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Disinvestment Strategies for Pharmaceuticals: An International Review

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The purpose of this international literature review is to evaluate the partial or full disinvestment policies of some publicly funded or subsidized drugs in five OECD countries (Australia, Canada, France, New Zealand and the United Kingdom). It is based on an international study published in the journal *PharmacoEconomics* in 2015. Disinvestment can take two forms, passive and active. The first is not linked to direct government intervention: a drug will be withdrawn from the market by the manufacturer for commercial reasons or because of identified safety problems. Active divestment is driven by a political will to improve the efficiency and quality of care by reducing the pressure on pharmaceutical budgets.

While countries rely more heavily on passive disinvestment, they tend to increasingly resort to active disinvestment. Governments are under increasing pressure to disinvest medicines with low therapeutic value in order to provide flexibility for innovative new medicines with recognized efficacy.

Pharmaceutical expenditure has increased rapidly across many OECD (Organisation for Economic Cooperation and Development) countries over the past three decades, from around US$160 per capita in 1990 to US$532 per capita in 2014 , or around 9.6 % per annum (unadjusted for inflation)[1].

This growth in expenditure is an increasing concern for governments and other third-party payers seeking to provide equitable and comprehensive healthcare. Consequently some countries may choose not to fund new high-cost drugs (1, 2). In order to stabilize expenditure growth, and create headroom for increasing utilization of existing drugs and in order to fund new high-cost therapies, there is an active push to "disinvest" from low-value medicines.

Numerous conceptualizations of disinvestment have been promoted, but the

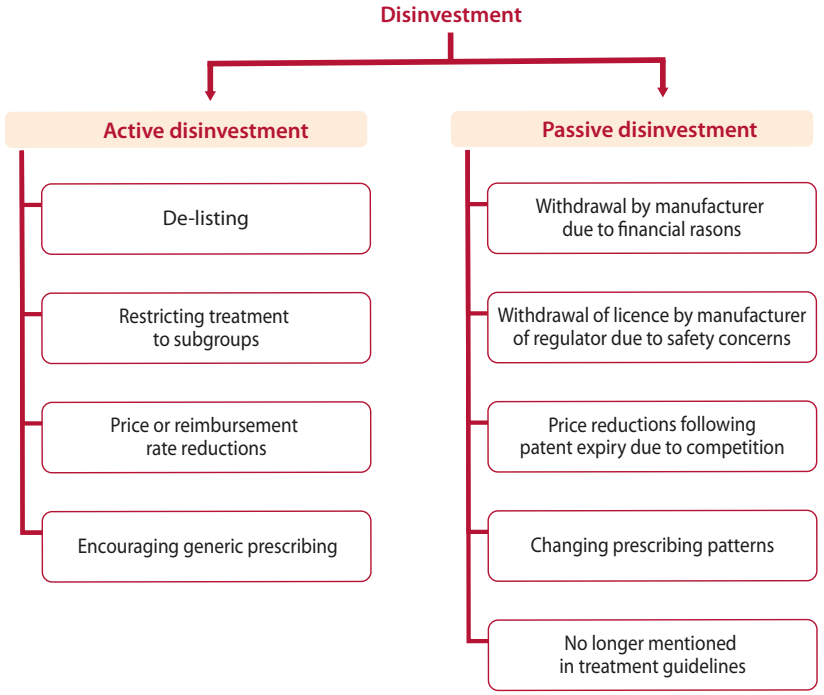
[1] http://www.oecd.org/health/health-systems/oecd-health-statistics-2014-frequently-requested-data.htm

core premise would see the "partial or complete withdrawal of health resources from any existing health care practices, procedures, technologies or drugs that are deemed to deliver little or no health gain for their cost, and thus are not efficient health resource allocations" with an explicit view towards reallocation to higher value applications (3, 4).

The aim of this *Issues of Health Economics*, which is mainly based on an international review published in *PharmacoEconomics* in 2015 (see box Approach), is to assess how reimbursement policy decision makers have sought to partially or completely disinvest from medicines in 5 OECD countries (UK, France, Canada, Australia and New Zealand) where they are publicly funded or subsidized (5). The experience in these countries may provide useful examples for other countries considering disinvestment and suggest directions to improve ability to fund costly innovative medicines. This is already happening, *e.g.* Brazil[2].

