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31 May 2017

Online at <https://mpra.ub.uni-muenchen.de/79481/>
MPRA Paper No. 79481, posted 02 Jun 2017 19:47 UTC

The Savings from the 2016-2020 Framework Agreement on the Supply and Pricing of Medicines in Ireland: Which Counterfactual?

by

Paul K. Gorecki*

Abstract

The Minister for Health claims savings of €600 million due to the 2016-2020 framework agreement (the Agreement) with the Irish Pharmaceutical Healthcare Association. *But relative to what? No agreement. That seems implausible since such State/industry agreements have been in operation continuously since 1969. Furthermore the State has powers to set medicine prices under the Health (Pricing and Supply of Medical Goods) Act 2013? Agreed, but what would be a more appropriate counterfactual? The status quo: replicating the 2012-2015 agreement and extending its length for one year. That seems a sensible credible alternative. But what would the savings be if the status quo is the counterfactual? €290 million. Wow, less than half the Minister's estimate. But won't that make the Health Service Executive (HSE)'s task in deciding which new high cost medicines to fund much harder? Yes. Perhaps the HSE should set out guidance as to when a new medicine will be funded, with, for example, an upper cost-effectiveness limit. But surely the methodology and assumptions underlying the Minister's claimed savings are published, as part of a transparent, open evidenced based policy? Afraid not. Why? Good question. This paper attempts, albeit partially, to fill the void in the analytics.*

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Keyword(s): medicine prices; government/pharmaceutical industry agreements; savings.

JEL Codes: I11; I18; H51;

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Acknowledgements: The paper has benefited enormously from the contribution of James O'Mahony, who suggested analysing Agreement and commented extensively on earlier drafts. Sean Lyons provided comments on the savings estimates; Francis O'Toole on the availability/pricing of new medicines. The Department of Health provided helpful clarification concerning the Agreement. The paper has also benefited from conversations with the Healthcare Enterprise Alliance and the Irish Pharmaceutical Healthcare Association. The usual disclaimer applies.

31 May 2017

INTRODUCTION

The latest in a long series of pharmaceutical pricing agreements for medicines supplied to the public health system in Ireland commenced on 1 August 2016. The “Framework Agreement the Supply and Pricing of Medicines” (the Agreement) will apply until 31 July 2020.¹ The signatories on behalf of the buyers of medicines for the State are the Department of Health (DoH), the Department of Public Expenditure and Reform (DPER) and Health Service Executive (HSE).² The signatory on behalf of sellers of medicines is the Irish Pharmaceutical Health Association (IPHA), which represents manufacturers of patent-protected medicines in Ireland.³

The comprehensive Agreement is twenty five pages in length. It applies to new medicines, existing patent-protected medicines and medicines that have lost exclusivity, including both biologics and biosimilars. The Agreement influences medicine pricing in four principal ways: the appraisal process for new medicines, including the timelines for appraisal and a decision-making authority cost-effectiveness threshold/net budget impact matrix; international reference price rules and realignment arrangements for existing medicines with exclusive supply; price reductions for patent-expired medicines upon loss of exclusive supply, which vary between non-biologic (i.e. generics) and biologic medicines (i.e. biosimilars); and, rebates.

The Agreement was welcomed by the Minister for Health, who stated it will result in savings of €600 million; “*the pricing provisions ... represent a significant improvement on those contained in the previous agreement*”; and, will “*ensure that Irish patients continue to have access to new and innovative medicines and that Ireland remains in the forefront of its*

¹ The Agreement may be accessed at: <http://health.gov.ie/wp-content/uploads/2016/07/Framework-Agreement-on-the-Supply-and-Pricing-of-Medicines-signed-copy.pdf>. Accessed 23 May 2017.

² In addition the Office of Government Procurement (OGP) was also involved in the negotiations (DPER, 2016, p. 26).

³ According to its website the IPHA “*represents the international research based pharmaceutical industry in Ireland.*” <http://www.ipha.ie/alist/about-us.aspx>. Accessed 23 May 2017. A list of the IPHA members that are signatories to the Agreement is contained in Schedule 2 of the Agreement.

European peers in terms of early access to medicines in an affordable manner within available resources.”⁴

There was no public consultation on the draft agreement or key aspects such as the cost-effectiveness threshold, measured using a Quality Adjusted Life Year (QALY), or the trade-off between early access to a new medicine and the likely higher price. Other pharmaceutical representative bodies do not appear to have been consulted. Apart from one unpublished table detailing the composition of the savings,⁵ the underlying analysis of the impact of the Agreement has not been released.⁶ There is, however, published research commissioned by the DoH/HSE to inform the State in its negotiations leading to the Agreement.⁷

The purpose of this paper is to provide a critical appraisal of the Agreement and associated savings claims. More specifically, this analysis addresses the two questions. (i) How credible are the claims of the savings due to the Agreement? (ii) Does the Agreement offer an improvement in achieving value for money over the previous agreement, which ran from 2012 to 2015?⁸ However, before addressing these questions it is necessary to provide some background to the Agreement.

BACKGROUND

Medicine Expenditure: Trends and Who Pays

The vast majority of medicines in Ireland are paid for by the State through general taxation.⁹ Nominal expenditure on State funded community drug schemes has increased in for each

⁴ Department of Health (2016, p. 1). There were also unspecified and unquantified additional savings from “non-IPHA companies.” However, subsequently the Minister put a figure of €150 million on these savings, but with no indication as to what they refer and how they were estimated (Harris, 2016). Hence we do not consider these unspecified savings further in this paper. As noted below at footnote 61 the IPHA accounts for the vast majority of the purchases by the State of medicines supplied by the international research based pharmaceutical industry in Ireland.

⁵ See Table 1 below for details. It was also cited in Mitchell (2016b).

⁶ Indeed, access was specifically denied. See Mitchell (2016b).

⁷ Brick et al (2013a) and Gorecki et al (2012).

⁸ The 2010 to 2015 agreement was extended for a year until the Agreement was signed.

⁹ It is difficult to get a precise estimate but appears to be around 85%. For details see Gorecki et al (2012, pp. 16-17).

year from 1991 to 2009, when expenditure peaked at slightly below €2 billion.¹⁰ Subsequently, such expenditure has declined somewhat and stabilised.¹¹ In 2014 community drug schemes accounted for 14.5% of the State health budget.¹² However, the evidence suggests that increased demand for medicines, especially in view of the high priced new medicines coming to market, is likely to bring renewed pressure on the State's community drug schemes.¹³

In the analysis below we pay particular attention to the General Medical Scheme (GMS) and the High Tech Drug (HTD) scheme. GMS is a means tested benefit that provides medicines free of charge subject to a €2.50 copayment per item dispensed which is capped at €25 per family per month.¹⁴ HTD medicines are generally prescribed or initiated in hospital and are often high priced. Access to HTD medicines is provided to GMS and Drug Payment Scheme (DPS) patients. DPS is a non-means tested benefit, with the patient (or family) paying the first €144 per month, the State the excess.

The HTD and GMS are the two largest community drug schemes, with, in 2015, total ingredient costs of €473 million and €695 million, respectively.¹⁵ While in 2015 there were for the GMS 2,166,159 eligible persons, there were only 70,321 HTD recipients. The average prescription cost in 2015 for GMS was €12, for HTD, €750. However, while the nominal total ingredient cost of the GMS has declined between 2009 and 2015 by 27%, despite the number of eligible persons for GMS increasing by 47%, the total ingredient cost of the HTD increased by 69%.

Controlling Medicine Costs

¹⁰ Barry (2015, Slide 3). Community drug schemes include the General Medical Scheme, the Drugs Payment Scheme, the Long Term Illness Scheme and the High Tech Drug Scheme. For further details of the schemes see HSE (2016a, pp. 6-7).

¹¹ Barry (2015, Slide 3), which presents expenditure for 2009 to 2014. In the latter year expenditure was around €1.8 billion.

