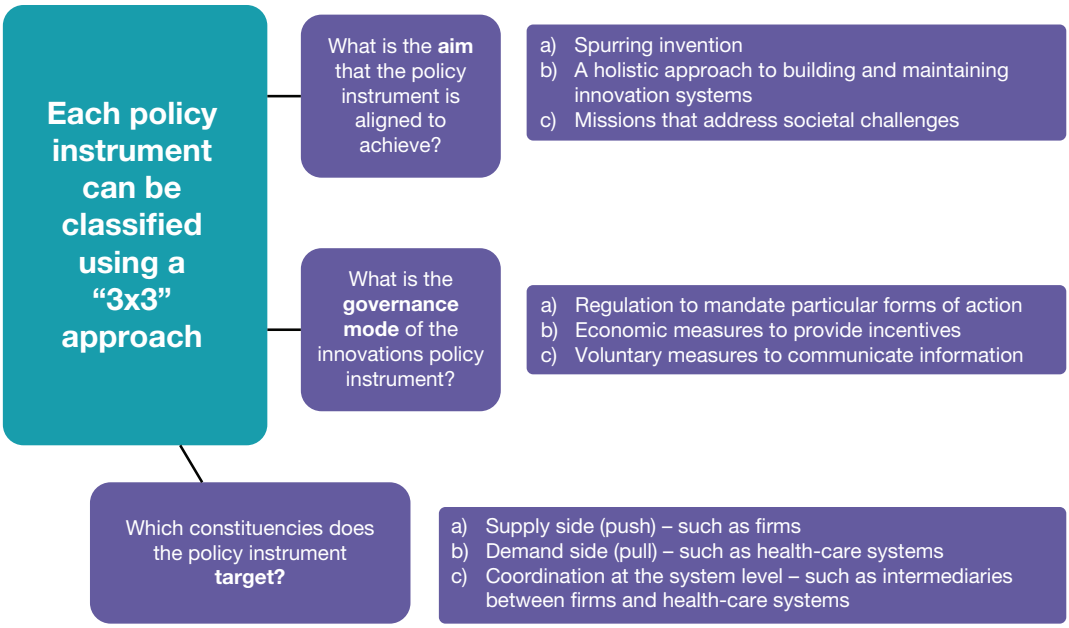
- **Innovations** are new creations (products and processes) of economic and societal significance, primarily carried out by firms (but not in isolation).
- **Innovation systems** determine and shape the innovations occurring within their boundaries, the processes that generate innovation and the nature of innovation that results from these systems. In broad terms, the innovation system is composed of "all economic, social, political organizational, institutional and other factors that influence the development, diffusion and use of innovations" *(18)*.
- **Innovation policy instruments** are policy interventions with a specific mechanism of action used to influence the innovation process. The choice of policy instruments constitutes a part of the formulation of the policy, and the instruments themselves form part of the actual implementation of the policy.
- **Innovation policy** comprises all combined actions undertaken by public organizations that intentionally and unintentionally influence innovation processes – including innovations, innovation systems and innovation policy instruments.

Complex political processes drive the decisions that determine the ultimate objectives of innovation policy. Influences include different national traditions – including areas of production and knowledge, public support (or its absence), local areas of need, forms of state-market society relations, and the ideology of the government in office *(17)*.

Governments can choose from an "ocean" of innovation policy instruments, and this variety is difficult to summarize succinctly *(17)*. Nevertheless, the evidence from the review of the literature presented later suggests that most instrument families could be more widely used in the context of medical innovation. Based on a review of the broader innovation literature, this report identifies three approaches for categorizing policy instruments, with each providing a further trifurcated perspective. This gives a "3×3" approach for classifying policy instruments and their interactions (Fig. 1).

2 The literature on innovation and innovation systems is expansive, and it is possible to discuss other framings – such as regional innovation systems and technology innovation systems – but because the intended audience of this paper is Member States of the WHO European Region, the focus here will be on national systems of innovation.

Fig. 1. A 3×3 approach for classifying innovation policy instruments



The three questions introduced in this section are complementary and provide different perspectives necessary to create understanding of how a given policy instrument functions. Further detail on each perspective is provided below.

2.2 What is the aim that the policy instruments are aligned to achieve?

Innovation policy is shaped by persistent aims that arise from historical context, two of which have been identified as co-existing and dominant in contemporary innovation policy discussions, and the third more recently rising in prominence *(19)*. These are:

- spurring invention, focusing on addressing market failures related to the R&D/ inventions phase;
- building and maintaining innovation systems, using a holistic approach to address system failures; and
- mission-oriented, targeting solutions to address specific (societal) grand challenges that are on the political agenda.

These three aims, introduced in turn below, are potentially complementary, in the sense that governments may employ these at the same time for different purposes and to achieve different goals.

2.2.1 Spurring invention: addressing market failures in R&D

Innovations such as new medicines rely on investments in R&D. A commercial return on that investment is required; for the private sector this is primarily (but not only) financial;

for the public sector the requirement is for safe, effective medicines that offer clinical and economic benefits over existing options – provided within a health-care system, however organized and funded. Firms may underinvest in the R&D required for the innovation, however, owing to perceived uncertainties. The reasons for these uncertainties are complex and varied. Crucially, firms do not know whether they will be able to appropriate returns from some forms of R&D. The impact of these uncertainties varies between different private-sector actors, with different tolerances for risk at the different stages of the product life-cycle (these include different types of investors and medicine developers that range from emerging small enterprises to global pharmaceutical companies). It may be difficult to prevent competitors from gaining cost advantages by free-riding on the hard-won advances of early movers – in part because the knowledge created by R&D has the properties of a public good[3] *(19)*. Knowledge is non-excludable (it is costly or impossible for one user to exclude others from using it) and non-rivalrous (when one person uses a public good this does not prevent others from accessing it too).

With all these uncertainties, goods and services that rely heavily on R&D are prone to market failure (that is, underinvestment in the R&D needed to meet market needs) that justifies state intervention to support the supply of knowledge *(19)*. This applies to biomedical R&D in particular – with its high costs, long duration and uncertain outcomes. In this case, policy instruments are needed to spur invention, including those that entail public funding of scientific research or strengthen/extend intellectual property protection, but leave the possible exploitation and diffusion of the invention (required for innovation) to the market.

2.2.2 Building and maintaining innovation systems: addressing system failures

Since the 1980s, academic studies have increasingly sought to understand the contextual influence on the innovation of systems composed of a range of actors working together, within a broader policy and economic framework.[4] The configuration of these actors and the types and strengths of links between them define the outputs – that is, the types and characteristics of innovation that are produced within the system, which is often (but not necessarily) a national government. As stated by Edler and Fagerberg *(20)*, "these systems are more than frameworks for interaction, however, they are also repositories of various resources that firms depend on in their innovation activities and home to various institutions influencing these". Those resources, often complementary, include knowledge, skills, finance and demand. And these factors, to a large extent, can be regarded as being provided by the national government (hence the term "national" systems of innovation).

The previous section argued that the notion of appropriability provides the basis for understanding market failure in R&D-intensive sectors, leading to socially beneficial products and services not being brought to market; the notion of a national system of innovation provides the basis for identifying system failures as a further reason for a deficit of innovation *(22)*. A system failure is said to arise when countries may have some elements

3 Another OMI technical report discusses innovation as a global public good in more detail *(21)*.

4 In the literature on innovation systems, this "holistic approach" is contrasted with the "linear model" that preceded it, which focused on addressing market failure in R&D.

crucial for innovation, but policies are needed to address gaps in the system or coordinate elements to work together. Where such gaps are identified, the rationale for government intervention goes beyond fixing market failures (say, by increasing or subsidizing R&D when there is underinvestment) to address system failures *(20)*. For example, if the linkages between actors are absent, or existing links are not sufficiently strong, facilitating links may be a helpful intervention. These types of instruments may be seen as 'soft', as opposed to hard interventions such as subsidies, but have risen in prominence over the last decades. As Martin *(22)* suggests, "policy instruments need to encourage networks of collaboration and alliances, as part of a mechanism for 'wiring up' national systems of innovation by getting the players to talk to each other more than they had done in the past". Importantly, they also focus on technological diffusion or take-up, as the systems approach emphasizes the connection between supply and demand, mediated by non-market as well as market processes. Of course, such wiring up need not simply be a matter of connecting players within one country: it could be done internationally too (assuming resources are provided to support these networks).

Examples of system-oriented policy instruments include alliances and coordination among actors, allowing them to learn from each other. They include encouragement of better user–producer relations, creation of networks to facilitate coordination and cooperation, fostering of more entrepreneurial activities from universities (such as spin-offs and licensing technology), production of foresight studies, and delivery of education and training to support the absorptive capacities of firms and other organizations.

It is important to acknowledge that a system failure may be due in part to a market failure (that is, a lack of demand/revenue can lead to poor levels of investment in certain essential areas), so that instruments aimed at addressing market and system failures may need to be complementary. For instance, if actors cannot access or are unaware of incentives provided for R&D, or if the system is not able to convert stocks of knowledge and skills into innovations, the incentives will be of little value. Indeed, taking a system-wide perspective opens the opportunity to add or remove policy instruments and adjust these, so that the system as a whole performs as required, including consideration of the direction of innovation and its social purpose.