F

Disinvestment in drugs typology



Source: Parkinson *et al.*, 2015 (5).

Differences between active and passive disinvestment

Two forms of disinvestment, passive and active, have been distinguished. Passive forms of disinvestment are those that are not reliant on direct intervention by reimbursement policy makers. A medicine or a brand of a medicine may be withdrawn from the market by the manufacturer due to commercial reasons or safety concerns by a regulatory authority, such as the ANSM in France (*Agence nationale de sécurité du médicament et des produits de santé,* National Agency for safety of medicines and health products). For example, benfluorex in France (2009) and rofecoxib worldwide (2004) were disinvested for safety reasons (2, 6).

Alternatively, policy makers may rely on market forces to reduce prices of medicines following patent expiry and the introduction of competition. They may also rely on clinicians to cease prescribing medicines that are considered less efficacious or have more adverse effects than more recently introduced medicines. Situations where certain medicines are purposely not mentioned in treatment guidelines could also be considered a form of passive disinvestment.

Historically, countries have relied on "passive disinvestment"; however, considering passive disinvestment process are no longer sufficiently reliable or authorities wish to speed up changes in drug utilization, some policy makers have now introduced active forms of disinvestment.

"Active disinvestment" results from a strong political will to improve the efficiency of health care by implementing measures that in the end will alleviate the pressure on pharmaceutical budgets and improve quality of care. This can be obtained by withdrawing certain medicines from public funding (de-listing), by restricting treatment to subgroups of patients, by modifying prices or reimbursement rates or by encouraging generic prescribing.

[2] www.researchgate.net/publication/279553804_Proposed_Brazilian_guideline_for_disinvestment

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Approach

This paper reviews disinvestment in France, the UK, Canada, Australia and New Zealand, but many of the policy tools discussed here are used by a range of health authorities in various countries. These countries were chosen on the basis of known documented activity in disinvestment. However, it is acknowledged that by selecting these countries, there is a risk of missing other policy tools that could be used to disinvest in drugs. Lower and middle income countries were not included since the principal goal of the authorities in these countries is to improve access to essential drugs rather than initiate "disinvestment strategies" (34, 35).

It is well-documented throughout the disinvestment literature (3, 7, 29) that traditional literature search strategies in the disinvestment area have very high sensitivity and poor specificity, with search results at a magnitude that is not well-targeted nor feasible to manage. In addition, there is publication bias resulting in government and payer disinvestment initiatives being absent from scientific publications. Consequently, the pharmaceutical policies discussed in this paper are based on those uncovered in a literature search, together with key papers in this field known by the co-authors and the expert knowledge of the co-authors regarding the policy situation in their country (including grey literature). We describe below the outlines of the search strategy used in support of this review, resulting in almost 5,000 English-language returns. The subsequent sorting process, and the incorporation of grey literature, is one that relied heavily on the judgement of the authors as experts in the field.

Research strategy

A Medline/PubMed search was performed on 2 May 2013 for English and French language articles with no date restrictions. References lists of relevant articles were pearled for additional material, including from the grey literature.

De-listing: A few obvious candidates for total disinvestment

Concerning de-listing, which can be seen as complete disinvestment, the outcomes of the active disinvestment reviews are mixed. In the UK, the National Institute for Health and Care Excellence (NICE) introduced in 2006 a pilot active program to identify candidates for disinvestment but concluded that there were few obvious candidates for de-listing, with antibiotics and diagnostics predominating (7). In Australia, the reviews conducted by Pharmaceutical Benefits Advisory Committee (PBAC) have resulted in only one drug being de-listed. In France, in the early 2000s, the Transparency Commission initially de-listed around half of the candidates considered suitable for disinvestment (840 of 1675 drugs). While many of these decisions were re-evaluated following pressure from pharmaceutical companies, over two-thirds of the de-listing decisions were maintained (525 of 763 drugs) [8]. In New Zealand, PHARMAC rarely de-lists medicines because of an active policy of price reductions allowing substantial discounts (95 %) that render other forms of disinvestment unnecessary. However, it is common for PHARMAC to delist pack options, brands and formulations.