¹² Joint Committee on Health and Children (2015, p. 14), the numerator is defined as "*reimbursements on medicines and appliances.*"

¹³ Barry (2015).

¹⁴ These charges were introduced on 1 December 2013. As of 1 March 2017, for those persons 70 years of age and over, the per item charge was reduced to €2.00 and the monthly maximum to €20 per family per month. For details see: <http://www.hse.ie/eng/services/list/1/schemes/mc/prescriptioncharge/>. Accessed 23 May 2017.

¹⁵ All figures in this paragraph are taken from HSE (2010, 2016a) various tables and text.

The pattern of medicines expenditure in Ireland since 2009 reflects, in part, a series of administrative and legislative public policy measures at various levels in the supply chain: ex-factory or manufacturer; wholesale; and, retail or pharmacy. These measures were a response to consistent criticism of high medicine prices, low penetration of generics and large mark-ups in the supply chain combined with the onset of tight budgetary controls occasioned by the financial crisis of 2008.

Reducing wholesale and retail mark-ups

Research commissioned by the HSE demonstrating high wholesale and retail mark-ups for medicines led to the HSE imposing dramatically reduced mark-ups at both levels in the supply chain between 2008 and 2011.¹⁶

Increasing generic penetration: the Health Act 2013

In response to persistent reports of the low penetration of generics in both the community and the hospital setting in Ireland, compared to other developed countries,¹⁷ the Health (Pricing and Supply of Medical Goods) Act 2013 (the Health Act 2013) was introduced. For the first time a legal basis was provided for generic substitution by the pharmacist. The medical practitioner could, of course, always have prescribed a generic medicine.

The Health Products Regulatory Authority (HPRA) was given responsibility under the Health Act 2013 for establishing, publishing and maintaining a List of Interchangeable Medicines (the Interchangeable List).¹⁸ The DoH directed the HPRA to “*assess the interchangeability of a number of active substances in 2014.*”¹⁹ The first medicine to be included on the Interchangeable List was atorvastatin on 7 August 2013. At the present time there are 76

¹⁶ For details see Gorecki et al (2012, Table 2.3, p.23; pp. 86-88; pp. 112-113). The wholesale mark-up was reduced from 17.66% to 8%; the retail mark-up from 50 to 20%. There was considerable resistance to such moves by wholesalers and pharmacies. The reduction applied to community drug schemes operated by the State. Note that some community drug schemes, such as the GMS, had no retail mark-up.

¹⁷ For details see Brick et al (2013a, pp. 89-92) and Gorecki et al (2012, pp. 126-130).

¹⁸ Full details may be found on the HPRA’s website: <https://www.hpra.ie/homepage/medicines/regulatory-information/generic-and-interchangeable-medicines/>. Accessed 23 May 2017.

¹⁹ <http://www.hpra.ie/homepage/medicines/regulatory-information/generic-and-interchangeable-medicines/consultations-and-updates-to-the-list>. Accessed 23 May 2017.

‘active substances’ on the Interchangeable List,²⁰ including, in some cases, combinations of separately listed substances.²¹

The HSE was given legislative authority for setting the reference price for a group of interchangeable medicinal products, once the HPRA had included the products on the Interchangeable List.²² Certain legislative criteria were set down in section 24(3) of the Health Act 2013 as to how the reference price is to be determined which reflects concerns over cost and the need to ensure cost effectiveness.²³ Furthermore the HSE “*may use a competitive process to set the reference price for a relevant group of interchangeable medicinal product.*”²⁴

In practice in setting the reference price the HSE pays considerable attention to the price charged in other EU Member States. In the case of atorvastatin the HSE stated prices were high in Ireland, even in relation to other small Member States, and that this difference “*supports substantial price reductions.*”²⁵

The evidence suggests that the State has been successful in reducing expenditure on medicines deemed interchangeable by the HPRA and for which the HSE has set a reference price. In the case of atorvastatin monthly expenditure fell by approximately 50% between

²⁰ The Interchangeable List may be found at: <http://www.hpra.ie/homepage/medicines/regulatory-information/generic-and-interchangeable-medicines/list-of-interchangeable-medicines>. Accessed 23 May 2017.

²¹ For example, amiodipine and perindopril are listed as active substances both separately and as perindopril/amiodipine. See previous footnote for source. Note that medicines consisting of three or more active substances are not included on the Interchangeable List.

²² Section 24, Health Act 2013. The reference price is that which the HSE reimburses the pharmacist under the various community drug schemes.

²³ These include: “*the value for money,*” “*the relevant prices of therapeutically similar medicines,*” “*the resources available to the*” HSE, “*the equivalent relevant prices (if practicably available) of the relevant listed items in all other Member States where one or more than one of the relevant listed items is marketed,*” and the terms of any agreement in place between the HSE and industry and other representative bodies.

²⁴ Section 24(4), Health Act 2013. Such competitive processes might include competitive tendering, although we are not aware of any examples of its application for community drug schemes.

²⁵ HSE (2013, p. 2). Since this was the first instance in which the HSE set a reference price under the Health Act 2013, the HSE released several explanatory background documents, which may be accessed at: <http://www.hse.ie/eng/health/hl/Generics/ref/development.html>. Accessed 23 May 2017.

August 2013 and August 2014;²⁶ for esomeprazole over the same period the reduction was 40%.²⁷

The European Commission (2016, p. 74) commented that interchangeability combined with reference pricing “has generated savings on off-patent medicines. It has also increased the penetration of generics (international non-proprietary name plus branded generics), which represented 38.7 % of the volume of total medicines covered under the public system and 11 % in value in Q3-2015.” However, the European Commission was concerned about the lack of progress of the use by prescribers of the international non-proprietary name.

Reducing ex-factory prices

Efforts to moderate the ex-factory price of medicines, especially new medicines, reflect longstanding and widespread concerns that medicines prices and per capita expenditure on medicines were high in Ireland compared to other developed countries.²⁸ Under successive agreements between the State and the IPHA the State has sought to exert downward pressure on medicine prices. Measures include the addition of some lower priced Nominated States in the basket used to determine the price of new medicines and additional discounts on medicines where patent protection has expired.²⁹

These and other measures, however, failed to assuage concerns about medicine prices and per capita expenditure on medicines as reflected in: the experience of Irish residents purchasing medicines in countries such as Spain while on vacation;³⁰ press reports;³¹ reports of the legislature;³² research, some of which has been sponsored by the DoH and the HSE;³³

²⁶ Based on State expenditure under the GMS and the DPS which in August 2013 was €8.6 million, in August 2014, €4.2 million. The reference price for esomeprazole became effective on 1 November 2013. For details see Barry (2015, Slide 13).

²⁷ Based on State expenditure under the GMS and the DPS which in August 2013 was €7.4 million, in August 2014, €4.5 million. The reference price became effective on 1 January 2014. For details see Barry (2015, Slide 12).

²⁸ This applied especially for new medicines and those with no generic competition (i.e. off-patent medicines with exclusive supply).

²⁹ These are discussed in Brick et al (2013a) and Gorecki et al (2012).

³⁰ Based on conversations with individuals visiting these countries.

³¹ See, for example, Mitchell (2016a).

³² See, for example, Joint Committee on Health & Children, Houses of the Oireachtas (2015).