It can also be the case that policy instruments may not succeed, for a variety of reasons. The resulting public policy failures are associated with four broad sets of contributing factors: overly optimistic expectations; implementation in dispersed governance; inadequate collaborative policy-making; and the vagaries of the political cycle *(23)*. In these cases, it may be challenging for innovation policy instruments to realize successful outcomes.[5] Indeed, in pursuing a holistic perspective on policy, the literature argues for a well coordinated government across the different ministries responsible for those factors previously alluded to (knowledge creation, finance, regulation, demand articulation and so forth). This coordination may be very difficult to achieve in practice, however; different ministries will be involved in supporting different parts of the innovation system, perhaps

5 Andrews *(24)* argues that it is difficult to assess the failure rate of policies and instruments because many public policy organizations – governments in particular – do not provide accessible views onto overall success or failure. Thus, the author analyses World Bank's failure rate, as a proxy, and finds different answers to the "how often" question, depending on how "failure" is actually measured. Further, he notes that "policy organizations like the Bank judge success based on whether planned products are delivered through an efficient process; not whether policies solve the problems that warranted intervention in the first place, or whether the policies promoted development outcomes".

with different policy priorities, potentially leading to a policy failure *(23)*. These difficulties may be even further complicated by regional policy-making within a country.

Finally, the international political economy, global norms and standards and the global state of the technological knowledge, as well as epidemiology/disease trends and unplanned events such as pandemics and epidemics, will influence the ability of national systems to address whatever failures may be identified locally. Thus, when considering which policy instruments to implement, there is a need to factor in that national systems operate within a wider global innovation system, and are influenced by multiple international forces. These international forces are certainly very important in the global health innovation space, although policy instruments that are coordinated at inter- or supra-national levels are beyond the scope of this report.

2.2.3 Mission-oriented innovation systems: addressing grand challenges

It is important to acknowledge that, beyond responding to market failures and system failures, governments also recognize the need to steer or direct innovation to align innovative capabilities with pressing social and environmental grand challenges – such as addressing climate change or the Sustainable Development Goals *(19)*. The increasing prominence of this steering in recent years has been characterized as a move towards "mission-oriented innovation systems" or "mission-oriented innovation policy" *(25,26)*,[6] consisting of "networks of agents and sets of institutions that contribute to the development and diffusion of innovative solutions with the aim to define, pursue and complete a societal mission" *(27)* or "big science deployed to meet big problems" *(26)*. Hekkert et al. *(27)* define a societal challenge-based mission as "an urgent strategic goal that requires transformative systems change directed towards overcoming a wicked societal problem".

Mission-oriented policy is quickly picking up momentum, but it is very much in line with existing notions like demand-based innovation policy and policy-induced innovation; however, one of its key characteristic is that "it does not only claim that policy should target public investments at facilitating urgent societal transformations, but also seeks to coordinate innovation efforts by a wider range of actors through the formulation and support of a well-defined objective" *(27)*. Schot and Steinmuller *(28)* suggest, however, that "mission-oriented policies could be productive if the missions are formulated in an open-ended way that encourages experimentation and diversity. New forms of engagement and networks are required between public, private and third sector actors."

Such policy instruments (with different labels) have been used in the past for defence purposes, for example, and before innovation policy or even innovation became part of the standard vocabulary in the political agenda. Other more specific and recent examples include the Apollo moon programme, Germany's plan for transforming its energy system (*Energiewende*), the 17 Sustainable Development Goals, the European Union's Horizon 2020[7] and the Paris Agreement.[8]

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6 Calling for greener production, increased social justice, a fairer distribution of welfare, sustainable consumption patterns and new ways of producing economic growth.

7 To address a number of societal challenges – for example, contributing to a transition to a low-carbon and inclusive economy, and influenced by the work of Mazzucato *(25)*, according to Hekkert et al. *(27)*.

8 With the ambitious goal to reach zero net carbon emissions in the second half of the 21st century.

2.3 What is the governance mode of the innovation policy instrument?

Rogge and Reichardt *(29)* categorize policy instruments according to how they work and, in particular, whether they provide:

- rules, regulations, norms and standards for social and market interactions, usually mandating particular actions;
- economic/financial incentives or disincentives to encourage/discourage certain behaviours; or
- support for evidence-based/better-quality decision-making, based on voluntary and non-coercive informational or communications-based measures.

These governance modes tend to be mutually exclusive. For instance, a policy instrument such as R&D tax credits would be an economic incentive, but not regulatory or voluntary.

2.3.1 Regulation to mandate particular forms of actions

Regulatory instruments include legal tools for the regulation of social and market interactions, influencing actors' behaviours. Under this category, regulations tend to be compulsory. These are instruments that governments are willing to use to define how interactions in society and in the economy should take place, and the market conditions for innovative products and processes. This category may be referred to as the government's "stick". Examples of policy instruments of this type include regulations (including laws, orders and directives) to protect intellectual property rights (IPR), to promote competition (anti-trust), to stimulate or steer R&D and innovative activities by firms in the market and to ensure the ethical conduct of research and proper treatment of human subjects. They also include some specific industrial sector regulations, such as manufacturing, technical or environmental standards.

2.3.2 Economic measures to provide incentives

Economic, financial and market-based instruments provide support for specific social and economic activities. These may involve economic means in cash or kind, and they can be based on positive incentives (encouraging or promoting certain activities) or on disincentives (discouraging or restraining certain activities). This type of instrument can affect the relative price of different factor inputs, and can provide enterprises with freedom to adapt to and selectively adopt the different instruments. Thus, market-based instruments seek to influence the market's performance. These instruments are sometimes referred to as "carrots". Examples include cash transfers/grants, prizes, subsidies, loans, tradable permits and provision of venture and seed capital.

2.3.3 Voluntary and information-based measures to influence action

The third governance mode is voluntary measures and information/communications-based instruments. These provide recommendations and make normative appeals, and formally influence social and economic action through information, which is why they

are sometimes also called “soft” instruments or “sermons”. The measures are optional, and firms and other stakeholders can choose whether or not to comply; however, non-compliance could come with a penalty or other negative consequences, such as reputational harm and knock-on effects for investment. The information can include measures undertaken to influence knowledge transfer, communicating an argument, persuasion, advice and moral appeal, among others. Ultimately, they provide users with better information to allow a rational choice between competing options. Examples of instruments under this classification include the use of news media campaigns, codes of conduct, recommendations, guidelines, public and private partnerships, voluntary standardizations, agreements and contractual relations. Reporting/indexes and benchmarking measuring performance against agreed good practice/objectives – either by the individual organization or by an independent one – are another example, as well as using environmental, social and governance factors to evaluate companies and countries on how far advanced they are with sustainability.

2.4 Which constituencies of the innovation system do the policy instruments target?

Policy instruments can:

- foster technological change from the supply side – those producing goods and services;
- induce and speed up diffusion of innovations through the demand side – direct or indirect users of goods and services; or
- act systemically by integrating and coordinating supply-side and demand-side stakeholders, thereby increasing wider efficiencies – also including intermediaries.

The targeted constituencies may or may not be mutually exclusive.

2.4.1 Supply-side innovation policy instruments

Supply-side or technology-push innovation policies focus on the supply side (on the originator firms supplying the innovations), and on the role of science and technology in promoting development. They are also referred to as technology-push policy instruments, as they foster technological change from the supply side (the innovators). Government-sponsored R&D and tax credits for companies to invest in R&D are examples of such instruments.

2.4.2 Demand-side innovation policy instruments

Demand-side or demand-pull policy instruments induce innovations and/or speed up their diffusion by increasing the demand for innovations, defining new functional requirement for products and services or better articulating demand. These instruments see demand as a driver of the rate and direction of innovation, arguing that demand factors both

increase the market for and improve the incentives for firms to innovate. Tax credits and rebates for consumers of new technologies and taxes on competing technologies are examples of these.

2.4.3 Coordination at the system level

Systemic policy instruments act at the level of the innovation system as a whole, instead of specific parts of it, and as a platform that facilitates the advantages of demand-side and supply-side instruments. They also align the instrument mix to the needs of the actors involved, and promote collaboration, coordination and knowledge transfer among market participants. Specific instruments include tax and subsidy reforms, infrastructure provision, cooperative R&D grants and programmes, and encouragement of clusters.

3

Policy instruments for medical innovation

This section focuses on policy instruments that can be applied to medical innovation. A total of 54 publications from the peer-reviewed literature and 50 documents from the grey literature were selected as the sources to provide a starting-point for the synthesis set out in this section. The details of the literature review can be found in Annex 2.

The sources identified 108 potential policy instruments,[9] which were ultimately consolidated into 19 families of closely related instruments, based on their mechanisms of action. The review identified policy instruments relevant to Member States in the WHO European Region. It captured national-level instruments that may have international dimensions (such as programmes for scientific collaboration), which may require countries to work together to combine their funding and influence to apply particular policy instruments collectively. Families of policy instrument that only work at the collective international level are not identified in this review. One of the 19 families of instruments focuses on price, and is therefore outside the scope of this review, but this is the only area of exclusion. The threshold for inclusion of each instrument family was intentionally very low – any distinct family of instruments found in the sources (and within the scope of this report) is included, regardless of its level of usage internationally, its impact or the number of times it is mentioned in the literature.

The following subsections present a high-level summary of the 18 policy instrument families identified in a series of tables and analysis, in the following order:

- section 3.1 introduces, categorizes and explains their core mechanism of action;
- section 3.2 describes how they fit the 3×3 approach for policy instruments more generally;
- section 3.3 examines the position in the product life-cycle where their effects occur;
- section 3.4 investigates their relative level of adoption globally;
- section 3.5 considers the main direct effects they are expected to have for developers of medicines; and
- section 3.6 sets out some key issues associated with their implementation.

These categorizations and analyses allow the report to draw attention to selection choices between policy instruments that address the same gap or have similar effects, and to highlight differences between coverage of innovation policy instruments in the literature on medical innovation and those discussed in the wider literature on innovation policy pertaining to other industrial sectors. Taken together, this highlights some considerable opportunities for greater use of a wider range of policy instruments for medical innovation globally. This section further demonstrates how the simple push/pull (supply/demand) framing of policy interventions could be widened to include policy instruments that encourage communication, collaboration and coordination.