There is one explanation that should be kept in mind when comparing the considerable differences in terms of de-listing between the 5 countries of our study. De-listing a medicine is only possible when the medicine has been actually listed before on a positive list and/or is still listed. At the time of the extensive delisting exercise in 2006, France had probably the largest list of reimbursed medicines among the 5 countries in this study with more medicines demonstrating efficacy being granted reimbursement than in other countries (9), thus offering more candidates for potential disinvestment. On the opposite, New Zealand was known for its more limited and delayed access to new medicines than Australia (10) and for its strong policy regarding introduction of me-toos (11-13).

There are several reasons why a decision maker may be reluctant to de-list a medicine: it reduces patient and prescriber choice, and can lead to perverse incentives which create stake-holder opposition to the disinvestment of medicines (5). As a result, de-listing of medicines can be met with pressure from clinicians, patients, pharmaceutical companies and the media. Sermet *et al.* noted that de-listing of medicines in France had "not been without problems, with both patients and physicians believing some of these products were effective despite a lack of scientific evidence" and there was pressure to reevaluate the disinvestment decisions from industry (8). Additionally, because much of the communication about the de-listing of medicines focused on their insufficient medical value, patients were led to believe that the medicines were not effective. Consequently, patients did not understand why medicines not worthy of reimbursement were still worthy to be sold over-the-counter, as it was the case for the majority of the delisted medicines.

Restricting treatment: A more common strategy

An alternative and more common strategy is identifying subgroups in which an intervention is most clinically and cost effective and applying restrictions, or tightening existing restrictions, on who may receive the treatment. This approach is commonly used in the UK. For example, in March 2008, NICE recommended the cessation of antibiotic prophylaxis against infective endocarditis for patients undergoing dental procedures and procedures at the following sites: upper and lower gastrointestinal tract, genitourinary tract, and upper and lower respiratory tract (14). Consequently, cessation of prophylaxis was not recommended for all types of procedures or for active or potential infections – only those mentioned. Subsequent to the introduction of the NICE guideline, Thornhill *et al.* found a significant 78.6% reduction in prescriptions for antibiotic prophylaxis (15). Restrictions are also applied in other countries as a form of disinvestment. For example, in France from 1st November 2014, clinicians must obtain prior authorization for each treatment initiation of rosuvastatin or ezetimibe. This restriction was introduced in order to avoid the constant growth in the prescribing of patent-protected medicines despite the increasing availability of generics (16).

Medicines may also be subject to 'conditional treatment continuation rules', where treatment is restricted to patients who achieve a certain health outcome, as can be seen with the discontinuation of treatment in performance-based risk sharing arrangements (17). For example, in Australia a review of anticoagulant therapies recommended restricting new oral anticoagulants to "patients unable to tolerate warfarin therapy and/or who are unable to obtain satisfactory international normalized ratio (INR) control despite specific measures" (18). Similarly, in France, a review of four medicines used to treat Alzheimer's disease resulted in two restrictions: limitation of the prescription to 1 year; and after 6 months, continuation of the treatment for Alzheimer's disease should be assessed by the prescriber[3]. In september 2016, HAS revealed the results of its latest assessment concluding that their medical value was no longer sufficient to justify reimbursement[4].

Price or reimbursement rate reductions

Many countries use price or reimbursement rate reductions as a form of disinvestment. An exception to this is the UK, which may be due to the limited remit of NICE to force price reductions and reluctance by manufacturers to offer price reductions as medicine prices in the UK are referenced by many other European countries (19).

In France, following the re-evaluation of the medicine's medical value (*Service Médical Rendu (SMR)*), the reimbursement rate was reduced. However, other countries may not be able to consider this option due to legislation restricting costs borne by patients. France, Australia

[3] www.has-sante.fr/portail/jcms/c_1108356/fr/medicaments-de-la-maladie-d-alzheimer-la-has-revele-les-resultats-de-sa-reevaluation

[4] www.has-sante.fr/portail/jcms/c_2680920/fr/medicaments-alzheimer-interet-medical-insuffisant

and New Zealand also all use effective monopsony power to create downward pressure on the price of originators and generic drugs. For example, in Australia, price reductions were sought from manufacturers as a result of the proactive cost-effectiveness reviews of treatments for Alzheimer's disease and biological disease modifying antirheumatic drugs. In addition, in order to lower the prices paid for off-patent medicines, Australia and France impose mandatory price discounts. France implemented reference pricing for certain medicines, by paying originators the same price as generics in order to promote generics. Australia has also implemented reference pricing, and more recently has introduced "price disclosure" with early evidence of success (20). Under price disclosure, pharmacies in Australia are required to reveal any discounts on pharmaceutical prices that manufacturers provide them. In turn, the Federal Government reduces the amount paid to pharmacies for each medication, leading to prices reductions. In Canada, tools such as reference pricing and price-volume agreements are also commonly used; however, price negotiation falls to each individual province. In New Zealand, PHARMAC uses a broad range of tools to lower prices (21). While some, such as reference pricing and price-volume agreements, are commonly used around the world, other tools, such as package agreements/bundling and tendering sole supply are less common (22, 23).