³³ See, for example, Brick et al (2013a) and Gorecki et al (2012), which were funded in this way, and IFAC (2015).

and, the European Union (EU) and the International Monetary Fund (IMF) which were responsible for providing financial assistance to Ireland after the financial crisis in 2008.³⁴

Preparations for negotiations with IPHA

In preparation for the negotiations with IPHA that led to the Agreement the negotiators on behalf of the State, were assisted by recommendations and suggestions as to how the ex-factory prices of new and existing medicines might be reduced and better value for money secured. These recommendations and suggestions were made relative to the 2012-2015 agreement (which was extended for an additional year to 2016) between the State and IPHA and included:³⁵

- The use of the lowest, rather than the average, of the basket of nine Nominated States, all in the EU,³⁶ used to set the external reference price of a new pharmaceutical.³⁷ A number of other countries, also relying on reference pricing, use the lowest as opposed to the average,³⁸
- The external reference price should be updated semi-annually (1 January and 1 July) rather than every two years. Ireland is often an earlier adopter of a new medicine with an initially high price. Hence it is important that the external reference price is updated to reflect its availability at lower prices in other countries in the basket of Nominated States.³⁹
- Parallel imports should be monitored by the HSE to validate the pricing information provided by the medicine manufacturers in setting the external reference price and in order to determine whether additional countries should be added to the basket of nine countries.⁴⁰

³⁴ See, for example, IMF (2013, p.90) which, together with the EU, demanded that a report be prepared on these issues, which resulted in Brick et al (2013a).

³⁵ These recommendations and suggestions are taken from Brick et al (2013a) and Gorecki et al (2012). In some instances these are reflected in the Joint Committee on Health & Children (2015) report on the cost of prescription drugs in Ireland, particularly the first three, but not the fourth.

³⁶ The nine Nominated States are: Austria; Belgium; Denmark; Finland; France; Germany; the Netherlands; Spain; and, the UK.

³⁷ Gorecki et al (2012, p.43).

³⁸ Gorecki et al (2012, Table 4.1, p. 40).

³⁹ Gorecki et al (2012, p.44).

⁴⁰ Gorecki et al (2012, p. 50).

- Consideration to a public dialogue on whether or not the appropriate cost-effectiveness threshold value of a QALY is €45,000 – as set out in the 2012-2015 agreement⁴¹ - given that the UK's National Institute for Health and Care Excellence (NICE) used a threshold range from €23,000/QALY to €35,000/QALY while NICE commissioned research suggested a lower threshold of €21,500/QALY.⁴²

Armed not only with a research base with which to inform itself in the negotiations with IPHA, the Health Act 2013 gave the HSE some additional powers that increased, in legislative terms at least, its bargaining power *vis a vis* the suppliers of new medicines in achieving price reductions. The Health Act 2013, for example, provided the HSE, once the 2012-2015 agreement had expired, the legal basis to set the price of new medicines unilaterally.⁴³

EVALUATING THE AGREEMENT

Introduction

There have been agreements between the State and the representative organization of the manufacturers of patented protected medicines setting the ex-factor price of medicines since July 1969.⁴⁴ In this section we outline the key features of the Agreement, how they compare to the 2012-2015 agreement (and, in some cases, earlier agreements) and the extent, where relevant, that the recommendations and suggestions informing the negotiations were reflected in the Agreement.

The €600 million savings claimed by the Minister for Health for the Agreement is aligned with key clauses of the Agreement (Table 1).⁴⁵ The most important category of savings is due, for example, to Clause 9, 'Rebate on Sales,' accounting slightly over a third of total savings. Hence in the discussion of the key features of the Agreement we will comment,

⁴¹ Annex 1, point 5, 2012-2015 agreement.

⁴² Brick et al (2013a, 25-29). See also Dillion (2015).

⁴³ Sections 18 and 21, Health Act 2013.

⁴⁴ In undertaking Brick et al (2013a) and Gorecki et al (2012), the DoH and HSE provided previous agreements. The July 1969 agreement, between the Pharmaceutical and Allied Industries Association and the DoH, was the earliest. It was five pages in length.

⁴⁵ The IPHA (2016) claimed that the savings due to the Agreement were €785 million. However, we do not have access IPHA estimates analogous to those in Table 1 and hence confine attention in this paper only to the DoH's estimates. Nevertheless, the IPHA estimates use no agreement as the counterfactual, while the estimates refer to only IPHA members. For a discussion of the IPHA estimates see Mitchell (2016b).

where relevant, on its implications for the State’s medicines bill. In other words, how credible are the estimates of savings due to the Agreement?

Table 1: Government Estimates of the Agreement’s Savings, Public Purchases, 2016-2020

Source of Savings (Clause of Agreement or 2012-2015 agreement)	Cumulative Savings 2016-2020 (€m)
Original Ex-Factory Price of New Medicine (Clause 6 & Assessment Principles) ^a	None
Annual Ex-Factory Price Alignments on Patent Protected and Exclusive Off-Patented Medicines (Clauses 5, 7.1.3 & 8.1.4) ^b	205
Pricing of Patent-Expired, Non-Exclusive (Excluding Biologic) Medicines (Clause 7)	
Existing Clause 6 (of 2012-2015 agreement)	90
Price Reduction Straight to 50% ^c	25
Pricing of Patent-Expired, Non-Exclusive Biologic Medicines (Clause 8)	55
Biologics less 30%	
Rebate on Sales (Clause 9)	
Existing Rebate (4%) Clause 9 (of the 2012-2015 agreement) ^d	115
Hospital Rebate (5.25% rising to 5.5%) ^e	70
Extra Rebate (1.25% rising to 1.5%) ^e	40
Total	600

- a. Original Ex-Factory Price of a New Medicine was not included in the DoH documentation, but DoH confirmed that there were no savings under this heading in the €600 million.
- b. “Extended Reference Basket & Price Realignments” in the DoH documentation.
- c. “Clause 7 (previous Clause 6) straight to 50%” in the DoH documentation. Instead of 30% in year 1 and 50% in year 2, the 50% reduction occurs in year 1.
- d. “PCRS Rebate” in DoH documentation. DoH confirmed that this referred to the 4% rebate in the 2012-2015 agreement and continued in the Agreement.
- e. The first increase occurred from 1 June 2016 to 31 July 2018; the second from 1 August 2018 to 31 July 2018.

Source: Based on information provided by the DoH.

It should be noted that there is no detailed account of the methodology, modelling, data sources or assumptions in the public domain concerning the DoH’s derivation of the €600 million. All that is available is the table itself and the press release issued by the DoH (2016a) on the announcement of the Agreement.^{46,47}

⁴⁶ The figures in the table were, for example, used by Mitchell (2016b).

⁴⁷ In a number of instances it was not entirely what the link was between the information provided on which Table 1 is based and the Agreement. DoH helpfully provided clarification.

The Counterfactual

In evaluating the impact of any policy intervention an important issue is relative to what? In other words, if the policy intervention had not taken place what would the world have looked like? This is sometimes referred to as the counterfactual. It provides a benchmark against which to measure the impact of the policy intervention.

In the case of assessing the impact on competition of a merger between two firms, the counterfactual is typically taken as the world in which these two firms continue to act as independent entities competing with one another; in other words, the status quo.⁴⁸ The state of competition between the two states – the status quo and the merger - is then compared to determine the impact of the merger on competition.

In a recent UK evaluation of the value of certain services (e.g. managing drug shortages, managing prescribing errors) provided by pharmacies, pwc (2016) assumed that under the counterfactual that although pharmacies would not provide these services, patients might be able to access the services via other existing channels. In other words, the counterfactual was not that the services would fail to be supplied at all, but that only one source or channel would cease to supply.

In the case of the cost-effectiveness analysis undertaken by the National Centre for Pharmacoeconomics (NCPE) for the HSE – which we discuss in more detail below – for a new medicine, the counterfactual is existing therapies, which may include other medicines. In other words, the counterfactual is how patients would be treated absent the new medicine. The alternative is not no treatment. The NCPE, on the basis of a comparison with the counterfactual, determines whether or not the new medicine is value for money/cost effective.

In the case of the Agreement the counterfactual is what would have happened absent the Agreement. The counterfactual in terms of HSE medicine expenditure can then be compared to the Agreement in terms of HSE medicine expenditure. The difference in expenditure can then be attributed to the Agreement.

⁴⁸ Competition and Consumer Protection Commission (2014, paras. 1.12-1.15).