9 There was relative consistency across the policy instruments discussed in both the peer-reviewed and the grey literature, although some additional options were identified from the grey literature.

3.1 Mechanisms of action

The 18 families of (non-price-related) policy instruments identified are shown in Table 1, with a description of their mechanisms of action and their scope. The mechanism of action is a principal feature that is common to all variations of a policy instrument of this type, and which is unique to this family. Relevant evidence for each family of policy instruments is presented in web-annex, along with a definition, description, mechanism of action, note of the extent to which it has been implemented internationally, evidence of impact and anticipated design issues.

Table 1. Policy instrument families for medical innovation

		Perspective								
		Aim			Governance mode			Targeted constituency		
Policy instrument family	Description and mechanism of action	Invention	Innovation system	Societal change	Regulatory	Economic	Voluntary	Supply side	Demand side	Coordination
1. Public R&D grant funding	States invest directly in R&D via public or quasi-public intermediary organizations – often termed public sector research funding agencies, research councils, or science granting councils. R&D funding supports fundamental (basic) or applied and translational research – including clinical studies – and potentially involves firms. Training of researchers is an important by-product. Funders usually expect a social return over the longer term.	✓	✓	✓		✓		✓		
2. Advice and facilitation of clinical development	Specific programmes offer advice (sometimes free of charge) to medicine developers on a product's adequate efficacy and safety data for their marketing authorization application. Additionally, not-for-profit organizations and governments may facilitate clinical research, with patient registries and timely reimbursement decisions.	✓			✓		✓	✓		

Table 1. Contd.

Policy instrument family	Description and mechanism of action	Perspective								
		Aim			Governance mode			Targeted constituency		
		Invention	Innovation system	Societal change	Regulatory	Economic	Voluntary	Supply side	Demand side	Coordination
3. Expedited regulatory pathways	For products that treat severe or life-threatening diseases with unmet medical needs and have superior therapeutic benefits over existing drugs, the regulatory pathway – including its review process – may be expedited in various ways, to hasten their availability.	✓			✓			✓		
4. IRP – patents	Patents are a form of IPR conferring to the owner of an invention (such as a product or a process) a temporary right to exclude others from commercializing that invention within a specific legal jurisdiction, such as a national government. Patents are granted by a patent office following application and examination.	✓			✓			✓		
5. IPR extensions via patents and market/data exclusivity	Further policy instruments can extend the market protection granted by IPR. These include patent restorations (extending the monopoly term) and other measures that provide market/data exclusivity by denying competitors temporarily from receiving product regulatory approval.	✓			✓			✓		
6. Patent pools and patent buyouts	Patent pools are agreements between two or more patent owners to license one or more of their patents to each other or to third parties. Patent buyouts occur when the government buys the patent and it is freely distributed to the public.	✓			✓		✓	✓		
7. Tradable vouchers	Tradable vouchers give medicine developers the option to sell or transfer two other policy interventions: priority reviews (included in policy instrument family 3) and market exclusivity (included in policy instrument family 5).	✓						✓		

Table 1. Contd.

Policy instrument family	Description and mechanism of action	Perspective								
		Aim			Governance mode			Targeted constituency		
		Invention	Innovation system	Societal change	Regulatory	Economic	Voluntary	Supply side	Demand side	Coordination
8. Financial guarantees for development and manufacturing	Financial guarantees increase a firm's expected revenue or the certainty of revenues resulting from its successful development of a product by guaranteeing price, sales volume and/or overall revenue in advance of development or production.	✓		✓		✓				✓
9. Prizes to reward medicine developers reaching milestones in the innovation process	Monetary prizes reward medicine developers for reaching certain milestones in the innovation process. Prizes can take a wide range of forms.	✓		✓		✓		✓		
10. R&D tax incentives to subsidize R&D costs	R&D tax incentives subsidize input R&D costs. This can be done via special R&D expense deductions or tax credits based on R&D spending, both of which are tied to R&D spending by companies.		✓			✓		✓		
11. Loans and loan guarantees	Low-interest loans can encourage medical innovation by reducing future loan repayments. Loan guarantees, by a government or other party to a company developing a new medicine or other technology, allow the lenders to share the risk of default on outstanding loans with the guarantor.	✓		✓		✓		✓		
12. Access to risk capital financing mechanisms	Financial mechanisms can be used to encourage development of new medicines by addressing market failures in the provision of capital for early development. They include a variety of tools, such as options, combined debt/equity funding and bonds.	✓		✓		✓		✓		

Table 1. Contd.

Policy instrument family	Description and mechanism of action	Perspective								
		Aim			Governance mode			Targeted constituency		
		Invention	Innovation system	Societal change	Regulatory	Economic	Voluntary	Supply side	Demand side	Coordination
13. Fees/taxes for medicine developers to incentivize them to use their capability to develop specific medicines	Fees and taxes can provide either a financial incentive (no regulatory review fee for those medicines) or a financial penalty for not doing so ("pay or play"). To date, they have only been suggested for antibiotics.			✓		✓		✓		
14. Collaborations and partnerships with the public sector	A prominent form of collaboration in drug development has been the product development partnership between pharmaceutical companies and academic institutes, with a specific focus on developing new treatments – usually for neglected diseases. Partnerships may be multilateral agreements, where strategic assets and know-how are shared across partners, in some cases leading to open innovation initiatives in the pre-competitive space.	✓	✓	✓		✓	✓			✓
15. Open knowledge principles around sharing of data, ideas and research outputs	A process of technological development under open knowledge principles essentially involves most or all information being shared openly or publicly, rather than being protected by confidentiality or intellectual property provisions (policy family 4). Other terms used for such an approach include "open data", "open source science" and "open access research". Under classic "open science", however, only the final outputs are shared.		✓		✓		✓	✓		

Table 1. Contd.

Policy instrument family	Description and mechanism of action	Perspective								
		Aim			Governance mode			Targeted constituency		
		Invention	Innovation system	Societal change	Regulatory	Economic	Voluntary	Supply side	Demand side	Coordination
16. General health service infrastructure, services and funding	Health services can influence the development of new medicines and new businesses, not only by demanding and using them but also by sending signals to medicines developers about the sorts of medical technologies that are in demand.		✓		✓		✓			✓
17. DRG carve-outs for medicines dispensed in hospital	DRG carve-outs are a financing mechanism for specified new hospital-dispensed medicines that allows them to be excluded from the DRG, which would usually limit the products and services used for treatment of particular conditions – e.g., to maintain cost control.			✓		✓			✓	
18. Limited indemnification from liability claims for medicine developers	Limited indemnification is a legal instrument that temporarily waives manufacturers' liability for a specific product at the moment it becomes licensed, and after approval of production batches by authorities, in the event of injury or death related to that specific use.	✓		✓	✓			✓		

DRG: diagnosis-related group; IPR: intellectual property rights; R&D: research and development.

3.2 Mapping policy instrument families onto the 3×3 approach

Table 1 also maps the identified medical innovation policy instrument families onto the 3×3 approach illustrated in section 2 (Fig. 1) from the wider literature on innovation policy instruments. Four points are highlighted from this analysis.

First, it is notable that debate in the literature on policies for medical innovation often uses the bifurcating "push/pull" distinction (distinguishing between supply-oriented and demand-oriented policies). This is a more simplistic categorization than that used in the wider literature on innovation policy in other sectors; a 3×3 approach is proposed for classifying policy instruments and how they interact. Second, most of the policy instruments in the literature spur invention (ultimately of a medicine being authorized

by regulatory authorities), rather than innovation systems (policies encouraging the use and uptake of these new medicines to ensure that inventions become innovations) or missions to address specific societal challenges. Third, policy instruments are most commonly governed by regulatory and economic (rather than voluntary or information-based) mechanisms. As argued above, few of the sources on medical innovation reviewed highlight the importance of coordination across different stakeholders. Fourth, these sources mainly focus on instruments that act on the supply side of the innovations system – the originators. Few target the demand side specifically, although more such possibilities for intervention do exist in other sectors. Indeed, the wider innovation policy literature emphasizes the need for a more holistic approach, and highlights the importance of the demand side as a key driver of innovation.

These last three points derive in part from the first. This analysis highlights some notable gaps in the literature on policy instruments for medical innovation, and emphasizes that more opportunities for intervention exist than might be apparent from the push/pull debate.

3.3 Position in the product life-cycle

The policy instrument families identified can be used to support medical innovation across the product life-cycle, which is distinguished across the following four stages:

- basic and preclinical R&D – from the earliest stages of research, up to and including testing in animal models;
- clinical development – formal phase 1, 2 and 3 clinical trials;
- regulatory review and registration, and launch/market access – interactions between developers and regulators/payers;
- post marketing – after the product has been approved for marketing and use.

The R&D process is described in more detail in another OMI technical report *(18)*.

Table 2 shows where the policy instrument families can have an effect on the product life-cycle (or stage of development); some address a specific stage, while others are relevant for developers of medicines regardless of the stage of the process they are engaged in. A range of policy instruments is available to support each stage of the product life-cycle, with relatively even distribution across the four stages.

