Review article

Are new models needed to optimise the utilisation of new medicines to sustain healthcare systems?

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Abstract

Introduction: Medicines have made an appreciable contribution to improving health. However, even high income countries are struggling to fund new premium-priced medicines. This will grow necessitating the development of new models to optimise their use. **Objective**: Review case histories among health authorities to improve the utilisation and expenditure on new medicines. Subsequently, use these to develop exemplar models and outline their implications. **Challenges and proposed models**: A number of issues and challenges have been identified including the limited innovation level of new medicines alongside increasing requested prices for their reimbursement especially for oncology, orphan diseases, diabetes and HCV. Models centre on the three pillars of pre-, peri, and post-launch including critical drug evaluation and multi-criteria models for valuing medicines for orphan diseases alongside potentially capping pharmaceutical expenditure **Discussion**: Proposed models which involve all key stakeholder groups are critical for the sustainability of healthcare systems or enhancing universal access. The models should help stimulate debate as well as restore trust between key stakeholder groups.

Introduction

Medicines have made an appreciable contribution to improving the health of patients and their survival (1-3). However, we are now seeing even high income countries struggling to fund new premium-priced medicines including new therapies to treat patients with cancer (4-9). Unless these problems are addressed, the number of struggling countries will grow driven by factors including changing demographics, increasing prevalence of non-communicable diseases (NCDs), rising patient expectations and the continued launch of new premium priced technologies (10-20). New medicines increasingly include novel biological drugs (21), often priced at between US$100,000 - US$400,000 (Euro74,000 – 296,000) per patient per course or year (8, 10, 18, 22, 23). The challenges of funding new premium priced medicines are augmented by lobbying, marketing and other strategies among pharmaceutical companies, including influencing guidelines to accelerate the uptake of new medicines (24-32), despite the imposition of multi-million dollar fines (33-36).

Challenges to be addressed include adequately dealing with demands for premium prices for new medicines with often limited health gain versus current standards including those for cancer and orphan diseases (23, 37-39). Funding new effective treatments for patients with hepatitis C virus (HCV) is a also growing concern given its prevalence and requested prices for new treatments (6, 14, 40). In some cases, concerns arise with patient safety when new medicines are used in a wider and less well-defined population than those enrolled into Phase III clinical trials (41). This was seen with the TNF alpha inhibitors when treating patients with immune diseases including rheumatoid arthritis as well as dabigatran in the prevention of stroke in patients with atrial fibrillation (41, 42). There has also been a lack of quality indicators for new medicines to optimise their prescribing (43). These various issues undermine the continued provision of equitable and comprehensive healthcare in Europe as well as the potential for universal healthcare coverage in countries striving for this (43, 44). This has resulted in several initiatives across countries to address this. Initiatives include the development of new models to optimise the managed entry of new medicines, instigating of registries to monitor the effectiveness and/ or safety of new medicines in routine clinical care, capped budgets, exploring the potential for differential pricing for new medicines as well as the development of multicriteria decision matrices for valuing new orphan medicinal products (OMPs).

Consequently, the principal objective of this paper is to review ongoing and planned activities among health authorities to address these challenges to provide future guidance. This will primarily be a descriptive review of case histories based on the considerable experience of the co-authors. Whilst this review is mainly aimed at medium high and high income countries, the models and other suggested activities are highly relevant to low and middle income countries as they tackle even tougher challenges with providing access to important new medicines and limited studies to date to guide their activities (45).

We recognise that health authorities must also seek ways to release additional resources to fund new valued premium priced medicines and increased drug volumes. Activities involve generic medicines (46-48), including ways to obtain low prices for good quality generics as well as increase their utilisation versus originators and patented (single-sourced) products in a class (48-52) They also involve appraising medicines and other technologies that should be discontinued (53-56) as well as potentially reviewing funding for the off-label use of medicines where there is robust evidence that they can act as alternatives to patented medicines, e.g. replacing the use of ranibizumab with bevacizumab to treat age-related macular degeneration (57-59). However, these activities are outside the scope of this paper.

Current challenges in optimising the use of new medicines

The challenges will be presented under two broad themes. These are: (A) valuing new medicines including disease areas where there are concerns with the budget impact; (B) Case histories of medicines where there are concerns with their effectiveness, safety or both.

A) Valuing new medicines

i) General

Only a small number of new medicines can be classified as innovative. Prescrire, a critical independent drug information journal, believed only 2% of new medicines or new indications for existing medicines in France were innovative and/ or offered a real therapeutic advantage over existing treatments despite the hype (Table 1). Most new medicines or new indications were seen as possibly helpful or similar to existing treatments (38).

Table 1 – Percentage ratings by the independent drug information journal Prescrire of the level of innovation of new medicines and new indications introduced in France between 2006 to 2011 (38)

Prescrire ratings/ criteria	2006	2007	2008	2009	2010	2011
Total number of new medicines/ new indications	**135**	**141**	**120**	**104**	**97**	**92**
Innovative medicine/ real therapeutic advance	1%	2%	0%	0%	1%	0%
Offers an advantage over current standards	6%	10%	5%	3%	3%	3%
Possibly helpful, minimal or no clinical advantage compared to existing standard treatments	74%	75%	68%	73%	73%	72%
Others including not seen as acceptable, including safety concerns, and judgement reserved due to for instance insufficient data from clinical trials	19%	13%	27%	24%	23%	25%

There were similar findings in other countries. Of the 217 approvals by the Australian Therapeutic Goods Administration between 2005 and 2007, only seven were rated as important therapeutic innovations (60). In Belgium, only 67 of 824 new medicine applications submitted to the authorities for reimbursement considerations between 2002 and 2004 claimed added therapeutic value, of which only half were eventually granted added therapeutic value by the Belgium authorities (61). Finally, since the mid-1990s, independent reviews have concluded that approximately 85-90% of all new medicines provide few or no clinical advantages for patients versus existing standards (37, 62).

The pharmaceutical industry relies heavily on incremental innovations, which can be called 'me-too' drugs, to sustain their profits (63). It is argued that since incremental innovations can be medically beneficial and should be encouraged (63). However, this will increasingly depend on requested prices given increasing pressure on resources (18, 39, 64). In addition, this will depend on available evidence with concerns with assessing the level of innovation of new medicines where only a placebo is used as the comparator (65, 66). This is leading to recommendations for more comparative data as well as longer term outcome rather than surrogate data to consolidate assessments of the value of new medicines (67).