It seems reasonable to assume that the State and the IPHA would have concluded *an* agreement covering the period 2016-2020. Such agreements have existed since 1969 and have been renewed and renegotiated on a regular basis. Hence while it may have made sense in 1969 to argue that the counterfactual was a world without a State/IPHA agreement, in 2016 it was more difficult, but it is an issue we will return to below and in ‘Implications.’

The next question is naturally what agreement. The simplest assumption or counterfactual – and the one we make in the analysis below – is to assume that the 2012-2015 agreement would have been replicated and its three year term extended by one year to 2020. In other words, the savings envisaged under the Agreement are derived by a comparison with the 2012-2015 agreement, the status quo.

The baseline projection for HSE medicine expenditure is the existing 2012-2015 agreement. If the State can negotiate better terms then there will be additional funds available to spend on medicines. The DoH press release announcing the Agreement is consistent with the view that the counterfactual is the 2012-2015 agreement, rather than no agreement.

The DoH (2016a) states, for example,

“The pricing provisions in this agreement represent a significant improvement on those contained in the previous agreement. They will see an expansion of the reference basket used to set prices in Ireland from the present nine to 14 countries, including for the first time Greece, Italy and Portugal. The agreement also includes, for the first time, an annual price realignment to ensure that the prices of medicines in Ireland reduce in line with price changes across the reference Countries. A rebate of 5.25% rising to 5.5% will further reduce the overall cost of medicines in the years ahead.”

In the ‘Notes to Editors’, the press release points out the key pricing elements in the Agreement, which highlight the improvements as compared with the 2012-2015 agreement.

Nevertheless, inspection of Table 1 and discussions with the DoH, confirm that the counterfactual underlying the €600 million estimate is no agreement. This is a hard position to justify given, as noted above, the long record of State/IPHA agreements stretching back

almost 50 years. Furthermore if for whatever reason a State/IPHA agreement could not be reached the counterfactual is not no agreement: the HSE has power under the Health Act 2013 to set the terms and conditions on which it will purchase medicines unilaterally.⁴⁹ Indeed, during the course of the negotiations leading to the Agreement, the State threatened to unilaterally use its powers under the Health Act 2013 to set medicine prices.⁵⁰ It is, however, an empirical question whether the choice of the no agreement counterfactual or the 2012-2105 agreement or status quo counterfactual makes a material difference in the estimate of the savings flowing from the Agreement.

Signatories to the Agreement

Agreement provisions

There are three signatories to the Agreement: on behalf of the sellers of medicines, IPHA; on behalf of buyers, the HSE and the State Negotiation Team.⁵¹ The State Negotiation Team also includes representatives from the DoH, DPER and the OGP.⁵² DPER was only created in 2011 and is responsible for monitoring public expenditure and, not surprisingly has issued a number of reports on the health service, including the community drug schemes.⁵³ As part and parcel of setting up DPER, the Irish Government Economic and Evaluation Service (IGEES) was the created, in part because of the perceived lack of economic expertise in central government departments at the time of the financial crisis of 2008.

A comparison with the 2012-2015 agreement

The 2012-2015 agreement was between the IPHA, on the one hand, and, on the other, the HSE and the DoH. Such a pattern is consistent with earlier agreements.⁵⁴ Hence the major

⁴⁹ See Box 1 below. Furthermore reference pricing is independent of the Agreement.

⁵⁰ For further discussion see Harris (2016) and Wall & Bardon (2016).

⁵¹ Agreement, p. 13.

⁵² Agreement, 'Introduction', p. 1. See also DPER (2016, p. 26).

⁵³ For details see: <http://igees.gov.ie/publications/economic-analysis/health/>. Accessed 23 May 2017. Callaghan (2015), for example, discusses the Primary Care Reimbursement Service (PCRS) of the HSE which administers the community drug schemes.

⁵⁴ Prior to the HSE coming into operation on 1 January 2005 the DoH signed the agreement in behalf of the buyers. The HSE was the sole signatory on behalf of the buyers for the 2006-2010 agreement.

change between the Agreement and earlier agreements is the addition of DPER to the negotiating team on behalf of the buyers.

Discussion

It is difficult to evaluate the involvement of DPER on the final Agreement. It is not possible to design a counterfactual without the involvement of DPER. Notwithstanding this, there are two areas where one might reasonably have expected the influence of a central government department concerned with public expenditure and value for money staffed by economists to have manifested itself.

The first is on the setting a cost-effectiveness threshold and strict criteria if this threshold is to be exceeded.^{55,56} However, as we shall see below, if anything, the cost-effectiveness thresholds appear to have been relaxed if not abolished, in the Agreement compared to the 2012-2015 agreement.

The second is publication of an analysis of the savings to be expected from the Agreement, together with the underlying methodology and assumptions. This could easily have been included in DPER's series of papers on health issues. However, no such analysis has been published to date.

Scope & Term

Agreement provisions

The Agreement refers "*solely*" to medicines of IPHA member firms included on the Reimbursement List and/or supplied to, or reimbursed by the HSE (under, for example, the community drug schemes) and/or State-funded hospitals.⁵⁷ Under section 17 of the Health

⁵⁵ This is pertinent when considering the original price of a new medicine.

⁵⁶ For example, a central government department would arguably have a strong interest in securing a consistent approach across government departments and agencies to issues such as the value of a QALY and/or the value of a life.

⁵⁷ Clause 2.1 of the Agreement. Relevant Agencies are covered by the Agreement. These are defined to include not only State-funded hospitals but also "*any other publicly-funded entities and State agencies in each case whose functions include the provision of*" medicines. Terms are defined in Clause 1.2 of the Agreement.

Act 2013 the HSE has to maintain a Reimbursement List of medicines which are eligible for patients on the community drug schemes and in State funded hospitals.⁵⁸

Although the Agreement is between the State and the IPHA,⁵⁹ it appears its provisions applies all suppliers of new medicines filing applications for inclusion on the Reimbursement List, irrespective of whether or not they are members of IPHA.⁶⁰ The Agreement's pricing arrangements refers to all medicines, including biologic and biosimilars.

Notwithstanding the wide applicability of the Agreement, the savings estimates presented in Table 1 only refer to IPHA members. However, since the IPHA accounts for the vast majority of the research based pharmaceutical industry, the omission of a small number of companies should not result in a serious underestimate of the impact of the Agreement.⁶¹

The Agreement commenced on 1 August 2016 and expires on 31 July 2020, with the expectation that negotiations for a successor agreement will commence six months before the expiry of the Agreement.⁶²

A comparison with the 2012-2015 agreement

There is a considerable degree of similarity in terms of the scope and term. The four year term of the Agreement is, for example, not significantly out of line with the duration of earlier such agreements. The first agreement between the State and the industry representative body ran for four years, more recently the length has been between three to four years.⁶³

⁵⁸ Interchangeable medicines would be included on the Reimbursement List at the reference price. The Reimbursement List also includes medical and surgical appliances. In some parts of the Health Act 2013 these are referred to as 'items'.

⁵⁹ Clause 2.2 of the Agreement.

⁶⁰ McCullagh and Barry (2016). The DoH (2016a) refers to additional unspecified savings for non-IPHA suppliers which would include Vertex Pharmaceuticals and Gilead Sciences Inc.

⁶¹ According to the IPHA its members account for in excess of 90% of the purchases by the State of medicines supplied by the international research based pharmaceutical industry in Ireland.

⁶² Clause 3 of the Agreement.

⁶³ See Brick et al (2013a, Table 3.1, p. 19). Three to four years refers to the length as set out in the 2006-2010 and 2012-2015 agreements. However, in both cases these agreements were extended and in one case an interim arrangement was put in place. If these extensions and interim arrangements are taken into account then the 2006-2010 agreement ran to 2012 and the 2012-2015 agreement ran to 2016. It may be, of course, be the case that the Agreement is extended beyond 2020.