Table 2. Policy instrument families for medical innovation, by level of adoption, product life-cycle and primary effects

Policy instrument family and evidence of use[a]	Product life-cycle stage[b]				Relevant primary effects									
	Preclinical R&D	Clinical development	Regulatory review and launch/market access	Post-marketing	Providing knowledge, capabilities and infrastructure	Providing new product opportunities	Creating assets	Reducing upfront costs/ capital at risk	Reducing uncertainty	Reducing time to market	Encouraging market entry	Reducing competition	Increasing financial returns	Incentivizing use
1. Public R&D grant funding					✓	✓	✓	✓		✓				
2. Advice and facilitation of clinical development					✓			✓	✓	✓				
3. Expedited regulatory pathways	n/a			n/a					✓	✓				
4. IPR – patents			n/a				✓				✓	✓	✓	
5. IPR extensions via patents and market/ data exclusivity	n/a	n/a	n/a								✓	✓	✓	
6. Patent pools and patent buyouts	n/a		n/a		✓	✓		✓	✓	✓	✓			
7. Tradable vouchers	n/a	n/a					✓		✓	✓		✓	✓	
8. Financial guarantees for development and manufacturing						✓			✓		✓		✓	
9. Prizes to reward medicine developers reaching milestones in the innovation process		n/a	n/a	n/a					✓		✓		✓	
10. R&D tax incentives to subsidize R&D costs			n/a	n/a			✓						✓	
11. Loans and loan guarantees								✓	✓				✓	
12. Access to risk capital financing mechanisms			n/a	n/a				✓	✓		✓			

Table 2. Contd.

Policy instrument family and evidence of use[a]	Product life-cycle stage[b]				Relevant primary effects									
	Preclinical R&D	Clinical development	Regulatory review and launch/market access	Post-marketing	Providing knowledge, capabilities and infrastructure	Providing new product opportunities	Creating assets	Reducing upfront costs/ capital at risk	Reducing uncertainty	Reducing time to market	Encouraging market entry	Reducing competition	Increasing financial returns	Incentivizing use
13. Fees/taxes for medicine developers to incentivize them to use their capability to develop specific medicines				n/a							✓			
14. Collaborations and partnerships with the public sector			n/a	n/a	✓	✓		✓	✓					
15. Open knowledge principles around sharing of data, ideas and research outputs			n/a	n/a	✓	✓			✓		✓			
16. General health service infrastructure, services and funding					✓	✓			✓		✓		✓	✓
17. DRG carve-outs for medicines dispensed in hospital	n/a	n/a	n/a						✓				✓	✓
18. Limited indemnification from liability claims for medicines developers	n/a	n/a	n/a					✓	✓		✓			
Total number of policy instrument families producing each effect					**6**	**6**	**4**	**7**	**13**	**5**	**10**	**3**	**9**	**2**

DRG: diagnosis-related group; IPR: intellectual property rights; R&D: research and development.
[a] The "traffic-light" colour coding identifies how often they are used: green – widely implemented; yellow – implemented in some areas; red – very limited implementation; grey – no known implementation.
[b] The colour coding identifies applicability to the stage of development: blue – policy instrument family affecting that stage; n/a – policy instrument family not applicable to that stage.

3.4 The relative level of adoption of policy instruments globally

Families of policy instruments have been implemented to varying extents, which can be classified into four categories (see Table 2 and web-annex for more details):

- widely implemented, across many countries and diseases areas;
- implemented in some countries/therapeutic areas but not others;
- very limited implementation – in terms of instances used, or relatively recent introduction;
- no known implementation (appears conceptually only).

The classificatory decisions made here are subjective, based on the knowledge of the authors (including from the separate mini-literature review undertaken independently for each topic). This report attempts to classify the relative usage of instruments in comparison to each other, as opposed to using precise quantitative thresholds, given the uncertainties around actual implementation globally. Decisions were reached via iterative discussions among the authors. The results are shown in Table 2 with a "traffic-light" colour coding.

It is notable that a large majority of these policy instrument families are yet to be widely implemented across countries and disease areas, and one family has yet to be implemented to any extent (family 13). This may indicate a bias in the sources towards applied rather than conceptual policy instruments. Nevertheless, the review suggests considerable scope for many countries to consider how a wide range of instruments could be adopted and implemented in a suitable manner for their domestic contexts. There is also a challenge, however: published evidence for many of these instruments on their effectiveness outside just a few contexts is limited. If governments are unlikely to experiment with new policy tools without some evidence of their potential impact, this will limit considerably their implementation. As governments move towards evidence-informed decision-making, more rigorous evaluations of policies and their impacts are needed to inform policy-making processes.

3.5 The main direct effects of policy instruments on developers of medicines

Policy instruments can drive innovation by supporting those functions of the innovation system that need to be in place to assist in the development of new products and services *(30,31)*. While there is a wide array of policy instruments, these functions are relatively few in number, so the effects of a wide range of policy instruments can be expected to fall into a few common categories. This report identifies 10 such possible effects, which collectively address those functions of the innovation system described in the literature. Each effect is described below in turn, highlighting the policy instruments that yield them, while Table 2 provides the tabular summary (in the column titled "relevant primary effects").

3.5.1 Providing knowledge, capabilities and infrastructure

Instruments can drive production of key resources that many organizations need in order to innovate. These include knowledge (such as that related to the understanding of diseases

or therapeutic strategies), capabilities (individuals with skills) and/or R&D infrastructure (such as laboratory facilities and databases). In particular, policy instruments that provide publicly funded R&D (policy instrument family 1) are a means to create new knowledge and to train human capital in established and emerging capabilities useful for medical innovation, as well as to develop and maintain the infrastructure required to support innovation. Policy instruments can provide infrastructure that can be thought of as not only the physical facilities for R&D, but also the systems for providing advice and support for those undertaking clinical development (family 2). Instruments can also provide the required expertise and facilities that are a part of the general health service infrastructure (family 16). Access to important knowledge may be facilitated by instruments that support open knowledge principles (family 15), and instruments to ensure that IPR is made accessible through pooling (family 6) or though collaboration/partnerships (family 14), which can also deliver access to additional knowledge, capabilities and infrastructure.

3.5.2 Providing new product opportunities

Instruments can provide new opportunities to develop products by generating starting points for viable development projects that can be taken up for further exploration by organizations involved in medical innovation. While these represent new possibilities, these are not yet tangible assets (see section 3.5.3). Policy instruments promoting public R&D (family 1) can directly drive the generation of new lines of research that can be developed into product opportunities. Instruments that provide for more open knowledge (family 15) and free up existing intellectual property, as in patent pools (family 6), can facilitate efforts to develop products that incorporate this knowledge, while provision of financial guarantees can reduce resource impediments to associated development and production (family 8). New product opportunities can be created by bringing together those in the general health service infrastructure (family 16) and wider stakeholders working in collaboration and in partnerships (family 14), reinforcing the importance of interactions with clinicians in driving innovation.

3.5.3 Creating assets

Instruments can provide a way to create assets of recognizable value that can be appropriated, developed and traded between organizations engaged in medical innovation, including encouraging publicly funded R&D to create assets for subsequent development into innovative medicines (family 1). Supporting IPR, such as patents (family 4) can help to create widely recognized assets that can be transferred and traded by organizations developing medicines. R&D tax incentives (family 10) can increase the volume of R&D geared towards creating these assets in the private sector, and provide tax credits that can potentially be used against offsetting taxes on other taxable income. Policy instruments can also allow agencies such as regulators to create tradable vouchers (family 7) that provide an advantage to developers, which also can become widely recognized as assets in their own right – although it is worth mentioning the potential negative effect of such vouchers, where the benefits are reaped by other treatments that might not necessarily address urgent needs.

3.5.4 Reducing upfront costs/capital at risk

Instruments can reduce, at least to some degree, the scale of investment in high-risk activities that would otherwise be required to bring a medical innovation to market, making the costs of projects easier to meet. The high costs of medical innovation were noted earlier as a barrier to their development – particularly those that are high-risk and early-stage, because the low chances of these generating a financial return on capital invested make them unattractive investments. Policy instruments can support public R&D (family 1) to undertake these "upstream" activities, while making the resulting knowledge and assets available free of charge or at low cost to medicine developers "downstream", thereby reducing these developers' exposure to projects with a high risk of failure. The availability of advice – in particular for expensive programmes of clinical development (family 2) – can help to reduce chances of failure by explaining the requirements of regulators to developers. Provision of existing intellectual property (family 6) reduces the need to invent around this or pay fees, while instruments that promote collaboration and partnerships (family 14) help developers to share costs, knowledge, risk and – more recently – even strategic assets. Policy instruments that support the financing of projects through loans, loan guarantees (family 11) or access to risk capital financing mechanisms (family 12) can reduce upfront costs that might otherwise prevent a project from starting, as well as reducing overall costs. The potential for future liability that also might dissuade development can be addressed by limited indemnification from liability claims (family 18).

3.5.5 Reducing uncertainty

Innovation is a highly uncertain activity. While it is possible to calculate risks associated with some aspects of R&D – such as chances of project failure – developers face considerable uncertainty about the likelihood of success for new approaches, and whether a given project will make a commercial return. Uncertainty may therefore be scientific or technical on the one hand and commercial or financial on the other. Moreover, while there are many highly experienced developers, more inexperienced developers may face greater uncertainty about how to proceed to maximize their chances of success. Instruments that reduce uncertainty help the developers of medical innovations to have a more certain pathway to success by providing advice, signals or validations for their assumptions or approaches. By reducing scope for missteps or errors, these instruments reduce developers' uncertainty about the potential for their innovation to be successful.

In particular, provision of advice and support around high-cost clinical development (family 2) and expedited regulatory processes (family 3) to benefit particular types of projects can reduce developers' scientific or technical uncertainty about this part of the process. Providing access to knowledge by promoting its open availability (family 15) can also reduce technical uncertainties.