The low level of innovation of most new medicines is leading to a more critical assessment of their value. This will continue.

ii) New treatments for cancer

Prices of new cancer medicines have increased up to ten-fold during the past 10 years, with prices likely to continue rising as most new cancer drugs are launched for targeted indications, with manufacturers typically seeking orphan status with associated high prices (19, 68, 69). This is a concern with expenditure on oncology expected to reach over US$100billion (€74billion) in 2017 and US$173 billion in 2020, up from US$83 to 88billion in 2016 (€62 - €66billion), limited correlation between resources spent on cancer care and mortality rates (69, 70), and new medicines to treat patients with cancer typically costing between US$6,000 to US$ 10,000 (€4,500 – 7,500) per month, often with little relationship between reimbursed prices and associated health benefit (18, 22, 69), e.g.:

- Of the 12 drugs approved by the FDA in the US for various cancer indications in 2012, 9 were priced at more than US10,000 per month with only 3 prolonging survival, two of them by less than 2 months (39)
- In renal cell cancer, 7 targeted therapies were approved in the US between 2005 and 2012. These include sunitinib (2006), everolimus (2009), pazopanib (2009) and axitinib (2012). All improved median progression-free survival (PFS) in the range of 3 to 6 months. However, this was associated with minimal or no improvement on overall survival times, at a cost of US$70,000 to US$140,000 (€52,500 to 105,000) annually (39).

A different challenge is seen with trastuzumab emtansine (KADCYLA), which is an antibody–drug conjugate combining trastuzumab with the maytansinoid emtansine, a potent microtubule-disrupting agent (71, 72). Trastuzumab emtansine has an estimated incremental cost/ QALY up to GB£185,600

(€ 235,000) due to a median increased survival of 5.8 months compared with standard treatment in HER2 positive patients with metastatic breast cancer no longer responding to the combination of trastuzumab and a taxane (8), and a cost of GB£90,000 (€114,000) per course (8, 73, 74). Other authorities though have calculated lower cost/ QALYs depending on the choice of comparator (73). In any event, this is considerably higher than trastuzumab alone even considering estimated costs of US$60 – 90 million (GB$36 – 55 million) for the development of new (successful) medicines (18, 22, 75), although other authors have quoted higher figures (76). Development costs may be lower than this for trastuzumab emtansine as this builds on an existing technology.

Challenges arise if pharmaceutical companies subsequently use the cost/ QALY for trastuzumab emtansine if reimbursed as a basis for future submissions. Media reports indicate the manufacturer may be putting pressure on European countries to reimburse trastuzumab emtansine at these prices by playing them against each other (77). There are also challenges to health authority budgets with annual peak sales for trastuzumab emtansine estimated at US$2 billion to US$5 billion (€1.5billion to €3.7billion) (78). This builds on global sales of trastuzumab alone at CHIF6079 million (GB£ 3985million, Euro5050million) in 2013 up from CHIF 5889 million in 2012 (79). Health authorities are aware that the prices of oral small molecules can be as low as 2% to 4% of originator prices (80-82), although cost-of-goods will be higher for biological products. In addition, they are aware pharmaceutical companies do spend appreciable monies on their marketing activities (28, 83). Consequently, it is likely health authorities will increasingly challenging companies on their pricing strategies for new oncology treatments as resource pressures grow (22). This will result in new cancer medicines increasingly being grouped with other new medicines for reimbursement considerations.

ii) New treatments for patients with hepatitis C virus (HCV)

As mentioned, funding new effective treatments for patients with HCV is a growing concern with more than150 to 185 million people worldwide believed to be infected with chronic HCV, high cure rates with second generation directly acting antivirals (DAAs) and associated costs (6, 14, 84, 85). For instance in Malaysia, the prevalence of HCV is estimated at 1.5% of the population (86). The primary goal of treatment is to cure the infection, defined as a sustained virological response (SVR) (14, 40, 87). Previous treatments have included pegylated interferon and ribavirin and more recently bocepravir and telapravir, first generation DAAs (6, 14). However particularly pegylated interferons and ribavirin caused serious side-effects in more than 80% of patients, resulting in less than 50% of patients completing the treatment course (6). Cure rates of up to 95% are now seen with second generation DAAs, sofosbuvir and semiprevir, providing shorter treatment courses as well as reducing side effects compared with current treatments (6, 14, 40, 87). Sofosbuvir combined with ledipasvir (HARVONI) has also achieved high cure rates with almost universal viral clearance after 8 weeks without the need for either pegylated interferons or ribavirin (84, 85).

However a 12 week course for sofosbuvir costs GB£ 35,908 to 71,816 (€45,235 – 90,470) depending on the genotype (40). The much quoted price in the USA is US$1000 per pill equating to US$84,000 (€63,000) for a standard course; however prices per course can be as low as US$900 in Egypt and some developing countries (6, 88). Prices for sofosbuvir combined with ledipasvir are similar at US$94,500 per 12 week course (89, 90). Sales of sofosbuvir were US$2.8billion in the third quarter of 2014, with sales of the second generation DAAs likely to appreciably increase with further launches (90). It has been calculated that if all 3 million people estimated to be infected with HCV in the USA are treated with second generation DAAs, annual spending on all prescription drugs will double from approximately $300 billion currently (6, 88). Uptake is likely to be more gradual than this though and expenditure is likely to fall in the future with an appreciable number of patients cured with the second generation DAAs.

iii) Funding new treatments for patients with diabetes

Funding new premium priced medicines for patients with diabetes is also a growing concern among health authorities with estimates that by 2035 nearly 600 million people world-wide will have diabetes and almost 500 million at risk for the disease (91). Diabetes, including its complications, is one of leading causes of deaths worldwide (16, 91). Morbidity and mortality rates alongside health care spending, which currently accounts for approximately 11% of total healthcare spending (91), will grow if not addressed (90). The increasing prevalence of patients with type 2 diabetes (T2DM) has

stimulated research into new treatment options, which now include α-glucosidase inhibitors, thiazolidinediones, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase inhibitors (DPPs or gliptins), sodium glucose co-transporter 2 (SGLT2) inhibitors and modified insulins (92, 93). As a result, global expenditure on medicines to treat patients with diabetes is estimated to reach US$48 to 53bn in 2016, with similar figures in 2017 (94, 95).

However, most guidelines recommend prescribing newer treatments as third line following metformin monotherapy and combinations of established agents, due to a lack of comparative effectiveness studies and given their considerably higher costs (96) . There are also concerns that the gliptins, e.g. saxagliptin, sitagliptin and vildagliptin, appear to have no proven efficacy on the complications of diabetes whilst adverse effects include immune disorders, pancreatitis and hypersensitivity reactions (97). Given the rising prevalence of patients with T2DM and the lack of robust data for the newer anti-diabetic medications, health authorities need to monitor their use and effectiveness in reducing micro- and macro-vascular complications. It is also important that health authorities focus on preventative measures that have been shown to be effective in controlling T2DM and related complications (98, 99).

iv) New medicines for orphan diseases

New orphan medicinal products (OMPs), some costing over €1 million per patient per year (20, 23, 100), are also putting pressure on healthcare budgets, especially with some OMPs achieving blockbuster status (9, 100, 101). This increases the debate whether pharmaceutical companies should also consider social good alongside financial returns (20), and whether health authorities should be more critical when assessing the value of new OMPs.