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Criteria used to identify potential candidates for assessment and disinvestment when conducting active disinvestment reviews

Country, Agency	Identification of potential candidates for disinvestment	Criteria for assessing candidates for disinvestment
Australia, Pharmaceutical Benefits Advisory Committee (PBAC)	*Ad hoc.* Drugs considered where there are concerns regarding the quality of use, cost effectiveness, clinical effectiveness, higher than predicted utilization and/or international difference	Drugs considered not sufficiently safe, sufficiently effective, or sufficiently cost effective following multiple technology assessment
Canada, Atlantic Common Drug Review	*Ad hoc.* Drugs considered where there have been changes in scientific evidence, regulatory status, cost effectiveness, or budget impact related to changes in the drug cost or the cost of its comparators	Drugs considered not sufficiently safe, sufficiently effective or sufficiently cost effective following multiple technology assessment
France, Transparency Commission	All listed drugs	SMR rating: (1) effectiveness and safety; (2) availability of alternatives; (3) disease severity; (4) impact on health of individual; and (5) impact on public health. Excludes cost effectiveness
New Zealand, Pharmaceutical Management Agency (PHARMAC)	Drugs facing price competition where there are alternatives that can deliver the same or similar health outcomes	Those not delivering value for money
UK, National Institute for Health and Care Excellence (NICE)	Any included in NICE cancer service guidance, clinical guidelines, interventional procedures and technology appraisals guidance since 2007. Cochrane reviews that conclude that interventions should not be used or could not be recommended	Drugs considered not sufficiently safe, sufficiently effective or sufficiently cost effective following multiple technology assessment

Source: Parkinson *et al.*, 2015 (5).

Encouraging generic prescribing

Policies that aim to encourage generic prescribing (*i.e.* prescribing by international non-proprietary name (INN)) can be considered another form of disinvestment as the objective is to replace more expensive originators with less expensive generics. In the UK, prices of high-volume generics can be as low as 3–12% of prices pre-patent expiry with multiple policies to encourage high INN prescribing and lower generic pricies (24). Consequently, encouraging generic prescribing (or prescribing off-patent medicines that are considered therapeutically equivalent to a patented drug) can result in considerable savings without compromising care.

All countries have some form of education or awareness campaigns regarding generic prescribing targeting clinicians and patients. For example, in the UK, clinicians are taught to prescribe by international non proprietary name (INN) in medical schools and receive academic detail regarding their generic prescribing patterns (24,25). In other countries awareness campaigns may aim to inform clinicians and patients about how originator drugs and generics are similar or encourage them to ask for generics.

In New Zealand, PHARMAC limits which medicines are subsidized to a certain brand, which could be the originator or a generic. Consequently, there is mandatory dispensing of generics when a generic is the only one subsidized. France has also recently implemented mandatory INN prescribing, but with a limited success as there are no sanctions for physicians not applying INN prescribing. Substitution between originator and generic is mandatory in France, with patients having to pay the pharmacist and being reimbursed later if they refuse substitution instead of health insurance paying directly the pharmacist. Since 1994 in Australia, while it is not mandatory to write prescriptions using INNs, pharmacists have been allowed to substitute between originator and generic drugs listed on the Pharmaceutical Benefits Scheme even if the prescription specifies a particular brand, unless the prescriber indicates that "brand substitution is not permitted" (26). In terms of financial incentives, France and the UK use prescribing targets coupled with some form of financial incentive to encourage the prescribing of generics *versus* patented products in a class by clinicians, while France and Australia provide incentives to pharmacists for dispensing generics *versus* the originator.