Regarding commercial uncertainty, access to critical intellectual property (family 6) can reduce uncertainty about freedom to operate, and is a powerful instrument to generate

innovation, while the possibility of receiving tradable vouchers (family 7) increases the potential returns of developing a medicine for less profitable areas. Policy instruments promoting collaboration and partnerships (family 14) can reduce commercial uncertainty for developers by promoting access to those with relevant experience and capabilities. Uncertainty about the commercial viability of projects can also be reduced by providing finance through prizes (family 9), financial guarantees (family 8), loans and loan guarantees (family 11) or risk capital financing mechanisms (family 12). Moreover, specification of particular conditions to qualify for such schemes provides clarity over the types of products that would be more welcomed by policy-makers, and thus reduces uncertainty about the types of products that should be developed to address specific markets. Similarly, DRG carve-outs for medicines dispensed in hospitals (family 17) and limited indemnification from liability claims (family 18) provide further certainty of the desirability of the products that will be in demand in particular regions. Policy instruments that promote access to well-informed users within a well-funded health-care service (family 16) can also help to address developers' uncertainties about products and market demand. Forecasting demand to understand the competitive market landscape and horizon scanning activities are critical for reducing such uncertainties.

3.5.6 Reducing time to market

The long times frames associated with medical innovation reduce the attractiveness to developers of certain projects, because capital is locked up for longer periods and returns are delayed. Overall returns are also potentially reduced, as the period of time on the market that products have patent protection is diminished by long development processes. In addition, lengthy delays in the development of new medicines and vaccines can mean patients waiting a long time for new treatments or for access to new treatment options that may require urgent treatment or prevention. Thus, some instruments have direct effects on the R&D process, by reducing the time it takes for medical innovations to reach the market, by speeding up progress of R&D projects through required processes, or by altering the processes themselves to make these less time-consuming to complete.

In particular, policy instruments that reduce time to market include public funding for R&D (family 1), where this reduces the scope of activities that developers need to engage in (and therefore the time to complete these). Advice and support on clinical development can help developers to reduce the duration of clinical trials (family 2), as well as directly adjusting the regulatory process to make this less time-consuming or to speed up the review phase – such as fast track, breakthrough or priority designations in the United States and priority medicines schemes in the European Union (family 3). Tradable vouchers can transfer regulatory benefits that shorten time to market (family 7), while medicines included in patent pools (family 6) might not need further studies, which would also reduce the time to market.

3.5.7 Encouraging market entry

Experienced and new commercial developers are attracted to markets by the prospect of a high return on investment, so policy instruments can attract market entry by providing indications that the market will generate lucrative returns. Instruments can thus support organizations participating in the supply of particular forms of medical innovation. Over time, this may have the effect of increasing competition in the market for approved products.

Many of the policy instruments discussed above can contribute to this, such as the prospect of defensible intellectual property (family 4) and extensions to periods of exclusivity (family 5). Providing financial support for product development such as financial guarantees (family 8) and access to risk capital financing mechanisms (family 12) could have the effect of inducing market entry, while prizes (family 9) could provide new entrants with opportunity to explore a new market, particularly where they are awarded for reaching early milestones. Policy instruments that support well-resourced health-service infrastructure (family 16) – including any demand aggregation/pooling and forecasting/foresight – also provide a more attractive target market for developers. Removal of potential threats, such as liability claims (family 18), might also reduce barriers to market entry for some developers. Also, in theory, fees/taxes could dissuade established medicine developers (family 13) from staying out of a market, forcing entry (or, perhaps more likely, influencing re-entry). While some of these instruments are associated with the use of exclusivity to attract entrants, it is also possible that in some circumstances the lowering of barriers for entry may entice new entrants, who many not be solely focused on revenue maximization. For these entrants, promoting open access to knowledge and data (family 15) and easy access to intellectual property (family 6) might make market entry easier.

3.5.8 Reducing competition

The uncertainties and high costs of medical innovation can be countered by the potential for high returns on investment. Some instruments reduce the competition that developers of medical innovation are likely to face in the market, thereby increasing the likelihood that they will gain higher revenues, while not guaranteeing that these revenues will be achieved. IPR such as patents (family 4) provide temporary monopolies to developers by providing them with the opportunity to exclude others from producing their inventions. The incentive that IPR and regulatory approval exclusivity creates can be increased and extended and also potentially traded between developers through the actions of regulatory agencies (family 5, family 7). The resulting reductions in competition provide an opportunity for developers to charge high prices and make supernormal profits – usually up to around 8–10 years on average of patent life remaining, once marketing authorization has been granted. While this may be socially undesirable in the short term, it is this potential profitability that makes these incentives so powerful for inducing innovation over the long term. Reductions in competition also come at the expense of reducing market entry (see section 3.5.7).

3.5.9 Increasing financial returns

The prospect of increased financial returns can incentivize developers to develop more products by making a wider range of these commercially viable. A wide range of instruments can have direct or indirect effect on revenue, rewarding the development or supply of particular qualifying forms of medical innovation. IPR such as patents (family 4), periods of regulatory approval exclusivity and extensions to these (family 5) and mechanisms to trade these (family 7) provide a wide range of developers with reasonable expectations of high revenues. Net revenue (that is, profits) can also be increased by tax relief schemes such as on R&D (family 10). Instruments that reduce costs from financing product development, such as financial guarantees (family 8) or low-interest loans/loan guarantees (family 11), can have the effect of increasing net revenues too, while prizes provide the opportunity to

increase revenues, albeit perhaps on a one-off basis and only for successful applicants (family 9).[10] Instruments that support a well resourced health service infrastructure (family 16) provide the potential for firms to generate increased revenues from those markets, while DRG carve-outs (family 17) can expand these markets.

3.5.10 Incentivizing use

Once a product has been authorized for marketing and use in a health-care system, an instrument to incentivize use can increase its adoption by stimulating demand, by removing financial and other barriers to use, such as perverse incentives. These instruments also signal to developers the forms of products that are valued. Policy instruments that support a well-resourced health-service infrastructure (family 16) provide a source of demand that may be more responsive to innovative medicines, while DRG carve-outs (family 17) incentivize use by removing barriers to adoption – albeit temporarily.

The effects described above can interact. For example, incentivizing the use of a product will usually increase the revenues associated with that product (although the reverse may not be the case), by creating demand. The intention here is to capture the range of primary effects that policy instruments have, and not their subsequent effects (which become dependent on a range of potentially complex further interactions). The observation that policy instruments have common effects also provides the opportunity for multiple policy instruments to be combined to reinforce each other, to increase the power of an effect (at least in theory).

3.6 Key implementation issues

A summary description of how each policy instrument family works is provided in web-annex, including anticipated implementation issues. Table 3 highlights some of these issues in a short format to draw policy-makers' attention to likely problems to anticipate at the design stage. The analysis suggests the following common implementation issues.

- Poor implementation of policy instruments may provide rewards for medicine developers without ensuring sufficient value in return.
- Individual policy instruments may not have the desired effect on their own; they may rely on other measures used in combination to be effective.
- Implementation may be expensive.
- Instruments may promote change in behaviour, but this may not necessarily be in the desired direction.
- Success may be reliant on engaging a large number of stakeholders sufficiently.
- Specific, yet difficult to acquire, capabilities may be required by policy-makers for instrument design, implementation and evaluation.

10 Price-related incentives are also important, but these are covered by other OMI technical reports *(13,14)*.

Table 3. Key implementation issues for the 18 families of policy instruments for medical innovation

Policy instrument family	Implementation issues
1. Public R&D grant funding	R&D may be costly, and outcomes may be uncertain. Demonstrating value for money raises complex challenges – in terms of determining the social value of and expected returns from basic research, for instance. There is a tension between allowing scientific autonomy and the pursuit of excellence (often interpreted as publication in elite journals) on the one hand and addressing local priorities on the other.
2. Advice and facilitation of clinical development	This has limited use, and expansion is difficult – in part, because it requires engagement with a wider community of stakeholders. Challenges relating to data collection, data entry and data analysis for patient-centred registries remain.
3. Expedited regulatory pathways	It has been argued that expedited review programmes have benefited the development of drugs that are less innovative and that treat less serious diseases. Global collaboration and harmonization among different authorization agencies is lacking, which can increase development costs.
4. IPR – patents	Patents give a temporary monopoly situation to innovators, irrespective of the "value" of the product, but it should be noted that the IPR system is not built to address the question of the value of the IPR protected: this is reliant on other forces, such as effective health technology assessment, selection and payment.
5. IPR Extensions via patents and market/data exclusivity	Exclusive access to a very small market may still not be attractive for the medicine developers (e.g., with some new antibiotics, their use will be limited – partly to manage the build-up of resistance – so sales will be low, and hence extended exclusivity might have little economic value); therefore, additional measures may be needed to incentivize investment. Companies can take advantage of multiple exclusivities to maximize their profits, delaying market access for genetic/biosimilar equivalents.
6. Patent pools and patent buyouts	Several issues can limit the impact of this family, including whether participation is mandatory or voluntary, the technologies included, royalties and the time required to reach agreement. Another potential limitation may be the scope and terms of the licence agreements included in the pool, such as commitments to register and sell in challenging geographies, to provide low pricing in middle-income or hybrid markets, and to take on liabilities. Other incentives may also be required to address patent owners' reluctance to join.
7. Tradable vouchers	The benefits of these are reaped by medicines developers who are not necessarily addressing urgent needs, although guardrails could be used to cap the financial reward. The value of the rewards is not directly linked to the actual effectiveness of the treatment. The financial value of the voucher and practical implementation challenges may limit the impact.
8. Financial guarantees for development and manufacturing	The design needs to consider the incentives (including financial), structure and goals for such initiatives; for instance, whether the advanced commitment is commensurate with the ultimate cost/benefit ratio. Attention to clear outcomes and monitoring of progress is important, as in any procurement programme. Ensuring that the participants in such purchasing agreements deliver on their commitments – companies, governments and agencies alike – is an important prerequisite for success. Similarly, ensuring that such measures do not descend into noncompetitive protectionism is important.