Expenditure on OMPs has been influenced by few marketing authorisation and reimbursement hurdles at requested prices (9, 102-107). However, this is changing with managed entry agreements increasingly needed for successful reimbursement. The use of multi-criteria decision matrices is also in development among European health authorities and other key stakeholder groups to address increasing concerns as well as reduce the evidence gap between countries for successful reimbursement (102, 108). These concerns are illustrated by the considerable controversy surrounding the reimbursement for enzyme replacement therapy for the symptomatic treatment of Fabry disease in the Netherlands at an incremental cost/ quality adjusted life-year of €3.3 million (9). The reimbursement body argued that continued reimbursement would reduce available resources for other, more cost effective, health technologies (9). A similar situation was seen with alglucosidase alfa to treat Pompe's disease at an estimated cost/ QALY of €0.3–0.9 million for the classic form up to €15 million/ QALY for the non-classic form (9). The draft advice was leaked prior to its official release, leading to vocal opposition and pressure on the Ministry of Health to ignore the advice (9).

A similar situation was seen in Lithuania with galsulfase (Naglazyme®) for the management of patients with for mucopolysaccharidosis VI. Whilst long-term treatment has been shown in studies to reduce progression and morbidity (109), currently funding all 10 patients in Lithuania with this condition would represent 17% of the total in-patient budget for medicines and medical aids and 3% of total reimbursed ambulatory care pharmaceutical expenditure. Pressure is being placed on the Ministry of Health and Health Insurance Fund to reimburse galsulfase for these patients despite concerns with its value.

A different challenge is seen with ivacaftor, which is a new medicine for the treatment of 5% of patients with cystic fibrosis (CF) who carry the genetic mutation G551D (20). Ivacaftor was granted reimbursement in the UK at a cost/ QALY, after an agreed discount, of £285,000/ QALY (€360,000) to £1.077million/QALY (€1.36million) (104). Ivacaftor's pricing strategy of $294,000 (€220,000)/ patient/ year for life was based on perceived similar prices for other treatments for rare diseases (110). Its use is likely to grow in patients with other genotypes as well as with potential combination with lumacaftor (111-113). The decision by the NHS Commissioning Board to recommend funding put pressure on Scotland, which resulted in funding despite advice from the HTA agency not to recommend use (104, 111, 114). This also caused a domino effect on Wales and Northern Ireland. In Australia, the manufacturer and patient groups are putting pressure on the government to fund ivacaftor, especially following a proposed managed entry agreement (115). If funded, this could result in companies

seeking funding for their new OMPs at similar cost/ QALYs, exacerbating future challenges across countries.

B) Case histories where concerns with the effectiveness, safety or both of new medicines

i) Transplantation therapies (Brazil)

Brazilian guidelines recommend that the principal medication used to prevent rejection following renal transplantation is ciclosporin, with concomitant azathioprine and corticosteroids (116). Alternatively, ciclosporin can be replaced by tacrolimus and azathioprine may be replaced by mycophenolate mofetil or sirolimus. However, it is currently unknown whether there are differences in renal graft and recipient survival rates between the different regimens especially with limited follow-up in Phase III trials. Studies have reported increased initial survival among transplant patients receiving a tacrolimus-based therapeutic regimen when compared with those receiving ciclosporin-based regimens. However, long term studies have not uniformly confirmed this apparent advantage of a tacrolimus-anchored immunosuppression regimen.

This information gap was narrowed by researchers in Minas Gerais, Brazil, performing an historical cohort case controlled study among 5686 patients who underwent renal transplant and received either ciclosporin or tacrolimus. A higher risk of treatment failure was associated with tacrolimus (HR 1.38, 95% CI 1.14 to 1.67), higher patient age at transplantation, donor types, median time of dialysis prior to transplantation, and diabetes as a cause of chronic renal failure (CRF) (116). After adjusting the model for possible confounding factors such as sex, age, graft origin, prior time of dialysis, and cause of CRF, the authors concluded that the risk of treatment failure of patients receiving tacrolimus was 1.38 times that of patients receiving ciclosporin - thereby justifying the continued recommendation of ciclosporin as first line treatment in these patients (116).

ii) Dabigatran to prevent stroke and systemic embolism/clot formation in adult patients with non-valvular atrial fibrillation (pre- to post-launch)

Concerns with the safety and the potential budget impact of dabigatran when prescribed in more elderly co-morbid populations that those recruited into Phase III clinical trials (13, 41, 117). These concerns resulted in a number of professional bodies and health authorities initiating extensive pre- and peri-launch programmes, some of which are listed in Table A1 (Appendix). These tactics were also driven by the manufacturer failing to share relevant information about the potential benefits of monitoring anticoagulant activity, and adjusting doses with physicians, to reduce possible major bleeds post-launch (118, 119).

iii) TNF alpha inhibitors in patients with rheumatoid arthritis

A range of studies have been undertaken across countries to assess the effectiveness and long-term safety of the TNF (tumour necrosis factor) alpha inhibitors in patients with rheumatoid arthritis due to concerns with their safety and value at launch . Two examples of healthcare initiated programmes are included in Table 2.

Table 2- Healthcare post-launch programmes to study the effectiveness and safety of patients with rheumatoid arthritis treated with biological medicines

Country	Study and findings
Italy(120)	• The objective of the study was to evaluate 4-year retention rates of TNF-α inhibitors adalimumab, etanercept, and infliximab among patients with long standing rheumatoid arthritis (RA) using the GISEA registry • Persistence over the 4 years was lower than 50%, with etanercept having the best retention rate • The main positive predictor of patient adherence was the concomitant use of methotrexate • The study also provided evidence that the management of patients with RA in the clinic may well be different from RCTs

Sweden ARTIS (Anti Rheumatic Therapies in Sweden) (42, 121)	• A study group of all rheumatology clinics in Sweden with high patient involvement in data catchment showed:
	  ○ RA patients treated with biological drugs are not at increased risk of invasive melanoma
	  ○ RA patients selected for TNF alpha inhibitor treatment are not at increased overall risk for cancer but have a 50% increased relative risk of invasive melanoma
	• Given the small increase in absolute risk, the authors concluded these findings do not shift the overall risk-benefit balance of anti-TNF alpha inhibitors in clinical practice, but might do so in patients at high risk of melanoma for other reasons

A retrospective review of the use of anti TNF alpha inhibitors in patients in Austria with ankylosing spondylitis showed that whilst patients were treated most often with adalimumab, patients on etanercept showed the lowest switching rate and the longest 1- and 2-year retention rate (122).

iv) Effectiveness and cost-effectiveness of new medicines post launch (US)

Drug utilisation studies are increasingly being undertaken in the USA to assess the cost-effectiveness of new medicines in clinical practice as part of formulary decisions. The introduction of health care reforms, and a significant focus on specialty pipeline medicines and their increased identification (123), is reinforcing the focus on the appropriate care of these patients.