In contrast to the 2012-2015 agreement, however, there is no provision for a Mid Term Review.⁶⁴ There is, however, a provision in the Agreement under “Oversight of Agreement” for “[T]he Parties to meet bi-annually on dates to be agreed between the Parties to review and discuss any issues arising from the operation of the Agreement.”⁶⁵ A similar provision appeared in the 2006-2010⁶⁶ agreement. Given the limited scope of the Mid Term Review, there appears to be a considerable degree of continuity in the review provisions across recent agreements between the State and the IPHA.

Original Ex-Factory Price of New Medicines

The agreement provisions⁶⁷

The Agreement contains provisions for the original or initial pricing of new medicines for inclusion in the Reimbursement List. Once the original price of a new medicine is set it is realigned on an annual basis as set out in Clause 5 of the Agreement and discussed in the next section. A new medicine is defined as one “with a Marketing Authorisation introduced into the State after the commencement of this Agreement, during the Term ...”⁶⁸

All applications by a supplier for a new medicine to be added to the Reimbursement List,

“shall be made in accordance with the relevant provisions of the [Health Act] 2013 ... and with the provisions set out in Schedule 1, the Principles and Processes for the Assessment of new Medicines in Ireland (hereinafter ‘the Assessment Principles’) which form an integral part of this Agreement.”

The Agreement then lists two mechanisms for the determination of the maximum supplier original price, depending on whether or not the medicine is available in at least one of the fourteen Nominated States set out in the Agreement on the date of application.⁶⁹

⁶⁴ Clause 12.1, 2012-2015 agreement. The Mid Term Review only referred to the “governance and operation” of the 2012-2015 agreement.

⁶⁵ Clause 13.6 of the Agreement.

⁶⁶ Clause 11.1, 2006-2010 agreement, which read: “The operation of this Agreement will be reviewed by the HSE and IPHA at regular intervals and any matter relating to the interpretation of these terms, including price terms or the operation of the Agreement, shall be resolved in discussions between the IPHA and HSE.”

⁶⁷ Clause 6 of the Agreement and the Assessment Principles.

⁶⁸ Clause 1 of the Agreement.

⁶⁹ The fourteen Nominated States are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the UK. (Clause 1.2 of the Agreement). Together

- if the new medicine is available in one or more of the Nominated States then the medicine's *maximum* proposed original price is the average price across the Nominated States in which the medicine is available; or
- if the new medicine is not available in any of the Nominated States, then the suppliers "*shall propose a price which shall be considered by the HSE in accordance with the [Health Act] 2013 ... and, as applicable, the HSE Assessment Principles.*"

Hence the supplier of a new medicine proposes a maximum original price based either on the mean across some or all of the Nominated States or on the provisions of the Health Act 2013 and the Assessment Principles.

*Assessment Principles*⁷⁰

The Assessment Principles, Schedule 1 of the Agreement, set out the "*central principles and guidelines that will underpin the assessment of new medicines in Ireland which seek to be added to the Reimbursement List ...*"⁷¹ The Assessment Principles are based on and reflect the provisions of the Health Act 2013. The principles are the responsibility of the HSE. After permitting IPHA to make representations, the HSE "*reserves the right to amend or update the content hereof as it deems appropriate with the [Health Act] 2013 ... and, as applicable, the HSE Assessment Principles.*"⁷²

The key features of the Assessment Principles with respect to the approval and pricing of a new medicine is as follows.

First, in assessing whether or not to include a new medicine on the Reimbursement List and at what price, the HSE shall have regard to the criteria specified in the Health Act 2013.⁷³ These criteria, which are reproduced in Box 1, provide the legal basis for considerations of cost-effectiveness, notably, explicitly framing the issue in terms of the opportunity cost of

with Ireland, these fifteen Member States constituted the EU15 prior to the accession of 10 candidate countries on 1 May 2004.

⁷⁰ Schedule 1 of the Agreement.

⁷¹ Agreement, p. 16.

⁷² Agreement, p. 17.

⁷³ Agreement, pp. 18-19.

other interventions foregone.⁷⁴ The other factor that is stressed in the Health Act 2013 is the resource implications of listing/pricing a new medicine in terms of the HSE budget

BOX 1: Panel A, Criteria to Add a Medicine to the Reimbursement List, Health Act 2013

Section 19(4) states that the HSE “shall not make a relevant decision” to add a new medicine to the Reimbursement List except in accordance with the criteria specified in Schedule 3. Part 3 of that schedule states that the HSE “shall have regard to”:

- (a) *the health needs of the public,*
- (b) *The cost-effectiveness of meeting health needs by supplying the item concerned rather than providing other health services,*
- (c) *....,*
- (d) *the proposed costs, benefits and risks of the item ... relative to therapeutically similar items ... provided in other health service settings and the level of certainty in relation to the evidence of those costs, benefits and risks,*
- (e) *the potential or actual budget impact of the item,*
- (f) *the clinical need for the item,*
- (g) *... ,*
- (h) *The efficacy (performance in trial), effectiveness (performance in real situations) and added therapeutic benefit against existing standards of treatment (how much better it treats a condition than existing therapies), and,*
- (i) *the resources available to the HSE.*

BOX 1: Panel B, Criteria to Set the Price of a New Medicine Added to the Reimbursement List, Health Act 2013

Section 21 (2) states that the HSE “when considering the proposed relevant price by the supplier of an item take into account”:

- (a) *the equivalent relevant prices (if practicably available) of the item on all other Member States where the item is marketed,*
- (b) *the relevant prices of therapeutically similar listed items,*
- (c) *the potential therapeutic benefits of the item for patients likely to use the item if it were to become a listed item,*
- (d) *the potential budget impact if it were to become a listed item,*
- (e) *....,*
- (f) *the resources available to the Executive, and*
- (g) *the terms of any agreement in place between the Executive and any representative body of the suppliers of drugs, medicines ... where the agreement relates ... to the price of the item.*

Note: Executive refers to the HSE; item to drug, medicine, or medical or surgical appliance which is not on the Reimbursement List.

Source: Health Act 2013

Second, in reaching a decision on the application of these criteria, the HSE draws on the expertise and advice of the NCPE.⁷⁵ The latter plays a vital role in reviewing all applications

⁷⁴ Implicitly this criterion recognizes the concept of opportunity cost, since the alternative to expenditure on a medicine non-medicine related healthcare expenditures. See O’Mahony & Coughlan (2016) for further discussion.

⁷⁵ According to its website, <http://www.ncpe.ie/>, “[T]he mission of the NCPE is to facilitate healthcare decisions on the reimbursement of technologies, by applying clinical and scientific evidence in a systematic framework, in order to maximise population wellness.” For a full account of the role played by the NCPE see McCullagh and Barry (2016).

by suppliers of new medicines⁷⁶ and pays particular attention to Part 3, Schedule 3 of the Health Act 2013, which is reproduced in Box 1.⁷⁷

Third, the Assessment Principles set out a decision-making authority cost-effectiveness threshold/net budget impact matrix which is reproduced as Table 2: the greater the budget impact and/or the higher the cost per QALY, the more likely that the senior most level of HSE management becomes the decision maker.

Fourth, Table 2 is the only mention of the application of cost-effectiveness threshold in the HSE decision making process in the Agreement. The table implies that there is no threshold in terms of either the cost per QALY and/or the budget impact of a new medicine, subject, of course, to any HSE budget constraint and the criteria in the Health Act 2013.

Fifth, there is a strict timetable laid down for the processing of an application for a new medicine to be included on the Reimbursement List. These are consistent with section 18 of the Health Act 2013.