Table 3. Contd.

Policy instrument family	Implementation issues
9. Prizes to reward medicine developers reaching milestones in the innovation process	A significant challenge is setting the right level of the prize in monetary terms that is commensurate with the value of the end-product. Prizes by themselves may not be enough to incentivize R&D for new medicines, particularly if these focus on the early stages of R&D for cost reasons. Indeed, prizes usually apply to early pre-competitive research to solve scientific questions rather than technology development, which becomes subject to commercial processes. They may need to be blended with other policy instruments.
10. R&D tax incentives to subsidize R&D costs	There are variations in how tax incentives are implemented in practice, with different definitions of R&D costs, deduction amounts, credit rates and eligibility rules. This leads to diverse degrees of the "generosity" of the incentives or complexity in the process. Tax incentives for R&D can lead to what is termed in international trade economics the "beggar-thy-neighbour effect": this benefits the country that implements it while harming that country's neighbours or trading partners (usually country-specific regimes). The risk of gaming the system is also heightened – requiring clear eligibility and assessment criteria.
11. Loans and loan guarantees	The design of government-backed innovation loans should avoid both projects with a high probability of success that would be funded by the private market regardless and those that do not justify public financing because their expected net impacts are negative. One problem with such schemes is that governments, their agencies and the officials managing them can sometimes prefer to stay safe and support firms that are relatively low risk and likely to be "successful", to maintain political and budgetary support. Finally, such loans and loan guarantee programmes need to have sufficient scale to make a meaningful impact. These may be more difficult to apply in routine innovation contexts as opposed to in emergency contexts when there is pressure to deliver solutions for society (such as in pandemic or epidemic contexts).
12. Access to risk capital financing mechanisms	Governments' relative lack of commercial and entrepreneurial expertise and issues in the level of understanding financial and commercial markets can be a barrier to implementation. Designing schemes to manage potential conflicts of interest, accountability and appropriate transparency is important, as is ensuring that the schemes ultimately achieve the objectives they have been designed for.
13. Fees/taxes for medicine developers to incentivize them to use their capabilities to develop specific medicines	This instrument has not been tested in practice, and it has only been discussed as a (theoretical) option to stimulate antibiotics innovation, so emergent issues are unknown. In theory, it is important not to incentivize gaming – defined as industry investing minimally in R&D to meet the required threshold, but not striving to bring new, high-value antibiotics to market. Implementation must not require expensive administrative processes, including formal audits of companies' investments. It is meant to supplement other national economic incentives rather than completely finance a market/economic incentive.
14. Collaborations and partnerships with the public sector	Conflicts of interest remain a significant barrier, as do misaligned incentives and the need to build trust across stakeholders on a project-by-product basis. The inclination, capacity and capability of the government's officials and independent academics to work with the pharmaceutical industry to implement such schemes is also critical.

Table 3. Contd.

Policy instrument family	Implementation issues
15. Open knowledge principles around sharing of data, ideas and research outputs	This might be more appealing for less lucrative areas with low financial return, even with patent protection, or when the aim is to encourage new firms responding to supply issues. An additional challenge is that open knowledge principles may be more appropriate for pre-competitive research, but could reduce the potential for academic contributions to new lines of competitive research that industry wants.
16. General health service infrastructure, services and funding	The reason for the rise of health system strengthening as a development strategy over recent decades is in part a recognition that building resilient, effective and well-resourced health systems is crucial for global health and development. However, this is expensive. Having systems that can allocate health resources effectively is important, and tools for that include health technology assessment and market-based systems; effective reimbursement, financing and procurement systems; demand forecasting/demand modelling; reliable supply chains; effective pharmacovigilance; and sound regulatory oversight, among others.
17. DRG carve-outs for medicines dispensed in hospital	A key challenge for this type of short-term instrument is to determine the eligibility criteria. Given their temporary nature and that they only apply to certain medicines, DRG carve-outs by themselves may not be enough to incentivize R&D for new medicines, so they need to be blended with other policy instruments that offer a financial return once the medicine is no longer subject to the carve-out.
18. Limited indemnification from liability claims for medicines developers	It should be expected that proposals on liability limitations will face potentially significant public – and hence political – opposition, but opposition would be less for "last-resort" treatments and those for emergency situations. COVID-19 has provided a recent example of a global compensation programme to limit manufacturers' liability. The possibility that this may incentivize companies to be less careful and push for broader indications results in a need for close government monitoring.

Source: Mini-reviews in web-annex.

4

Systematic use of policy instruments for medical innovation

Countries across the world share the challenge of finding ways to better support innovation processes in order to bring new socially important, affordable medicines into use in a timely manner. This report provides an overview for policy-makers on the broad array of instruments available to countries (excluding those with the primary aim of determining prices, which are discussed elsewhere in the OMI technical report series *(13,14,20)*), providing descriptions of these and discussing their implementation, evidence of their impacts and potential challenges relating to their design. While the review focuses on identifying policy instruments that can be applied at the national level, some may have a greater effect on achieving their desired aim if countries work together to combine their funding and influence to apply them collectively.

This concluding section reflects on the difficulties of selecting and combining policy instruments; key messages on how to apply these in practice; some limitations of this technical report; and suggestions for further research.

4.1 From policy instruments to policy instrument mixes

By identifying and describing policy instruments, this technical report provides a set of possible "ingredients" for the policy instrument mix, which need to be combined and blended on a case-by-case basis by decision-makers to suit specific local needs. This is because the opportunity for medicine developers and countries to benefit from policy instruments for medical innovation will depend on multiple factors, including:

- past history;
- available resources (such as risk finance/capital);
- the scientific knowledge base and know-how;
- the political environment;
- local disease burdens;
- national priorities (including health care and health security, but also economic and geopolitical priorities);
- attitudes to risk;
- culture; and
- future aims and strategies to achieve these.

Box 1. Combining medical innovation policy instruments for improved access to advanced therapy medicinal products

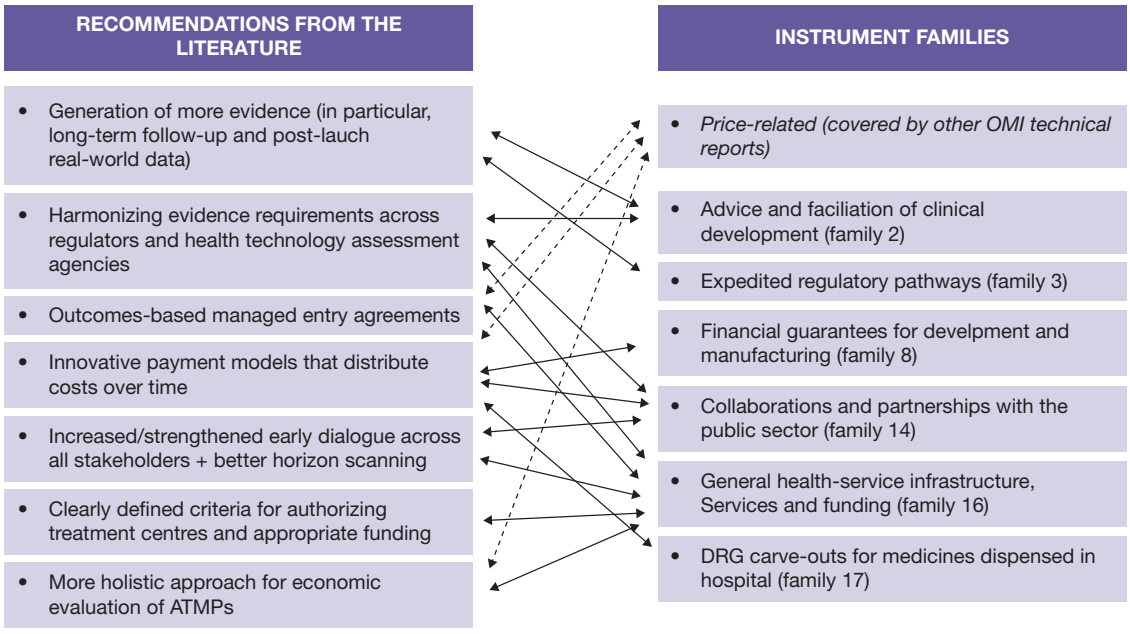
The OMI remit is to improve access to effective, novel, high-priced medicines, which includes advanced therapy medicinal products (ATMPs). These are medicines for human use that are based on genes, tissues or cells. They potentially offer ground-breaking new opportunities for the treatment of disease and injury *(34)*. Those recommendations advocated to support ATMPs in recent literature are identified below, and mapped according to the policy instruments families described in this report. This approach demonstrates which types of policy instruments are deemed most relevant for ATMPs, while also showing how policy instruments may be combined systematically to address a specific challenge.

Five sources were identified from the literature that specifically address ATMPs *(35–39).* These address a relatively consistent set of issues; importantly, many of the points raised are around determination of their prices or payment models, which are covered elsewhere in the OMI technical report series *(13,14)*. Relevant non-price issues include:

- uncertainty in terms of their value (including safety and efficacy) at time of launch;
- the potentially curative nature of treatments and long-term benefits;
- organizational and scaling issues within the health-care system;
- the potential "one-shot" nature of treatment;
- significant upfront costs for payers (in part due to complex processes for manufacturing and administration).

Some common policy recommendations from the literature reviewed here fall within a number of the instrument families, as defined in this report. Fig. 2 shows this mapping, including price-related instruments covered by other OMI technical reports.