Models are being created that look at comparator products in therapeutic class combined with their costs, including pharmacy and medical costs, to identify differences in the clinical outcomes of the different therapies and their associated costs. This includes comparing new medicines with established standards and determining the most appropriate clinical end points. The models developed by managed care organisations typically focus on overall cost and event reduction including reduced hospitalization, emergency room visits, and per member per month (PMPM) costs.

These approaches also provide insight into potential models for different member populations to improve care in the future within finite resources with the increase in accountable care organisations.

Proposed models and advice to optimise the utilisation of new medicines

i) Proposed model (general)

These examples illustrate the need for a comprehensive model to optimise the clinical uptake and safety monitoring of new medicines as well as their costs post-launch. This approach requires closer collaboration between researchers, policy makers and pharmaceutical companies as well as the development of critical drug evaluation skills among all key stakeholder groups and a defined role for experts and professional groups such as clinical pharmacologists, clinical pharmacists and health economists, working with health authorities in the development of robust treatment guidance pre- and post-launch of new medicines (124-128). This close collaboration between pharmacotherapeutic experts, clinical pharmacologists and other key stakeholder groups is seen as essential to maintain high standards of evaluations and recommendations.

The proposed model starts pre-launch (Figure 1). Pre-launch activities incorporate horizon scanning and potential budget impact analysis as well as starting to develop potential quality indicators for new medicines. Peri-launch activities include critical drug evaluation, cross-discipline guideline development as well as pricing and reimbursement deliberations (41, 43, 129-134). It is envisaged health authorities will become more critical in their reimbursement deliberations for new medicines given concerns with the limited health gain of most new medicines alongside ever increasing requested prices and their associated budget impact. Post-launch activities include assessing the effectiveness, safety and value of new medicines in clinical practice especially if patients in clinical practice will be older and more co-morbid than those enrolled into Phase III studies (135, 136). They also include assessing prescribing against agreed guidance and in line with any developed quality indicators, and subsequently instigating additional activities including educational initiatives if needed.

Figure 1 – Proposed model to optimise the managed entry of new medicines (adapted from references (41, 137)

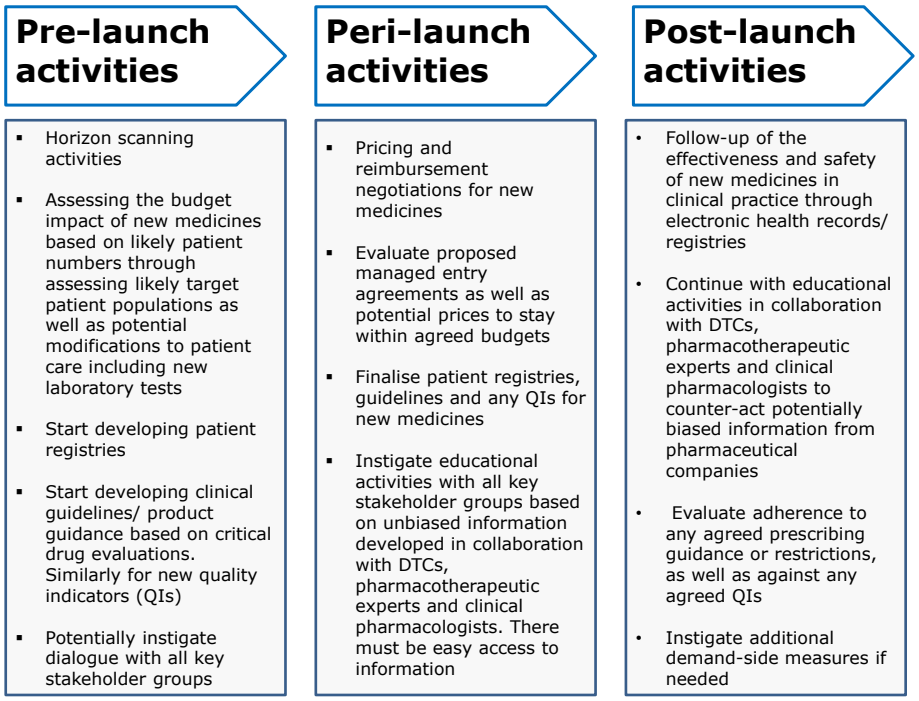

Table A2 expands on potential activities pre- to post-launch (Figure 1). New Zealand, Poland and Turkey provide guidance on potential ways to keep expenditure on new medicines within agreed limits (below).

Quality indicators (Figure 1) are increasingly used as a method to help achieve safe and quality clinical care, cost-effective therapy, for professional learning, remuneration, accreditation and financial incentives. A substantial number focus on drug therapy; however, few have addressed the introduction of new medicines (43). A suggested framework and indicator testing protocol among health authority personnel and other interested groups for subsequent introduction into clinical practice has recently been developed (43).

ii) Early dialogue between key stakeholder groups in the development of new innovative medicines (Pre-launch)

There is an increasing need for all key stakeholder groups to interact earlier in the development process for new innovative medicines especially as there are no specific guidelines that combine the requirements of both regulators and payers when assessing the efficacy, safety and potential value of new medicines (128). However, this is beginning to change (67).

As mentioned, Phase III clinical trials are typically conducted under ideal and highly controlled conditions to seek high internal validity (41, 138). However, this may lead to substantial differences from their subsequent use in clinical practice (13, 138). In addition, there can be concerns with surrogate markers, e.g. progression free survival in solid tumours may not always translate into improved clinically relevant or 'hard' outcomes (5, 39).

Consequently, interaction between key stakeholder groups during clinical development to discuss early-stage scientific reimbursement advice should assist with development plans, especially where there are areas of concern including issues of clinically relevant comparators as well as clinical and patient-relevant outcomes (67). This should also help reduce duplication between the requirements of the different government groups as well as build trust between the various groups. This is already happening in Australia and Europe (128, 139), building on initiatives to try and harmonise information requirements between payers and HTA bodies across continents (67).

iii) Capped budgets and other mechanisms to potentially optimise utilisation and funding for new medicines (Peri- and post-launch)

The reimbursement body of New Zealand (PHARMAC) operates within a fixed budget prioritising funding for new medicines on strict criteria including the potential for funding their use in defined sub-populations where their value is greatest (Box 1), balancing funding for the new premium priced medicines against potentially better investments with existing medicines (140-142). There is also the potential for cross-company deals, with PHARMAC agreeing to fund a new medicine at an agreed price in a defined patient population in exchange for the manufacturer lowering the cost of their other listed medicines (140). This in turn may result in a lower reference prices for particular classes as a whole further conserving resources.