Table 2: Decision Making Authority for New Medicines, by Budget Impact & QALY, Ireland, 2016-2020^a

		QALY Threshold as per NCPE Assessment		
		Up to €20,000	Up to €45,000	Above €45,000
Net Budget Impact as per NCPE Assessment for each medicine	Budget Neutral- €5m	HSE (non-leadership)	HSE (non-leadership)	HSE Leadership
	>€5m <€20m	HSE (non-leadership)	HSE Leadership	HSE Leadership
	>€20m	HSE Leadership	HSE Leadership	HSE Leadership

Note: The HSE reserves the right for all medicines to be considered by the Leadership. The NCPE's estimate of the budget impact is over five years but is subject to a gross budget impact of less than €30m for the two lower thresholds in the table.

Source: Agreement, p. 24.

⁷⁶ Agreement, p. 20.

⁷⁷ This is reproduced in Box 1. The use of Part 3 of Schedule 3 of the Health Act 2013 is explicitly acknowledged in the diagram at p. 23 of the Agreement.

Sixth, where a medicine cannot be funded by the HSE from existing resources, the HSE may inform the DoH “of its decision in this respect. The Department of Health may, as it deems appropriate, bring a memorandum to Government in relation to the funding implications and requesting consideration of same.”⁷⁸ So far as we are aware this does not appear to have happened to date.⁷⁹

*Implementation: the NCPE/HSE Review Process*⁸⁰

The supplier submits to the HSE its proposed price and any associated documentation for a new medicine for inclusion on the Reimbursement List. The HSE initially refers the material to the NCPE for a Rapid Review (within four weeks) with respect to the budget impact and cost-effectiveness – the two dimensions of the decision matrix in Table 2.⁸¹ The NCPE’s Rapid Review recommends whether or not the new medicine should be subject to a Health Technology Assessment (HTA).^{82,83} New medicines that lie in the south west quadrant of Table 2 – high cost per QALY and/or high net budget impact – are typically subject to a HTA.⁸⁴ In some cases the supplier will decide not to proceed to a HTA where this has been recommended by the NCPE, in others the supplier will propose price reductions to avoid an HTA.⁸⁵

The NCPE, based on the HTA, recommends to the HSE whether or not the new medicine should be added to the Reimbursement List at the submitted price.⁸⁶ It is the HSE’s decision as to whether or not to add a medicine to the Reimbursement List and if so at what price

⁷⁸ Agreement, para. 12, p. 21. See also the NCPE’s Process Flowchart, <http://www.ncpe.ie/submission-process/process-flochart/>. Accessed 23 May 2017.

⁷⁹ With one possible exception. See footnote 93 below.

⁸⁰ For details see diagram on p. 23 of the Agreement. McCullagh & Barry (2016) provide a through description of the process based upon their experience in the NCPE.

⁸¹ Over the period 2010 to 2015, 230 Rapid Reviews were conducted, with an HTA recommended in 122 or 53% instances. For further details of the outcomes see McCullagh and Barry (2016, p. 8).

⁸² For references to the HTA methodology see: <http://www.ncpe.ie/submission-process/hta-guidelines/>. Accessed 23 May 2017.

⁸³ McCullagh & Barry (2016, p. 4) discusses the factors that determine whether the NCPE recommends the medicine should be added to the Reimbursement List at the Rapid Review stage. For example, the medicine covers only “a small eligible population ..., an unmet need and an associated low budget impact (p. 4).”

⁸⁴ This is stated by the NCPE: <http://www.ncpe.ie/pharmacoeconomic-evaluations/>. Accessed 23 May 2017.

⁸⁵ McCullagh & Barry (2016, p. 8).

⁸⁶ A short summary of the HTA is published on the NCPE’s website. However, there are no summaries available of the Rapid Reviews.

and any possible conditions. However, the HSE does not issue any reasoned decision concerning acceptance/refusal of a new medicine for reimbursement purposes.⁸⁷

In terms of cost effectiveness the NCPE uses a QALY threshold of €45,000.⁸⁸ Table 3 presents ten instances between August 2016 and January 2017 where the verdict “*Reimbursement is not recommended at the submitted price*” was the outcome of the NCPE’s HTA.⁸⁹ In several instances the cost per QALY at the submitted price is exceeds the €45,000 threshold by a factor in excess of 10 or 20 fold. The budget implications in some cases exceed €100 million. HSE reimbursement decisions on these medicines will be made in the coming months.⁹⁰

Table 3: National Centre for Pharmacoeconomics, Reimbursement Not Recommended at Submitted Price,^a Ten Examples, August 2016 -January 2017.^b

INN ^c	Brand	QALY ^d	Five year Budget Impact Gross/Net ^e (million)
obinutuzumab	Gazyvaro	€52,248	€6.5/€5.6
colimetinib	Cotellic	€108,284 - €326,868 ^f	€22.1/€15-16.5
human alpha-1 proteinase inhibitor	Respreeza	€581,322	€37.1/€n.a.
elosulfase alfa	Vimizim	€1,032,228	€11/€11
vortioxetine	Brintellix	€3,210,230	€13.4/€10.2
carfilzomib	Kyprolis	€73,449 & €125,759 ^f	€26.4/€9.7
evolocumab	Repatha	€286,182-€452,741 & €204,700-€299,336 ^f	€152.3 to €258/€n.a
ivacaftor ^g	Kalydeco	€465,546	€21.0/€15.3-€22.7
nivolumab ^h	Opdivo	€202,393	€57.1/€56.3
ruxolitinib	Jakavi	€320,600	€11.7/€10.5

a. Typically the medicine is approved for particular treatment. It is possible that the medicine has already been approved for certain treatment and the supplier is applying for further treatment uses. See, for example, footnotes g and h below.

b. 16 August 2016 to 26 January 2017. Dated by when the NCPE completes its evaluation, as per the NCPE’s website.

⁸⁷ Under point 15 of the Assessment Principles the “HSE will publish a Drugs Group meeting note in relation to its deliberations on each medicine considered by the Drugs Group. This will be published at the final conclusion of the reimbursement application process and following notification to the Company of the final decision.” However, after an examination of the HSE’s website, we were unable to locate these minutes.

⁸⁸ For details see: <http://www.ncpe.ie/submission-process/>. Accessed 23 May 2017.

⁸⁹ Note that a medicine in Table 3 may have already been approved by the HSE for reimbursement for particular indications. However, the supplier has decided to file an application for an extension of the medicine’s uses.

⁹⁰ In the case of human alpha-1 proteinase inhibitor the Alpha One Foundation has already called on the Minister to intervene. This has attracted a certain amount of media attention. For details see <http://www.alpha1.ie/news-events/latest-news/289-decision-not-to-fund-respreeza>. Accessed 23 May 2017.

- c. International Nonproprietary Names.
- d. The Incremental Cost Effectiveness Ratio is reported in this column. It is the ratio of the incremental costs of the medicine divided by the incremental QALY due to the medicine. Only NCPE's preferred estimate(s) are included.
- e. In some cases the net and the gross are the same, since there is no displaced treatment cost offsets associated with the uptake the medicine being assessed.
- f. In some instances the medicine might be compared to more than one alternative, resulting in more than one QALY estimate. Only the NCPE's preferred estimate(s) is included.
- g. For use for children with cystic fibrosis aged 2 years and older and weighing less than 25kg who have one of the relevant gating (class III) mutations in the CFTR gene.
- h. For treatment of locally advanced or metastatic non squamous NSCLC after prior chemotherapy in adults.

Source: NCPE.

If the NCPE recommends against listing, the HSE and the supplier may enter into negotiations concerning the price and any other associated conditions for acceptance. When agreement is reached the price is not always revealed.⁹¹ In such instances it may form part of a confidential Patient Access Scheme (PAS).