Fig. 2. Mapping of literature recommendations and relevant policy instrument families



ATMP: advanced therapy medicinal product; DRG: diagnosis-related group; OMI: Oslo Medicines Initiative.

These local conditions and existing policies (both in the target sector and those set more widely that impinge on the sector) provide a "policy mix" that new instruments are blended into, for better or worse. It is important to note that the same policy intervention will often not be effective, or will not have the same effects, when transferred across settings because of these different starting conditions *(32)*, as well as unexpected and unrelated events that may happen subsequently and impinge on the anticipated outcomes – such as financial crisis, pandemics, civil unrest or changes in government direction. As such, the interventions deemed appropriate will vary for different geographical and disease contexts. No "one-size-fits-all" solution or outcome should be expected, even for the same problem *(17)*. Nevertheless, there are some common considerations in relation to the application of policy instruments, which can be usefully discussed here.

First, policy instruments interact with each other in ways that may be complementary or in conflict *(33)*. They may interact by amplifying each other's intended effects, and/or one may be catalytic for another. A clear example can be seen with policy instruments that both provide advice and facilitate clinical development, expedited regulatory approval and health technology assessment, funding and reimbursement (Box 1).

Alternatively, one policy instrument may cancel out the positive effects of another; for instance, open knowledge principles and patent pooling that limit intellectual property protection might deter entry to private organizations reliant on this protection to secure temporary market power over potential competitors. Indeed, initiatives based on open principles are usually more appropriate for pre-competitive activities, but once there is a product to be clinically tested, intellectual property might be required to secure private efforts to fund the generation of evidence.

Overall, the combination of positive expectations based on promising signs of scientific and technological progress, combined with suitable entrepreneurial activity and supportive policies, can lead to generative cycles of growth. If one of these elements is missing or failing, however, a degenerative cycle is created, and enthusiasm and support for a given technology or sector wanes (*30,40)*.

Second, some policy instruments will be dependent on other prerequisites in order to work, or on the appropriate configuration of other policy instruments to have the desired effect, even if they are demonstrably in demand by stakeholders and seem to be appropriate. For instance, having a well-resourced health-service infrastructure and a strong R&D science base, combined with strong links across stakeholders, can be a catalyst for clinical research that leads to the development – and uptake – of innovative medicines covering a health need. Additionally, and especially in less mature systems, countries may need some capacity-strengthening and support with policy instruments requiring strong regulatory and health technology assessment processes to support innovation.

Third, when a policy instrument is designed and applied in another context – even if based on a similar policy elsewhere – it can still be highly adapted in its configuration (related to the amount of resources invested, the range of beneficiaries, inclusion/exclusion criteria or interpretations of value, for example). This will shape its effectiveness, and potentially those of wider policies it is associated with (*31,41)*.

Fourth, policy instrument mixes should be appropriate for their time and context, and the instruments should be introduced in a suitable sequence for these to be effective *(42)*. Delivering coherent systems to support innovations that address the needs of citizens requires government capability in policy evaluation, to assess when policy instruments should be introduced into a mix, as well as a joined-up approach to policy formulation from different ministries or agencies. If resources are not available for instruments to be implemented successfully when needed, accumulated momentum and progress can leak away.

Policy instruments may be combined as part of a single policy initiative – for example, as part of an act or law, or as a strategy that seeks to address an issue comprehensively – or they may accumulate in an ad hoc manner over time. Prominent examples are the United States and European Union legislation on orphan medicines, which combine various families of policy instruments. Policy instruments may be evaluated, adapted (occasionally or continually) or retired. Alternatively, the performance of policy instruments may be unmonitored and continue unchecked, with the result that inefficient use of resources may be allowed to continue.

Periodic evaluation should ensure the suitability of policy instruments and inform their redesign. Evaluation of complex systems of policies is challenging, however. It can be very difficult to define precisely instrument mixes, their interactions and their effects over time *(43)*, as well as to define the counterfactual. Indeed, the study, characterization and evaluation of systematic instrument mixes for innovation policy remains at an early stage *(44)*.

4.2 Key messages on applying policy instruments in practice

It is beyond the scope of this report to give specific recommendations on which policy instruments could, or should, be used in any given context to encourage the development of new medicines. This is partly because of the limited evidence available on the impacts of the different instruments, and partly because it would require further analysis on the country or geographical region in question, or the particular health need or context (for example, routine, emergency or neglected tropical diseases/small markets) for which innovation is required, as policy instruments must be configured to suit their context in order to be effective. Some key messages for policy-makers on improving the mix of policy instruments are provided here, however, based on the literature reviews conducted for this report.

- There appears to be considerable scope for the systematization of policy instruments to provide more coordinated policies to support, guide or even steer medical innovation. This may take the form of disease-specific missions (such as reducing antimicrobial resistance) or industrial strategies (such as supporting domestic firms or seeking to attract foreign direct investment). These will rely on carefully designed policy instrument mixes, and may even address specific niches – such as antimicrobial resistance, chronic diseases, paediatric medicine or ATMPs – which may have their own challenges and innovation dynamics. Box 1 uses the case of ATMPs to provide an illustration of a dedicated policy instrument mix to address a specific set of challenges that emerge with new technological possibilities. This will require large, expensive and long-term commitments, however, with non-trivial questions around what kinds of governance requirements may be required for successful outcomes.

- This review has also demonstrated the many choices of policy instrument, although evidence of their evaluation is often lacking. Thus, policy-makers should not expect there to be a well-developed evidence base for some families of policy instruments because these have simply not been widely used. Instead, there is an opportunity to tie robust evaluation to policy experimentation to help build the evidence base and share lessons learned, bearing in mind idiosyncratic political economy and circumstantial conditions that vary in each country and point in time. Moreover, a continuous monitoring, review and adjustment process is recommended to course-correct policies/policy mixes.
- Policy-makers can use the frameworks presented to perform gap analysis on existing innovation systems to understand gaps in policy support for medicine developers. This will help to indicate those policy instruments that could be used in a given country, region or context. The mapping will necessarily need to be done in the context of the desired outcomes, rather than as a "blank canvas" exercise, and would require identification of relevant/applicable policies and gaps/opportunities.
- Policy-makers can then look at opportunities to improve the policy framework, according to the strategic priorities and desired outcomes specified by the government, by selecting new policy instruments that are complementary and that address barriers, weaknesses and identified gaps. There remain important points of consideration to further determine which policy instruments should be used in a particular context, however, and how these instruments can be configured, implemented and combined to address local needs.
- Policy instruments need to be costed, as far as possible, and financial commitments made to support their design, launch, implementation and review, as well as for evaluation, adjustment and completion. Financial and human capacity/resource are essential to consider when designing policy instruments. Moreover, local research and evaluation will be needed to provide the evidence to determine the appropriate course of action for a particular context.
- Policy goals can be at odds with each other. Some may have focus on attracting foreign direct investment, job creation and encouraging innovative capabilities that may lead to increased exports or improved health care. Others may focus on improved cost–effectiveness of health-care spending or more affordable access to medicines. There may be trade-offs in meeting these goals, as one configuration of policy or mix of policies may be optimized to achieve one goal but not another.
- Tensions between policy goals should ideally be identified prior to launch, or at least acknowledged with risk mitigation approaches considered to ensure that one goal is not undermined by another and/or ideally to help divergent policy goals become complementary.
- Demand is critical for shaping interest by companies, and demand-side interventions are often under-represented in the medical innovation policy literature (as highlighted in Table 1). Global health interventions show that

demand-side innovation policy instruments are effective, and that policy-makers should place more emphasis on developing approaches to ensure that:

- underserved areas are known to the R&D and innovation community;
- the sizes of markets are well understood; and
- buyers/payers send effective signals of interest; have ability to pay on an ongoing, timely and regular basis; have capacity to select products systematically and according to recognized norms and processes; and can negotiate or set prices, among others.

- Policy-makers have the opportunity to move beyond the simple push/pull (supply/demand) framing of policy interventions that has been prevalent in the discourse around medical innovation. They can include more focus on communication, collaboration and coordination, leading to system strengthening and stewardship/governance, in order to support most fully those medical innovations that address societal needs.

Finally, it is important to highlight that a number of factors could be enablers or could constrain the effectiveness of particular policy instruments in different contexts. While examining these factors systematically was outside the scope of this technical report, several factors should be considered, including:

- the level of appetite locally for long-term versus short-term policy impacts;
- the level of prioritization given to health care and medical innovation over other priorities;
- linked to this, national demographics, wealth inequalities and associated disease burdens;
- the availability of funding for policy instruments;
- national prominence in global markets (associated with market size and profitability, ease of doing business);
- attractiveness for foreign direct investment – linked to the point above;
- capabilities for local policy design and implementation, including support for relevant agencies with experience;
- openness to consultation/evaluation and policy learning.

4.3 Limitations of this study

The framing of this study brings with it a number of limitations that need to be acknowledged. The design of the method used sought to identify and present a diversity of policy instruments, based on the mechanisms they target, regardless of their level of usage to date. The approach taken was to synthesize reviews of policies and policy

instruments discussed in the published peer-reviewed and grey literature. However, the published literature that discusses instrument use may not reflect actual usage levels internationally. Some practices will not be published (or perhaps publications on these will not be found). Some policies will also be discussed in publications but not implemented. There will therefore potentially be divergence between the report's findings and policy practice.

It is also likely that, in this dynamic field, some more recent policy instruments have been unintentionally overlooked. It is also possible that others will soon emerge, especially in the light of the COVID-19 pandemic – which has led to the use of a range of instruments to stimulate innovation that were underutilized until now, such as advanced financial guarantees from governments or patent pools/voluntary licensing from medicine developers – although the pandemic's lessons may relate to quite specific market conditions. Periodic replication of this review is encouraged to provide stakeholders with up-to-date information on potential policy instruments.