Box 1 – New Zealand's key decision making criteria for new medicines (adapted from references (140, 142-144)

- Health needs of all the eligible population with a particular focus on the health needs of Maori and Pacific peoples
- Availability and suitability of existing medicines, treatment devices, and related products
- Clinical benefits and risks of the new medicine in all/ sub-populations
- Cost effectiveness of meeting health needs by funding the new medicine in all/ sub-populations rather than using other publicly funded health and disability support services. There is no set cost/ QALY threshold. However, between the 1998 and 2007, individual new investments made by PHARMAC varied between 25 QALYs gained for every NZ$1 million (Euro623,000) saved by the NZ health sector and less than 5 QALYs gained for every NZ $1 million spent. Expressed as costs per QALYs, investments varied between saving NZ$40,000 per QALY gained (-Euro25,000) and spending over NZ$+200,000 per QALY (Euro125,000)
- Budgetary impact of any changes to the medicine schedule from reimbursing the new medicine at agreed prices in agreed populations
- Direct cost to health service users
- New Zealand government's priorities for health funding
- Such other criteria as PHARMAC thinks suitable after appropriate consultation

A recent comparative analysis of the approval and funding of new drugs showed that only 59 (43%) of the 136 medicines listed in the Australian PBS between 2000 and 2009 were listed in the New Zealand reimbursement l schedule, with listings occurring on average just under three years after Australia (145). This may at least be in part due to the reimbursement body in New Zealandoperating within a fixed budget, prioritising new medicines against each other and against access to all medicines (141, 142).

In Turkey, the Turkish Medicine and Medical Devices Agency is responsible for key areas including licensing, pricing, quality control, pharmacovigilance and clinical drug trials. A reference pricing system has been in existence since 2004 based on the lowest ex-factory price in either Greece, France, Italy, Portugal or Spain as well as the country in which the pharmaceutical is being

manufactured. The Social Security Institution is responsible for reimbursement decisions. Companies must provide evidence demonstrating cost-effectiveness of their new medicine versus current standards to be considered for reimbursement, and are expected to give a discount from ex-factory prices except where retail prices are less than 3.56 TL (€1.24) per dispensed item. At the end of 2009 and 2011, price cuts and discounts were instigated by the Government to keep pharmaceutical expenditure under control. Between 2010 and 2012, a global budget was also implemented to further control pharmaceutical expenditure. This led to additional price cuts for both new and established medicines.

In Poland, the National Health Fund drug budget cannot exceed 17% of the total yearly budget for all sectors. This has resulted in one reimbursement list which is divided into three categories (Box 2), with an economic analysis (typically either a cost-effectiveness analysis or cost-utility analysis) required to assess the potential reimbursement for new expensive medicines alongside a budget impact analysis (146). The economic assessments are undertaken by the HTA agency (AHTAPol) (Box 2), which was established in 2005 in Poland by the Ministry of Health, which became law in 2009 (146).

Box 2 – Categories for the reimbursement list as well as the activities of AHTAPol (37, 41, 146-150)

A) Three categories for the reimbursement list

- An ambulatory care reimbursement list where patient co-payments can vary between 0%, 30%, 50% as well as a lump sum of €0.8 per prescription
- Healthcare programme lists for costly medicines for use in hospitals with strict inclusion and exclusion criteria and no patient co-payments
- Hospital's chemotherapy list.

B) Influence/ impact

- Among the 151 drug technologies appraised between 2007 and 2009 in Poland, 34 medicines were appraised and reimbursed, 117 were appraised and not reimbursed and 29 were reimbursed and not appraised. Even when new medicines are reimbursed in Poland, there can be restrictions, e.g.14 of medicines had major restrictions, 11 had minor restrictions and 5 without restrictions
- The most common restriction was recommendations for prescribing at a lower price and restrictions to specific sub-populations. Restricting reimbursement of premium-priced medicines is also seen in other European countries to contain costs
- Common reasons for rejection included insufficient clinical data, poor efficacy or safety, or an unacceptable cost-effectiveness ratio

- A recent analysis undertaken by the HTA agency (AHTAPol) comparing the outcomes of their recommendations for new antineoplastic medicines issued in 2013 with the reimbursement list officially published by the Ministry of Health in January 2014, found that only 6 of 26 (30%) oncology medicines were included in the reimbursement list, with all of them being positive recommendations by AHTAPol
- Recommendations relating to reassessments, off-label use of medicines or individual treatment agreements were excluded from this analysis
- No new oncology medicine with a negative recommendation appeared on the reimbursement list
- Consequently, it appears that new medicines with negative recommendations will probably not be accepted for reimbursement from public sources in Poland, endorsing the approaches in Poland to enhance the efficient use of resources allocated for new medicines

iv) Models for differential pricing strategies for new medicines (per- and post-launch)

There have been a number of proposals and examples for differential (or tiered) pricing arrangements for new medicines and new vaccines, especially among lower income and developing countries where affordability is an issue (151). This is seen in the differential pricing for sofosbuvir between Egypt and the United Kingdom(6). More recently, the European Pharmaceutical Industry Federation (EFPIA) proposed tiered pricing strategies for countries struggling to fund new medicines provided certain pre-conditions are met (Box 3)

Box 3 – Suggested pre-conditions from the industry federation (EFPIA) to enhance access to new medicines through differential pricing (152)

- Any scheme should be the result of bilateral voluntary arrangements at a national level that protect the confidentiality of any net pricing arrangement
- International reference pricing schemes should be founded on best practices to ensure consistency
- Member States should take the necessary steps to ensure that medicines specifically priced for patient groups who would not otherwise be able to afford them are delivered to those patients and are not otherwise diverted

However, such strategies decrease transparency and increase information asymmetry between pharmaceutical companies and health authorities with production and pricing information typically kept in confidence by the manufacturers (153). There is also currently no systematic global framework on potential pricing approaches for middle-income countries, which can result in protracted and damaging negotiations pitting manufacturers against public health institutions, including health authorities, country-by-country and commodity-by-commodity (153). Such arrangements also amount to more developed countries subsidizing medicines for less developed countries.

Initiatives to increase affordable access to medicines, including low and middle- income countries, advocated in the literature include countries encouraging robust generic competition as well as taking advantage of public health intellectual property flexibilities to enhance competition generally (151, 154). This is because manufacturers do not typically have strong incentives to re-evaluate tier prices in the absence of competition (151). It is recognised though that tiered pricing may be a potential option to meet short-term needs in special cases where affordability to new essential medicines is a major issue. These include situations when market volumes are small and there is currently no competition. However, we recommend steps should be taken to ensure affordability and availability in the long term as well as stimulating competition (151).

v) Initiatives to improve the interface management for drug therapies

Post launch activities increasingly include improving prescribing cohesion between hospital and ambulatory care, with the majority of new biological medicines typically initiated by specialist physicians in hospitals. This is called ‘interface management’, and is increasingly instigated across countries starting with active drugs and therapeutic committees (DTCs) in hospitals (126) (Table 3). Improved interface management can increase the quality of prescribing as well as reduce costs in ambulatory care especially if the prices of new medicines are heavily distorted in hospital through the considerable discounts offered by pharmaceutical companies to increase their prescribing (126, 155).