It is not unreasonable, however, to assume that the implied QALY at the negotiated price will exceed €45,000. For example, in the case of ipilimumab (Yervoy) the NCPE recommended on 2 September 2011 against reimbursement on the basis that the QALY was €147,899 at the submitted price. Notwithstanding this recommendation, after much public discussion and negotiations between the HSE and the supplier, ipilimumab was added to the Reimbursement List in September 2013 at a price implying a QALY of €116,000, or more than twice the €45,000 threshold.⁹²

The application of these provisions and principles does not, however, lead to a simple yes or no in terms of the HSE accepting the maximum price proposed by a supplier as appropriate. Rather judgments are made by the HSE concerning the QALY, the budgetary impact and other factors mentioned in the Health Act 2013 (Box 1) as to the appropriate reimbursement price. As a result there is often an extensive negotiation between the HSE and the supplier which on occasion is played out in the media, particularly when the

⁹¹ For example, for the medicine Orenzia, which was subject to a NCPE HTA, commencing 2 July 2013 and completed on 11 November 2013, the outcome was: "*Reimbursement not recommended at the submitted price.*" This outcome reflected the NCPE's finding that the most plausible QALY was €79,510, well above the €45,000 threshold used by the NCPE. However, the NCPE report that in November 2015, two years later, that "*The HSE has approved reimbursement following confidential price negotiations.*" For details see <http://www.ncpe.ie/drugs/abatacept-orencia/>. Accessed 23 May 2017.

⁹² Barry (2014, slides 19-20) and <http://www.ncpe.ie/drugs/ipilimumab-yervoy/>. Accessed 23 May 2017.

beneficiaries of a new medicine perceive it to their advantage to make a public issue of the listing decision.⁹³

A comparison with the 2012-2015 agreement

There are four important differences between the 2012-2015 agreement and the Agreement. First, five additional Member States are added to the list of Nominated States used to determine the average maximum original ex-factory price of a new medicine submitted by the supplier to the HSE. This is part of a longer term trend of adding more Member States to the list of Nominated States.⁹⁴ Second, the approach to setting the price has arguably changed with the passage of the Health Act 2013, which contains specified criteria, which were set out in Box 1. Third, the cost-effectiveness procedures, which are a relatively recent addition to setting the original price of new medicines,⁹⁵ are outlined in much greater detail. Fourth, the cost effectiveness threshold that existed in the 2012-2015 agreement has been eliminated or at least attenuated. We consider each in turn.

⁹³ This occurred with respect to lumacaftor/ivacaftor (Orkambi). The NCPE recommended against reimbursement on 1 June 2016. The QALY was €649,624; the five year budget impact was estimated to be €391.9 million. (For details see: <http://www.ncpe.ie/drugs/lumacaftorivacaftor-orkambi/>. Accessed 23 May 2017). Subsequent to the NCPE report there has been considerable press coverage of the negotiations between the HSE and the supplier, with contributions by the Minister for Health and a representative body for the beneficiaries of the medicine, Cystic Fibrosis Ireland (CFI). CFI held a number of demonstrations in support of adding Orkambi to the Reimbursement List. In May 2017 the HSE (2017) announced that an agreement had been reached for this to occur, but with the details still to be finalised. It is not clear if Orkambi will be funded from the HSE's budget or whether a letter has been sent to the DoH from the HSE concerning funding. When a government spokeswoman was asked where the funding would come from for Orkambi - the HSE or new monies - she refused to answer claiming, somewhat improbably, that this was "*commercially sensitive*" (Cullen, 2017).

⁹⁴ The linking of Irish pharmaceutical prices to those in foreign markets (i.e. Nominated States) has featured since the 1983-1985 agreement. In clause 2 of that agreement the benchmark was UK prices due to the fact that "*the great majority of drugs and medicines used in the health service originate in the United Kingdom.*" In clause 9.2 of the 1990-92 agreement the benchmark changed: the price of a new medicine "*shall not exceed ... the lesser of the currency adjusted UK Wholesale Price and the average of the currency adjusted wholesale prices in the following EC States, Denmark, France, Germany, the Netherlands and the UK.*" In clauses 5.2 and 5.7 of the 2006-2010 agreement the benchmark for a new medicine was the average currency adjusted price in Belgium, Denmark, France, Germany, the Netherlands, Spain, the UK, Finland and Austria. Hence the importance of the UK as a benchmark has decreased and reference pricing captures to a greater extent the European price of a new medicine as more and more Member States are added to the list of Nominated States.

⁹⁵ The right of the HSE to "*to assess new and existing technologies (pharmaceuticals, diagnostics and devices) that may be high in cost or have a significant budget impact on the Irish healthcare system*" was first included in clause 4.3 of the 2006-2010 agreement. Such assessments were to be "*conducted with the existing agreed Irish Healthcare Technology Assessment [HTA] Guidelines.*" Clause 4.3 of the 2012-2015 agreement used similar language, but also contained "*Annex 1: Principles and Process for the Reimbursement of New Medicines in Ireland.*"(Principles and Process).

The Agreement added five countries to the list of nine Nominated States in the 2012-2015 agreement: Greece; Italy; Portugal; Sweden; and Luxembourg. As the DoH (2016a) note the list includes some Member States that typically have lower prices such as Greece. However, it is unlikely that adding these five Member States will influence the price of new medicines. Ireland is an earlier adopter of new medicines.⁹⁶ Such medicines are initially available in higher priced Member States such as Germany or UK rather than (say) Greece. This reflects a so-called launch sequence strategy by suppliers, which is *“used to delay or avoid launching new drugs in countries with lower prices ...”*⁹⁷

Under the Agreement the supplier submits a maximum original ex-factory price, which is then subject to a NCPE Rapid Review and possibly a full HTA. If the cost per QALY is above €45,000/QALY threshold and/or the net budget impact is substantial then NCPE recommends against adding to the Reimbursement List and the HSE may enter into negotiations as to the price. However, it is the HSE which makes the decision concerning price and reimbursement, guided by the Agreement, the NCPE evaluation and the legislative underpinning of the Health Act 2013.

An examination of the 2012-2015 agreement suggests that a similar procedure was in place although the description of the procedure in this agreement appears to be somewhat different.⁹⁸ While it is the case that the Health Act 2013 gives the HSE a legal basis for considerations of cost-effectiveness and budget impact, it appears that these factors were as relevant in assessing new medicines submitted under the earlier agreement.⁹⁹ Hence the approach to setting the price of new medicines has arguably remained largely unchanged, except perhaps with respect to the threshold cost per QALY as discussed below.

⁹⁶ McCullagh & Barry (2016, p. 3), Toumi et al (2014, p. 99) and European Commission (2009, Figure 36, p. 152). However, more recently the IPHA has claimed that the reimbursement process is lengthening in Ireland (McDonagh, 2017).

⁹⁷ Toumi et al (2014, p. 27, but see also pp. 31-2).

⁹⁸ Clause 5.2 of the 2012-2015 agreement states that the original price of a new medicine will be the average price in the Nominated States or as set out in Annex 1 of that agreement, Principles and Process which, says that the new medicines that do not require a HTA or those which receive a positive HTA outcome will receive pricing approval either at the lower of the price submitted for the HTA or the average of the Nominated States. However, it is not clear how the price submitted for the HTA is estimated. One interpretation is that it is the price resulting in a QALY of equal to or less than €45,000.

⁹⁹ For a discussion see McCullagh & Barry (2016).

The Agreement sets out in much greater detail the cost-effectiveness procedures and principles than the 2012-2015 agreement. In the latter case these procedures and principles are set out in the one page Annex 1, Principles and Process.¹⁰⁰

The most striking difference between the Principles and Process and the Assessment Principles is the treatment of the threshold QALY. In the Principles and Process it is stated specifically at point 5 that “*The QALY threshold to be used in the HTA process is €45, 000,*” but with the qualification at point 11 that for “*exceptional products*” that exceed the €45,000 threshold “*for a variety of reasons,*” may be processed after discussions with the HSE, DoH and relevant clinicians.¹⁰¹

As noted above the Agreement contains no reference or discussion of the relevant QALY threshold except for Table 2, although, somewhat paradoxically, the NCPE continues to use this threshold. The Agreement does not state, for example, that the €45,000/QALY threshold can be exceeded in exceptional circumstances.