Identification of potential candidates for disinvestment

France has a highly proactive record in this area, having conducted a comprehensive review of all listed medicines between 2000 and 2004. Consequently, capturing any legacy items as well as incorporating any new evidence that had become available since the medi-

cine had been reimbursed (8). However, this approach is resource intensive and requires a high level of will by many actors, including political will. The other countries have opted to only consider subsets of medicines for review. In the UK, NICE piloted a process involving consultation and nomination to identify candidates, but found that many suggestions for de-listing were based on "social judgments" rather than evidence of poor clinical or cost effectiveness (7). NICE abandoned the pilot and now relies on identifying candidates for disinvestment through its existing processes. In Australia and in the Canadian Atlantic provinces, reviews of both individual medicines and entire classes have been undertaken, some of which have led to disinvestment decisions.In New Zealand, PHARMAC identifies candidates where price competition has been made possible as a result of a medicine, or its therapeutic equivalent, losing patent protection. When considering which drugs should be subject to disinvestment, Australia, the UK, Atlantic Canada and France all consider the effectiveness and safety of the medicine *versus* any relevant comparators, including any new evidence that has become available.

In terms of disinvestment decisions, PHARMAC in New Zealand mainly considers costs, as there are alternatives to the drugs considered that can deliver the same or similar health outcomes.

One key reason for disinvestment: Modification by the decision makers of their assessment of a given drug

In the past, countries have relied on "passive disinvestment". However, there is now an increasing focus towards "active disinvestment" whereby countries systematically identify medicine suitable for disinvestment. One key reason why a country may actively disinvest in a given medicine is that decision makers have modified their assessment of its effectiveness, safety or cost effectiveness due to the availability of new evidence or to "leakage" in drug utilization. The other key reason is that there may be a failure of the market in that the price of medicine used to treat the same condition (including bioequivalent, biosimilar and therapeutically superior drugs) have not responded to increased competition.

Disinvestment decisions in medicine may be reversed depending on the availability of other treatments

Policy makers should also be aware that disinvestment in a medicine may be reversed depending on the availability of other treatments. For example, in France in 2004, Lamaline®, a fixed-dose combination of paracetamol, opium and caffeine, was considered to have low therapeutic value and was subjected to a reduction of its reimbursement rate from 65 to 35 % and later from 35 to 15 %. In 2012, following a new assessment by the Transparency Commission, its medical value was revised to high and the reimbursement rate was restored to 65 % (27). The reason given was that after the withdrawal of dextropropoxyphen from the market due to safety concerns, this combination was one of the few viable alternatives in the mild opioid class for the treatment of pain.

De-listing of medicine risks engendering substitution effects: Policy makers should also consider other forms of disinvestment

Considering only de-listing as a disinvestment strategy may prove unsuccessful in terms of identifying suitable candidates, unpopular among various stakeholders and potentially inappropriate. Furthermore, de-listing of medicine risks engendering substitution effects; some of which may be anticipated while others may be unexpected and sometimes harmful or expensive.

In France, substitution of the de-listed medicine with a medicine from another inadequate therapeutic class was observed after the de-listing of expectorants and mucolytics (16), and the substitution of phytotherapy used in the treatment of anxiety and insomnia with more expensive and potentially more dangerous psychotropic drugs was observed following the discontinuation of phytotherapy reimbursement (28). Substitution can also take the form of alternative non-pharmaceutical treatments as it was seen after the de-listing of phlebotonics in France, where an increase in the prescription of support stockings was noticed (Sermet C, unpublished data).

Stakeholder Management can help diffuse any resulting politics

Haas *et al.* noted that disinvestment in medicine creates losses to clinicians, patients and manufacturers, while any savings from disinvestment may not be realized for some time (29). Furthermore, these savings are dispersed among a number of different parties such as payers, other parties or the public as tax payers. Hence, "losers" from a disinvestment decision have a stronger incentive to lobby for the continued funding of a particular medicine. Stakeholder management can help diffuse any resulting politics, particularly by communicating with stakeholders upfront and throughout the process regarding what research is required; what level of evidence is required for continuing funding of the medicine (*i.e.* pre-specify levels of effectiveness or cost effectiveness); what are the ramifications of not supplying the evidence required; and what are the alternative uses of funds (*e.g.* the treatment of other patients with the concept of opportunity costs within fixed budgets).

How to go further in disinvesting?