Given the variability between contexts, this report has not sought to provide an evaluation of instruments in terms of their suitability or level of effectiveness – because their performance will vary – and, indeed, the suitability of these instruments could be appraised very differently by stakeholders exploring them from different perspectives.

Although the authors have taken steps to ensure that the study does not simply reflect the policies used in the Europe Union or the United States, there is undoubtedly likely to be a bias towards sources written in English; as a result, some important contributions in the non-English language literature will have been missed. It is possible that some conclusions that policies are not being used have been drawn because such policies are simply not reviewed in the sources drawn upon.

Finally, the heavy emphasis on "push" and "pull" in the literature reviewed is partly the result of the search strategy used, which uses these terms as keywords. Yet this is in itself a result of the authors seeking to ensure that a prominent part of the literature was captured. Other actions were taken to try to mitigate this potential bias; for example, much of the grey literature was not picked up by keyword search, but by a search for institutions known or expected to have policy reports on medical innovation – although these too contribute to the push/pull dichotomy.

4.4 Opportunities for further research

Two areas of evaluation appear to require further research to advance the application of the policy instruments discussed in this report. The first is product-related evaluation. Some of the policy instruments reviewed seem to require good information on potential cost/benefit ratios of products for their implementation in advance of decision-making, and this is often difficult for governments to assess. Modelling in this domain requires detailed and expert multidisciplinary analysis, while the outcomes of such calculations are highly political, as future investment may be contingent on these calculations. There may be suspicion of new methods, too. Yet, data are needed to support investment decisions, and will be lacking without accepted methods and funding for studies.

The second area of evaluation relates to the performance of policy instruments. The mini-reviews found a lack of evaluations of policy instruments in some contexts; when considering that the results of these studies are sensitive to their context, the paucity of relevant data to inform implementation is likely to be even more acute.

Given the complexity of policy interventions as part of a dynamic innovation system, evaluations on the impact of policy instruments may be difficult to perform. Evaluation is especially difficult over the short term, and particularly where instruments affect all the targeted actors in a system (as opposed to allowing a "treatment" of some projects or organizations and not others – providing evidence of a counterfactual).

It can also be difficult to evaluate the effectiveness of single instruments that perform as part of complex policy mixes, while it is even more tricky to assess the performance of mixes of policy instruments, and prospective appraisal of policy instrument mixes are rare *(38)*.

These difficulties highlight the need for more development of approaches to support evaluations that can provide acceptable forms of evidence for policy-makers. Given the high costs of medical research, and the importance of the issue, it may be justified to undertake more formal appraisal of policy instrument mixes, prospectively and retrospectively, at the national level, while taking care to involve a diverse range of stakeholders. Such studies may inform decision-makers about the current needs of the local system, potential policy implementation problems and policy interaction effects and evaluation. They may also provide opportunities for learning how to enhance the performance of policies and the innovation system as a whole.

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ANNEXES

Annex 1.
Search strategy for section 2 on wider innovation policy instruments

Section 2 provides a series of perspectives drawn from a wider peer-reviewed literature on innovation policy instruments as a basis for classification of policy instruments relevant to medical innovation. This review is based on publications identified by the following search strategy:

1. Given the objective of the review and the enormous literature on "innovation", "innovation systems", "innovation policy" and "innovation policy mixes", the starting-point were papers with the phrase "innovation policy instruments" in the title, regardless of any sectoral focus.

2. The inclusion criteria were papers (in English or Spanish), published from 2000 onwards, with references to multiple innovation policy instruments under some general perspective/framework/classification. Papers looking only at just a single specific innovation policy instrument without reference to any wider framework were excluded.

3. A semi-systematic approach was used to extract the following relevant information from each of the selected papers, in an Excel document (in this order): reference number; title; authors; journal/source; publication year; paper's stated objective; terms used for innovation policy instruments and their definitions; and whether it focuses on a specific sector (e.g. environmental policy instruments) or applies generally.

4. The search strategy was carried out using Web of Science on 24th February 2021, and further references were identified via 'snowballing'.

The authors identified 74 papers as potentially relevant, and after reviewing the abstracts, 41 papers were considered for review. Given the limitations of our search strategy, a conscious effort was made to follow any specific references from these 41 papers that explicitly stated the use of other frameworks or general overviews published (and not included in the original list of papers), identifying a further eight papers via this 'snowball' method. One further paper with which the authors were familiar, which was not picked up in the literature review (because it did not contain the words "innovation policy instruments" in the title) was added, given its relevance. In total, 50 papers were included to review in full. Nine were excluded following full text review for various reasons, including if they were deemed not relevant, if they provided instrument types without describing a framework, if they were not available in English or Spanish, or if the full text was not available.

Annex 2.
Search strategy for section 3 on policy instruments to encourage medical innovation

Section 3 provides a review of policy instruments that have been discussed in relation to medical innovation in recent years. This review is based on sources identified through two distinct approaches seeking to capture relevant instruments from sources identified in the peer-reviewed literature and grey literature. This strategy ensures a high chance that any given type of relevant instrument can be identified and included in the review.

Instruments are included regardless of their level of usage in practice, their prevalence in the literature or geographic perspective. Policy instruments were excluded from this section if they did not focus on medical innovation.

Peer-reviewed literature

A search was performed on 20 May 2021 using Web of Science, for peer-reviewed publications published since 2000 up until the present. A combination of phrases was used, with innovation, policy, medicine, drugs, push, pull, incentives and business model used as keywords. Table AB1 summarizes the hits obtained under each search.

Table AB1. Search terms and hits: Peer-reviewed literature.

Search terms in TITLE ONLY	Number of hits
Innovation policy medicine*	8
Innovation policy drug*	31
Push Incentiv* drug*	2
Pull Incentiv* drug*	4
Push Incentiv* medicine*	0
Pull funding	36
Business model* drug*	20

Search terms in TOPIC	Number of hits
Pull Incentiv* drug*	54
Push Incentiv* drug*	79

Source: authors' analysis from Web of Science, 20 May 2021

Abstracts were then screened, with the following inclusion criteria:

- The source provides an overview of policy instruments for medical innovation.
- The source may be focused on one/reduced group of specific instruments, while still providing some overview/narrative of other instruments.

Studies were excluded for not describing policies in detail, and for focusing on generic medicines, which fall outside the scope of this review.

Three additional (peer-reviewed) sources were included through snowballing because they were mentioned by other papers and provided good overviews. In total, after excluding non-relevant papers and duplications, 54 papers were selected for inclusion.

Grey literature

A targeted approach was used for the grey literature, directing the search towards websites of organizations which might include relevant material for the report's purposes of identifying different policy instruments to encourage innovation in the form of new medicines. For this reason, a two-pronged approach was used for the search strategy: (i) internet search engine (Chrome anonymous browser for de-personalized Google search without geographical bias) and previous authors' knowledge to identify organizations that publish documents relevant to the research question, and (ii) targeted website searching of the organizations identified from the first step. For each search strategy, different combinations of two sets of keywords, "innovation, policy, medicine" and "policy, incentive, medicine" was used.

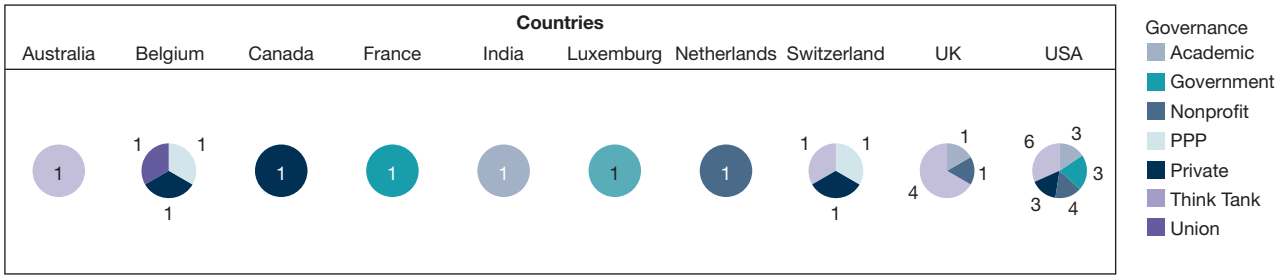
In the first step, a total of 39 organizations were identified. For the second step, their websites were searched using similar combination of keywords as with the peer-reviewed literature, to identify press releases, news, stories, essays, events, multimedia, projects and others that discuss innovation policy instruments for medicines. The applied search strategy included phrase searching, truncation, wildcards and proximity operators. Search terms used a combination of keywords. For six organizations, direct reports on the research topic were retrieved without using the keywords.

The same inclusion criteria were used as with the peer-reviewed literature (see above). When a very large number of hits was retrieved, the search was limited to the highly ranked hits, following manual screening to determine relevance. 50 references were included for further review.

The geographical location of the organizations publishing the reports above was mapped to understand which countries are active in devising and reviewing innovation policy instruments. Organizations were also categorized according to their governance, under one of each of the following options: government-led, think-tank, not-for-profit,

public–private partnership (PPP)-led, academic, or 'union', which refers to the European Commission. It should be noted the categorization of the organizations is based on authors' interpretation of the information contained in their respective websites. Most of the organizations included in the review are located in the United States and United Kingdom. Authors identified that a large fraction were think-tanks, followed by private and not-for-profit organizations. These characteristics are depicted in Figure A2.1.

Figure A2.1. Country-wise number of organizations found in grey literature and their governance



Governance (color) broken down by Countries.

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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