Table 3 – Strategies to improve interface management (13, 81, 82, 125, 126, 156-158)

Country	Strategy
Scotland	• Mutual list of recommended medicines for primary and hospital care has been present in Scotland in the various regions for over 20 years, with high physician adherence rates to the recommendations • There is active involvement of both ambulatory care and hospital physicians in the regional Drug and Therapeutics Committees (DTCs) and in developing joint recommendations and guidelines to enhance adherence, i.e. no "carte blanche" for specialists, with the formulary guidance applying equally across all sectors. Non-formulary prescribing is permitted but only if it can be justified • Prescribing guidance and guidelines are based on evidence based assessments of the safety and efficacy of medicines with costs an additional factor • Encouraging good communication and development of clinical networks between the sectors as well as the development of electronic information systems as well as educational activities including academic detailing
Spain (Catalonia)	• DTCs in the region have developed and instigated prescribing indicators for new and existing medicines to improve patient care across all sectors as well as cost-effective prescribing • The Catalonian electronic systems permit sharing of clinical data between sectors. This includes the ability of GPs to debate and challenge specialist recommendations where this is seen to contradict advice from the health authority
Sweden (Stockholm Healthcare Region)	• There has been a long tradition of selecting and recommending evidence-based medicines for common diseases in ambulatory care in the Stockholm Metropolitan Healthcare Region (leading to the 'Wise List'), directed by a high degree of involvement of prescribing physicians as well as respected pharmacotherapeutic experts and clinical pharmacologists with scientific training through joint appointments within healthcare and university settings in developing the 'Wise List'. This contains approximately 200 medicines, with a separate list for hospitals • The long term strategy has been to advocate that "each recommended medicine should be of high value to the patient" • Respected specialists, working jointly with clinical pharmacologists, pharmacists and general practitioners in over 20 expert groups, suggest which medicines should be selected and included in the 'Wise List'. Suggestions are subsequently debated by the DTC for potential inclusion in the new 'Wise List' • The recommended medicines are subsequently collated, widely communicated and disseminated each year in different versions for healthcare staff and the public • High physician adherence to this voluntary 'Wise List' when prescribing, reaching 87% of all prescriptions in primary care in 2009, has been achieved through a number of factors. These include physician trust in those developing the prescribing guidance, robust handling of conflicts of interest, involvement of prescribers and drug experts in its development, active dissemination strategies, regular yearly updates as well as regular monitoring of physician prescribing against prescribing guidance

vi) Valuing new orphan drugs – Transparent Value Framework (TVF)

The Transparent Value Framework (TVF) was developed as part of the European project on coordinated access to orphan medicinal products (MoCA) under the platform Access to Medicines (101, 159). Its development arose as a result of the ongoing challenges posed by pricing and funding of the new orphan medicinal products (OMPs) (108), conceived as an aid to the MoCA process by providing a framework for discussions on clinical effectiveness, recognizing that it would be more efficient to avoid duplication of effort for appraising OMPs among the member states.

In particular, it was envisioned that these discussions would lead to an agreement among stakeholders, including payers and pharmaceutical companies, on the therapeutic value of a new OMP, subsequent to discussions between and among key stakeholders on which value (high/medium/low) to assign to which attribute (Unmet need/Degree of net benefit, Response rate, Degree of certainty). Consequently, the development of the TVF through the collaborative process should improve consistency in decision making between European countries, reducing evidence gaps that currently exist. Consequently, the first step to address this critically important issue.

The TVF (Table 4) consists of four elements of value coupled with the extent to which each criterion is met as a basis for price negotiations. It is recognized that the framework is 'indicative, non-prescriptive and non-binding', acknowledging that reimbursement decisions for new OMPs are the responsibility of individual EU Member States (108).

Table 4 - The Transparent Value Framework adapted from (108)

Criterion	Low Degree	Medium Degree	High Degree
Available Alternatives / Unmet Need (defined as the degree to which the new OMP addresses the unmet need over existing therapies). Where no pharmaceutical alternatives exist, other non-pharmaceutical treatment can be used as the benchmark	Alternatives available New medicine does not address unmet need	Alternatives available but major unmet need still exist	No alternatives exist except supportive care, Major unmet need is met
(Relative) Effectiveness, Degree of Net Benefit relative to alternatives including no treatment. Net benefit includes for instance the degree of clinical improvement with the new OMP, including improved Quality of Life (QoL) versus current treatments, measured against the potential side effects from the new OMP	Incremental	Major	Curative
Response Rate (will vary depending on which measure, including surrogate markers and time frames are used as well as the available clinical data)	<30%	30-60%	>60%
Degree of Certainty (defined as the certainty of the claim made by the market authorization holder for their new OMP)	Promising but not well-documented	Plausible	Unequivocal

There is ongoing research to assess the utility of the TVF in practice and make subsequent recommendations to aid future decision making in this critically important area. This may lead to an adaptation of the TVF in the future. In the meantime, potential strategies could include health authorities reviewing the criteria for granting orphan status as proposed recently by Garattini (160).

Discussion

The case histories demonstrate that health authorities are using a number of approaches to optimise the managed entry of new medicines starting pre-launch (Figure1). This also includes valuing new OMPs (Table 4) as well as looking at considerations such as capping budgets for the future sustainability of healthcare systems. This is becoming crucial given increasing prices for new medicines, especially biological medicines, and their potential budget impact. The Pharmaceutical industry is a global industry and often successful market access techniques are replicated across countries. Health authorities must recognise this and develop, test and share approaches among themselves to sustain their future. This resulted in the proposed model to optimise the managed entry of new medicines (Figure 1), which can be used across all countries including developing and emerging countries challenged with both new expensive medicines to treat prevalent infectious diseases as well as increasingly non-communicable diseases (14-16). Instigating this model will require (clinical) pharmacologists, clinical pharmacists, health economists, biostatisticians and other healthcare professionals to improve the critical drug evaluation skills of physicians starting pre-launch and continuing post-launch (13, 126, 161). This approach will help counter-act the influence of pharmaceutical companies where this is a concern (28, 33, 83). The development of these models will also require healthcare systems to invest in independent drug expert competence to ensure a critical mass of available experts and staff to critically evaluate the potential role and value of new costly medicines as well as undertake additional educational activities. Health systems will also need to invest in continuous professional development to improve the knowledge among prescribers and

healthcare staff on how to optimally use medicines including new medicines to balance against the marketing activities of pharmaceutical companies (28, 29, 126, 162-164). Such initiatives will require close collaboration between organisations and establish key roles for DTCs as well as the involvement of therapeutic experts and academics. The use of such personnel has worked well in the Stockholm Healthcare Region with developing the 'Wise List' and achieving high adherence rates (Table 5) (125, 126).. Development of these models (Figure 1) together with improvements in critical drug evaluation skills, including appropriate outcome measures, should also reduce some of the inconsistencies that exists in Europe when authorities assess the relative value of mew medicines (165).