As the impact of the disinvestment policies described above seems to be limited, policy makers should also consider other forms of disinvestment, including applying or further restricting treatments, applying price or reimbursement rate reductions, and tightening cost-sharing arrangements (*e.g.* dose caps or price:volume agreements). These types of disinvestment strategies are more likely to be acceptable politically and the threat of delisting makes manufacturers more

amenable to accepting disinvestment strategies.

Beyond disinvestment of medicines already on the market, there is a need to consider other approaches for newly introduced medicines in order to ensure that they reach their expected "value for money". This is the aim of Coverage with Evidence Development (CED) arrangements which link population-level payment or reimbursement to prospective data collection (17). These types of arrangements may be considered when uncertainty regarding the clinical effectiveness, safety or resource use associated with a new medicine is high, which can be reduced by conducting additional research in the form of a clinical trial or an observational study. For CED arrangements, there is a risk that the medicine is subsequently found to be not as effective or cost effective as initially predicted, as seen initially with the beta interferons for the management of multiple sclerosis in the UK (below) [30]. As a result, a policy decision maker may wish to disinvest in such a medicine. However, there is a significant risk that the disinvestment never takes place. CED can, therefore, create a wedge effect – a pharmaceutical foot in the door – that introduces challenges for decision makers (principally resistance from clinicians, patients, industry and the media) in the event that the evidence calls for the reversal of interim funding. This happened in Netherlands regarding enzyme replacement therapy for the symptomatic treatment of Fabry disease and alglucosidase alfa to treat Pompe's disease which were not cost effective at incremental cost of €3.3 million to €15 million per quality-adjusted life-year gained. The National Health Insurance group recommended removal of conditional reimbursement at these high cost/ QALYs; however, the decision was not implemented following media and other pressure (31).

NICE in the UK in 2002 rejected b-interferons and glatiramer acetate to treat patients with multiple sclerosis on the basis of unfavourable cost effectiveness (32,33). Despite the rejection, the UK Department of Health approved the drugs conditionally on the results of a 10-year monitoring study where the price would be adjusted to achieve the original incremental cost-effectiveness ratio (£36,000/quality-adjusted life-year) if they failed to show benefits consistent with the economic model. In 2009, it was reported that, based on patient registry data collected between 2005 and 2007 and compared to historical control data from London, Ontario, Canada (which was used in the economic model), disease progression was not only worse than predicted, but worse compared to the control group (30). However, to date there does not appear to be an amendment of prices.

Other approaches are possible depending on health systems. In France, the coexistence of mandatory health insurance (MHI) and complementary health insurance (CHI) could make it possible to develop new organization to fund medicines. Until now, MHI is funding around 82% of the reimbursed cost of medicines and CHI acts as a complementary payment for the remaining 18%; however, only if the medicine is included in the list of reimbursed medicines by the MHI. By disconnecting the reimbursement of MHI from the reimbursement of CHI, it would be possible to shift the funding of medicines with limited value to CHIs and make budgetary space for new valued higher priced innovative medicines in the health basket of MHI. The generalization of CHIs that occurred in 2016 make this shift possible without increasing inequalities in the access to healthcare.

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In the past, countries have relied on 'passive disinvestment'; however, there is an increasing focus towards "active disinvestment". Pressures are mounting for countries to consider disinvesting from low-value medicines to create headroom for new valued innovative new medicines; when CED arrangements, increasingly in use, point to the need to reverse funding arrangements; and when findings from post-market reviews reveal concerns with the safety of new medicines in routine clinical care, lower than expected real-world effectiveness or cost effectiveness, and/or product leakage.

Throughout this paper, we have drawn out the distinction between disinvestment initiatives that are mandatory (*e.g.* de-listing), those that are incentivized (*e.g.* dispensing incentives for pharmacists) and those that are merely encouraged (*e.g.* clinical guidelines). Likewise, we have made the distinction between blanket (*e.g.* encouraging generic prescribing) and targeted (*e.g.* restricting treatment to subgroups) approaches.

Policy decision makers ought to ensure that other avenues for disinvesting are pre-identified prior to approval (*e.g.* price discounts, restrictions) or pre-agree to rebates in order to ensure that the medicines they reimburse are still cost effective in the face of new evidence or changed circumstances such as the first product in the class or related class losing its patent. ♦.

For further information

1. Dudding A. (2008). "A Bitter Pill: 10 Drugs You Can't Have". *Sunday Star Times,* 30(C1-2).
2. Malmstrom R.E., Godman B.B., Diogene E., Baumgartel C., Bennie M., Bishop I. *et al.* (2013). "Dabigatran - A Case History Demonstrating the Need for Comprehensive Approaches to Optimize the Use of New Drugs". *Front Pharmacol,* 4:39.
3. MacKean G., Noseworthy T., Elshaug A.G, Leggett L., Littlejohns P., Berezanski J.,*et al.* (2013). "Health Technology Reassessment: The Art of the Possible". *Int J Technol Assess Health Care*, 29(4):418-23.
4. Elshaug A.G., Hiller J.E., Tunis S.R., Moss J.R. (2007). "Challenges in Australian Policy Processes for Disinvestment from Existing, Ineffective Health Care Practices". *Aust New Zealand Health Policy*, 4:23.
5. Parkinson B., Sermet C., Clement F., Crausaz S., Godman B., Garner S. *et al.* (2015). "Disinvestment and Value-Based Purchasing Strategies for Pharmaceuticals: An International Review". *PharmacoEconomics*, 33(9):905-24.
6. Godman B., Paterson K., Malmstrom R.E., Selke G., Fagot J.P., Mrak J. (2012). "Improving the Managed Entry of New Medicines: Sharing Experiences across

For further information (More)

Europe". *Expert Rev Pharmacoecon Outcomes Res*, 12(4):439-41.