National patient association groups also need to work alongside health authorities pre- and peri-launch to help fully assess potential patient populations for new medicines, especially if there are safety concerns and where the potential budget impact in all proposed patients will affect the sustainability of healthcare systems (13, 166). Such groups may also be employed to develop and disseminate factual information for patients peri- to post-launch (41), thereby helping communicate the rationale behind funding decisions and enhancing the focus on existing evidence-based systems (167).

Finally, it is recognised that maintaining agencies for designing, conducting and evaluating ongoing and future policies and strategies is disproportionately more burdensome for smaller countries than for developed countries with a large base of contributors. On the other hand, some medicines are not made available in smaller markets, due to economic considerations, exacerbating the difficulties these countries face when providing healthcare (168). The cross-border healthcare directive across Europe is also putting pressure on countries to ensure continuity of treatment after patient movement. Ideally, this will require similar quality of health technology assessments for new medicines . Cooperation to evaluate and debate these key issues is ongoing starting pre-launch (67). Organisations involved include EuroScan (133, 169), the Piperska group (who provided the majority of co-authors for this paper (10, 129)), EUnetHTA , which is working on EU-wide collaboration producing product evaluations and the MEDEV group representing the payers. Co-operation is demonstrated by the proposed model to improve the managed entry of new medicines (Figure 1) as well as the initiation of MoCA to develop potential frameworks to value new OMPs (Table 4). Such activities will grow given ever increasing pressure on resources.

Conclusion

We hope we have demonstrated why new models are critical to improve the managed entry of new medicines. Without these, countries will increasingly struggle to fund new premium priced medicines as well as maintain equitable and comprehensive healthcare or achieve universal access. The various models and their implications were discussed to provide exemplars to countries given ever-increasing pressure on resources, and should help restore trust between all key stakeholder groups, which has been diminished in recent years.

Expert commentary and five year review

All countries, even high income countries, will struggle to fund new premium priced medicines in the future driven by a number of factors. These include the launch of new biological drugs at ever increasing prices, including those for cancer and orphan diseases, often with limited health gain versus current standards. The launch of new medicines in diseases of high prevalence, including patients with Type 2 diabetes and HCV, is putting additional pressure on healthcare systems which needs addressing. This has necessitated the development of new models. This includes greater scrutiny over the value of new medicines at requested prices as well as restrictions to sub-populations where they provide the greatest value. It also increasingly includes potentially capping pharmaceutical expenditure. These developments are likely to apply to all new medicines including those for cancer and orphan diseases especially as a number of these products have already achieved blockbuster status. As a result, decrease the difference in evidence gaps that currently exists between countries for reimbursement considerations. However, this must not be at the expense of diminishing research into identified priority disease areas. These developments will require (clinical) pharmacologists, clinical pharmacists, health economists, biostatisticians and other healthcare professionals to improve

the critical drug evaluation skills of physicians starting pre-launch and continuing post-launch. It will also require health systems to invest in continuous professional development.

Key issues

- Medicines have made an appreciable contribution to improving healthcare. However, even high income countries are now struggling to fund new premium priced medicines
- The number of struggling countries will grow unless addressed driven by factors including changing demographics and the continual launch of new premium priced medicines often with limited health gain versus current standards
- High prices are a particular issue for new medicines for cancer and orphan diseases. This includes trastuzumab emtasine and ivacaftor
- Another challenge facing health authorities are the launch of new effective but high priced medicines for hepatits C as well as new premium priced medicines for patients with Type 2 diabetes given the prevalence of both diseases
- Professional bodies including physicians and health authorities have also instigated measures including educational activities, prescribing restrictions and registries where they have been concerned with the effectiveness and/ or safety of new medicines in clinical practice especially when the population is older with greater co-morbidities than patients enrolled into Phase III clinical trials
- Health authorities have instigated a number of measures to address these challenges including developing new models to optimise the managed entry of new medicines. These start pre-launch with horizon scanning and budgeting. Peri-launch activities include the critical evaluation of the role, value and place in therapy of new medicines with post launch activities including evaluating prescribing against guidelines and quality indicators as well as addressing concerns with interface management where these exist. Other activities to optimise pharmaceutical budgets include expenditure caps with trade-offs between prices of new and established medicines as well as the development of multi-criteria matrices to standardise the valuation of new medicines for orphan diseases
- Clinical pharmacologists, clinical pharmacists, health economists, biostatisticians and other healthcare professionals will need to play a key role with improving the critical drug evaluation skills of physicians to optimise the use of new medicines. Health systems will also need to invest in continuous professional development for their long term sustainability

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Supplementary Appendix – Are new models needed to optimize the utilisation of new medicines to sustain healthcare systems?

Table A1 – Case histories of health authority activities across countries pre- to post-launch of dabigatran

Country	Details of activities undertaken
Ireland (1-4)	• The National Centre for Pharmacoeconomics (NCPE) stated in August 2011 that 'dabigatran etexilate could be considered cost effective treatment for the prevention of stroke in patients with AF'. However there were concerns with some of the clinical data, model assumptions and budget implications leading to recommendations to reduce the price • Following this, the manufacturer reduced its price leading to NCPE now considering dabigatran cost effective • Dabigatran prescribing was investigated post launch - 5012 patients for >35 days. A high proportion of patients were found to be concurrently receiving medicines which may increase the risk of bleeding; 36% receiving dabigatran for >35 days were found to be prescribed at least one "caution" drug (defined in the Summary of Product Characteristics) • This analysis followed various publications in Ireland which had expressed concern regarding the potential for inappropriate prescribing of dabigatran in clinical practice • Following the analysis, a letter was sent by the authorities to all physicians in Ireland reminding them of the appropriate prescribing of new oral anti-coagulants (NOACs). The National Medicines Management Programme has also published concise prescribing advice summaries regarding the NOACs as part of ongoing efforts to reduce the potential for prescribing errors.
Malaysia (5, 6)	• The Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) had receive 58 reports and 83 adverse reactions regarding dabigatran from 2009 till March 2013 • Based on the high number of cases reported, a guidance on the monitoring of dabigatran usage in public and private facilities was developed. This comprised details of suggested usage, workflow and a checklist in the prescribing and dispensing of dabigatran emphasizing on the importance of monitoring patient's renal status. Detailed programmes for initiating and maintaining dabigatran therapy was also included in the guidance • As part of the initiative, dabigatran can only be initiated by consultants in public health institutions. In addition, it is mandatory that all patients prescribed dabigatran be counselled by pharmacist at the point of dispensing • The National Drug Safety Monitoring Centre has also issued advice (Reaksi – Drug Safety News) on the prescribing of dabigatran
New Zealand (1, 7, 8)	• A regional study did not ascertain any inappropriate prescribing of dabigatran according to patients' renal function, which reflected extensive local educational initiatives by the Best Practice Advisory Centre (BPAC) pre- and peri-launch as well as initiatives by local prescribers (BPAC is a national programme but there are regional initiatives. In some localities prescribers did not adhere to the recommendations resulting in unnecessary bleeding and deaths) • This contrasted with a high number of adverse events (ADRs) reported to the national New Zealand Centre for Adverse Drug Reaction Monitoring following the launch of dabigatran. However, increased publicity on ADRs and increasing knowledge about dabigatran, especially renal function, has resulted in a reduction in reported ADRs in recent months
Slovenia (1)	The prescribing of dabigatran was restricted post-launch to reduce potential bleeding. The restrictions include: o Only reimbursed if initiated by an internist or neurologist and prescribed according to agreed indications with patients typically followed in a tertiary or secondary anticoagulation centre o Anticoagulation centres have to report once yearly regarding the number of patients experiencing minor and major bleeding, thromboembolic events, as well as any deaths from bleeding or thromboembolism with dabigatran Analysis of utilisation patterns post launch would suggest the restrictions are being followed in practice to reduce the potential for bleeding