7. Garner S., Littlejohns P. (2011). "Disinvestment from Low Value Clinical Interventions: NICEly Done?" *BMJ*, 343:d4519.
8. Sermet C., Andrieu V., Godman B., Van Ganse E., Haycox A., Reynier J.P. (2010). "Ongoing Pharmaceutical Reforms in France: Implications for Key Stakeholder Groups". *Appl Health Econ Health Policy*, 8(1):7-24.
9. Nguyen-Kim L., Or Z., Paris V., Sermet C. (2005). « Les politiques de prise en charge des médicaments en Allemagne, Angleterre et France ». Irdes, *Questions d'économie de la santé,* (99):6.
10. Wonder M., Milne R. (2011). "Access to New Medicines in New Zealand Compared to Australia". *N Z Med J.* 2011;124(1346):12-28.
11. Ragupathy R., Aaltonen K., Tordoff J., Norris P., Reith D. (2012). "A 3-Dimensional View of Access to Licensed and Subsidized Medicines under Single-Payer Systems in the US, the UK, Australia and New Zealand". *PharmacoEconomics*, 30(11):1051-65.
12. Gauld R. (2014). "Ahead of Its Time? Reflecting on New Zealand's Pharmac Following its 20th Anniversary". *PharmacoEconomics*, 32(10):937-42.
13. Godman B., Malmstrom R.E., Diogene E., Gray A., Jayathissa S., Timoney A. *et al*. (2015). "Are New Models Needed to Optimize the Utilization of New Medicines to Sustain Healthcare Systems?" *Expert Rev Clin Pharmacol*, 8(1):77-94.
14. NICE [National Institute for Health and Clinical Excellence] (2008). "Prophylaxis against Infective Endocarditis: Antimicrobial Prophylaxis against Infective Endocarditis in Adults and Children Undergoing Interventional Procedures". London.
15. Thornhill M.H., Dayer M.J., Forde J.M., Corey G.R., Chu V.H., Couper D.J. *et al*. (2011). "Impact of the NICE Guideline Recommending Cessation of Antibiotic Prophylaxis for Prevention of Infective Endocarditis: Before and after Study". *BMJ*, 342:d2392.
16. Pichetti S., Sermet C., Godman B., Campbell S.M., Gustafsson L.L. (2013). "Multilevel Analysis of the Influence of Patients' and General Practitioners' Characteristics on Patented versus Multiple-Sourced Statin Prescribing in France". *Appl Health Econ Health Policy*. 11(3):205-18.
17. Garrison L.P, Jr., Towse A., Briggs A., de Pouvourville G., Grueger J., Mohr P.E. *et al*. (2013). "Performance-Based Risk-Sharing Arrangements-Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force". *Value Health,* 16(5):703-19.
18. DoHA [Australian Government, Department of Health and Ageing]. (2012). "Review of Anticoagulation Therapies in Atrial Fibrillation". Canberra.
19. Leopold C., Vogler S., Mantel-Teeuwisse A.K., de Joncheere K., Leufkens H.G., Laing R. (2012). "Differences in External Price Referencing in Europe: A Descriptive Overview". *Health Policy*, 104(1):50-60.
20. DoHA [Australian Government, Department of Health and Ageing]. (2012). "Summary of Claimed Prices and Brand Premiums for 1 April 2012". Canberra.
21. Morgan S., Hanley G., McMahon M., Barer M. (2007). "Influencing Drug Prices through Formulary-Based Policies: Lessons from New Zealand". *Health Policy,* 3(1):e121-40.
22. Adamski J., Godman B., Ofierska-Sujkowska G., Osinska B., Herholz H., Wendykowska K. *et al.* (2010). "Risk Sharing Arrangements for Pharmaceuticals: Potential Considerations and Recommendations for European Payers". *BMC Health Serv Res,* 10:153.
23. Ferrario A., Kanavos P. (2015). "Dealing with Uncertainty and High Prices of New Medicines: A Comparative Analysis of the Use of Managed Entry Agreements in Belgium, England, the Netherlands and Sweden". *Soc Sci Med*, 124:39-47.
24. Godman B., Bishop I., Finlayson A.E., Campbell S, Kwon H.Y, Bennie M. (2013). "Reforms and Initiatives in Scotland in Recent Years to Encourage the Prescribing of Generic Drugs, their Influence and Implications for Other Countries". *Expert Rev Pharmacoecon Outcomes Res*, 13(4):469-82.
25. Godman B., Wettermark B., van Woerkom M., Fraeyman J., Alvarez-Madrazo S., Berg C. *et al*. (2014). "Multiple Policies to Enhance Prescribing Efficiency for Established Medicines in Europe with a Particular Focus on Demand-Side Measures: Findings and Future Implications". *Front Pharmacol,* 5:106.
26. Beecroft G. (2007). "Generic Drug Policy in Australia: A Community Pharmacy Perspective". *Aust New Zealand Health Policy,* 4:7.
27. HAS [Haute Autorité de santé]. (2012). « Avis de la Commission de transparence sur la Lamaline ». France.
28. Riou Franca L., Vidal C., Bourechak N., Jeunne P.L., Deville G.S., Massol J. (2013). "A Cohort Study of Therapeutic Prescriptions after the End of Phytotherapy Drug Reimbursement by French Social Security". *Pharmacoepidemiol Drug Saf*, 22(7):760-8.
29. Haas M., Hall J., Viney R., Gallego G. (2012). "Breaking Up Is Hard to Do: Why Disinvestment in Medical Technology Is Harder than Investment". Aust Health Rev, 36(2):148-52.
30. Raftery J. (2010). "Multiple Sclerosis Risk Sharing Scheme: A Costly Failure". *BMJ,* 340:c1672.
31. Simoens S., Picavet E., Dooms M., Cassiman D., Morel T. (2013). "Cost-Effectiveness Assessment of Orphan Drugs: A Scientific and Political Conundrum". *Appl Health Econ Health Policy*, 11(1):1-3.
32. NICE [National Institute for Health and Clinical Excellence]. (2012). "Beta Interferon and Glatiramer Acetate for the Treatment of Multiple Sclerosis". London.
33. Thomas S., Prince A., Humphries C., Smith J., Seymour H., Donaldson T. *et al*. (2000). "Assessment of Interferon-Beta and Glatiramer for the Treatment of Multiple Sclerosis: Report Commissioned by the NHS Health Technology Assessment Programme on Behalf of the National Institute for Clinical Excellence". Newcastle upon Tyne.
34. Seiter A. (2010). "A Practical Approach to Pharmaceutical Policy". Accessed 21 September 2016. Available from: http://documents.worldbank.org/curated/en/751541468325451548/pdf/552030PUB0Phar10Box349442B01PUBLIC1.pdf.
35. Godman B., Acurcio F., Guerra Junior A., Alvarez-Madrazo S., Faridah Aryani M., Bishop I. *et al*. (2014). "Initiatives among Authorities to Improve the Quality and Efficiency of Prescribing and the Implications". *J Pharma Care Health Sys,* 1(3):1.

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