Sweden (Stockholm Healthcare Region) (2)	Extensive activities were undertaken by the Drugs and Therapeutics Committee in the Stockholm Healthcare Region to limit potential ADRs with dabigatran post launch. These included: • Appreciable number of pre-launch meetings and training sessions with all physician groups • Key messages broadcasted both to the public and to prescribers through websites of the DTC as well as the Swedish Medical Journal • Production of educational folders regarding dabigatran, slide kits, published articles, and data on the Janus website as well as widely distributing published information to patients • Developing a laboratory method to monitor dabigatran in plasma It is believed these activities limited the extent of any excessive bleeding with dabigatran in the Stockholm Healthcare region post launch

Table A2 – Summary of potential activities for new medicines amongst key stakeholder groups

Activity	Summary of activities/ suggestions to optimise the utilisation of new medicines

Pre-launch activities(1, 2, 9-21)	• Horizon scanning activities of new medicines:
	  ○ Defined as: "*identifying new medicines or new uses of existing medicines that are expected to receive marketing authorisation from the Regulatory Authority in the near future and estimating their potential impact on patient care*", typically instigated up to three years before likely launch dates.
	  ○ Generally incorporate a limited number of Phase II study results as well as possibly interim or final Phase III results, balancing timeliness with accuracy. Prioritisation of medicines for evaluation typically includes their likely health benefit versus current standards and their potential budget impact. This can also include potential adverse reactions if there are safety concerns with new medicines in wider co-morbid populations than those included in Phase III trials, e.g. dabigatran. Table A3 contains the current filtering process for new anti-cancer medicines in Austria
	• Forecasting the potential influence of the new medicine on the healthcare organization, identification of needs for continued medical education as well as their potential budget impact. One example of forecasting combining a number of factors to determine potential drug expenditures is the model developed in Sweden (Stockholm Healthcare Region). Development of a structured process for the introduction of new medicines and protocols to monitor prescribing post-launch including developing quality indicators
	• Preparing physicians on how to handle new medicines through targeted educational activities, e.g. dabigatran
	• Appraising the possibility of following-up prescribing through registries and Electronic Health Records
	• Early dialogue between pharmaceutical companies and health authorities including key comparator and outcome data for Phase II/ III clinical trials.
	During the pre-launch phase, as well as during the other phases, it is critical to ensure the involvement of independent pharmacotherapeutic experts, clinical pharmacologists and pharmacists as part of a professionally guided organization, e.g. Drug and Therapeutic Committees (DTCs) or similar organizations in the three phases of the model. This will ensure access to competence regarding basic and clinical sciences, and well as build trust around conflict of interest considerations when recommending and using new medicines. Advice on how to design and carry out critical drug evaluations have been published

Peri-launch activities (2, 9, 22-36)	• Different approaches are used across countries to value new medicines. In some European countries, agreed reimbursed prices are based on the perceived level of health gain versus current standards broken down by established criteria, e.g. Austria, France and Germany. In others, decisions are based on economic criteria such as the incremental cost/ QALYs (ICERs) versus current standards (with or without suggested ICER threshold levels) • Pricing and reimbursement considerations increasingly include appraising risk sharing arrangements or managed entry agreements (MEAs) given ever increasing requested prices and resource concerns. MEAs include financial based schemes such as price: volume agreements and price capping schemes as well as outcome based schemes including payment by result schemes and coverage with evidence schemes. However, the lack of publications discussing MEAs and their outcome is a concern among health authorities across countries • Determining the "best point of care", i.e. where and by whom the decision is made to initiate the prescribing of new medicines , and where prescribing should be initiated and carried on, e.g. teaching hospitals or other specialized centres, primary care physicians or other facilities with a degree of specialisation in between.
Post-launch activities (1, 2, 11, 18, 28, 30, 31, 37-40)	• Monitoring prescribing against agreed restrictions, prescribing guidance or quality targets issued by national medical organizations and DTCs. This should reduce potential adverse drug reactions that could arise from inappropriate prescribing of new medicines • Targeting prescribing to sub-populations is increasingly possible with the growing use of sophisticated information technology systems, including e-prescribing and electronic health records. The growth in pharmacogenomics will help • Assessing the effectiveness and safety of new medicines in routine clinical practice using patient registries, databases and electronic health records combined with a clear strategy for their integration into clinical practice with associated follow-on research • Any drug utilisation studies undertaken should be integrated into clinical research agendas, agreed peri-launch between universities and healthcare organizations and national stakeholders involved in the Rational Use of Medicines • Since most new innovative medicines are launched worldwide, monitoring should ideally enable the concentration/ combining of worldwide datasets to achieve maximum validity

Table A3 – Filtering process and prioritisation of new anti-cancer medicines in Austria (14)

- **Criteria for filtration**
  - New (early post marketing)
  - Emerging (Phase II or III Clinical Trials)
  - Use in adults including solid malignancies, leukaemia and lymphomas
  - Likelihood of extended indications beyond the initial submitted indication
- **Prioritisation criteria**
  - Number of patients eligible for the cancer medicine under consideration
  - Intended use of the new medicine, i.e. as add-on to existing regimes or as a replacement to existing regimes
  - Estimated impact on patients' outcomes
  - Estimated budget impact
  - Potential for off-label use to increase the budget impact

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