It could thus be argued that the 2012-2015 agreement placed a firmer constraint on the QALY threshold than the Agreement with the result that original new medicine prices will be higher than they otherwise would be under the Agreement. On the other hand, the €45,000/QALY threshold in the 2012-2015 agreement might have led suppliers to use this as a floor rather than a ceiling, with the result that the lack of a cost-effectiveness threshold in the Agreement gives the HSE greater flexibility in the pricing of new medicines. However, based on available information, we are unable to distinguish between these two views.

Given the similarity in determining the price of new medicines under the Agreement and the 2012-2015 agreement, we conclude that Agreement will not result in any additional savings compared with the 2012-2015 agreement counterfactual. Furthermore, no savings are attributed by the DoH in Table 1 to the Agreement in the pricing of new medicines under the no agreement counterfactual.

¹⁰⁰ See also clause 4.3 (“Pharmacoeconomic Assessment Prior to Reimbursement,” of the 2012-2015 agreement.

¹⁰¹ This interpretation of the threshold is confirmed by Hennessy (2015, p. 3).

Discussion

New medicine prices set the benchmark for expenditure on medicines and the base for subsequent price reductions. As noted above the price of new medicines is anticipated to put considerable pressure of the HSE's medicine budget over the period covered by the Agreement. Nevertheless, none of the suggestions and recommendations concerning ways in which such prices could be reduced is reflected in the Agreement. Therefore, it seems relevant to ask why so little changed in the Agreement.

The suppliers of new medicines desire to keep prices high in Ireland because, according to an executive of a leading pharmaceutical supplier writing to the Taoiseach in 2012, prices in Ireland are used to set prices in 11 other European countries and up to 37 additional countries worldwide.¹⁰² Hence if the list or posted price declines in Ireland then this has adverse repercussions for pharmaceutical firms across EU and non-EU markets.

The Minister for Health in announcing the Agreement stated that

“The Government wants to ensure that Irish patients continue to have access to new and innovative medicines and that Ireland remains at the forefront of its European peers in terms of early access to medicines in an affordable manner within available resources.”¹⁰³

If Ireland wishes to be in the forefront of new medicine adoption then prices need to be high or else the launch sequence strategy of suppliers will place Ireland further down the pecking order to receive a new medicine. This is, of course, a tension with the goal of affordable prices.

One way in which the suppliers desire for a high price for a new medicine and the desire of the Minister for Health for early adoption can be matched, while at the same lowering the State's medicines budget, is to find alternative methods of effectively lowering prices, but leaving the list or posted prices unchanged. In this connection the increase in rebates in the Agreement, accounting for more than a third of the €600 million savings, is one obvious way in which the circle can be squared. As a recent European Union publication noted, while

¹⁰² Brick et al (2013a, p. 25).

¹⁰³ DoH (2016a).

Member States such as Ireland gets the benefit of the rebate other Member States “do not benefit from the lower prices since they refer to undiscounted higher prices.”¹⁰⁴

Future Policy on Pricing New Medicines

The current process for setting new medicine prices lacks predictability, transparency accountability resulting in a substantial degree of discretion by the HSE concerning reimbursement decisions.¹⁰⁵ The airwaves and newspapers are frequently filled with patient groups demanding that the HSE fund this medicine or that medicine.¹⁰⁶ Elected representatives press for new medicines to be added to the Reimbursement List, by for example, raising the issue in the Dail.¹⁰⁷ There is a danger that reimbursement decisions are made on the basis of those who shout or lobby the loudest.

This lack of clarity, especially with respect to the cost effectiveness threshold and the criteria for when this threshold should be exceeded, places great pressure on the HSE in making decisions concerning reimbursement. The HSE is put into an invidious position in making such decisions, but arguably without sufficient guidance.

This has been apparent for some time.¹⁰⁸ In considering whether or not ivacaftor should be reimbursed in 2013 – the NCPE’s evaluation determined at the submitted price the QALY varied between €449,035 and €855,437¹⁰⁹- the Drugs Group, HSE, in its somewhat understated advice to the HSE stated that,¹¹⁰

“Although it may be unpalatable to society to acknowledge this, a positive reimbursement decision might ultimately have implications (opportunity costs) for other social services which might be provided (including health

¹⁰⁴ Volger (2015, p. 36).

¹⁰⁵ Compared, for example, with the reason regulatory decision making processes of the Commission for Energy Regulation or the merger decisions of the Competition and Consumer Protection Commission.

¹⁰⁶ See for example the cases referred to in footnotes 91 and 93 and associated text in the first case.

¹⁰⁷ For example, the discussion on Okambi which was raised during leader’s questions on 1 March 2017; see <http://oireachtasdebates.oireachtas.ie/debates%20authoring/debateswebpack.nsf/takes/dail2017030100003?opendocument>. Accessed 23 May 2017.

¹⁰⁸ In addition to the example discussed in the text see Hennessy (2015, Appendix Vii, pp. 22-25) with respect to eculizumab (Soliris).

¹⁰⁹ For details see: <http://www.ncpe.ie/wp-content/uploads/2013/01/ivacaftor-Summary.pdf>. Accessed 23 May 2017.

¹¹⁰ Letter from Director General Designate, HSE to the Minister for Health, ‘Re: ivacaftor (Kalydeco) for treatment of Cystic Fibrosis.’ 31 January 2013. The quotes from the letter are taken from Brick et al (2013, p. 28).

services). Some of those other health services would be highly cost effective to support.”

It continued,

“The Drugs Group decided that it does not have a formal understanding of societal views as to guide it in decision making on such issues. On balance the group felt that society would like that the medicine be funded given the possibility of significant survival benefits. The group recognises that other international authorities have arrived at the same conclusion.”

One option for resolving the HSE’s dilemma would be for it to review the appropriate cost effective threshold and the factors to be used the threshold should be exceeded. This could then be used as basis for consultation. The outcome would be to provide the HSE with robust guidance on precisely how it should interpret the legislative criteria with respect to cost-effectiveness.

It is not uncommon for those charged with administering law to issue such guidance after consultation.¹¹¹ Unless such an action is taken decisions over new medicine reimbursement will continue to be played out in the public with the possibility that those who can shout the loudest or lobby most effectively being the winners.

We will return to this issue in ‘Implications.’ Suffice to say at this stage, as noted above, the HSE has the authority under the Agreement, after consultation with the IPHA, to review the Assessment Principles. In other words, reform in the pricing of new medicines does not have to wait until the expiry of the Agreement in 2020.

Annual Ex-Factory Price Realignment of Patent-Protected and Off-Patent Exclusive Medicines

Agreement provisions¹¹²

The ex-factory price of patent-protected medicines and off-patent exclusive medicines¹¹³ shall *not* increase over the term of the Agreement.¹¹⁴ The price of such medicines can only

¹¹¹ This is the case, for example, with respect to competition policy, both at the level of the Member State and the European Commission.

¹¹² Clauses 5, 7.1.3 and 8.1.4 of the Agreement.

be realignment *downwards* over the course of the Agreement: on 1 August 2016 and thereafter on 1 July of each subsequent year to 2019. The ex-factory prices for the purposes of realignment are determined by taking average ex-factory price for those Member States in which the medicine is available across the basket of fourteen Nominated States¹¹⁵ specified in the Agreement as of 1 May prior to the realignment in August or July.

Annual realignments thus apply to medicines for which the supplier has no competition. It is the exclusive supplier, irrespective of whether or not the patent is extant. The provision is likely to be particularly relevant to new medicines, especially those that where the medicine was not available in any of the Nominated States when it was initially listed in Ireland. There is an expectation that as a new medicine becomes more widely available across the Nominated States that it will face downward revisions in price.

Implementation

The first realignment under the Agreement occurred on 1 August 2016. The HSE (2016b) published on-line the ex-factory price of each individual medicine by dosage form and strength before and after the realignment. We characterise the realignment in two ways: first, for the leading 10 GMS medicines subject to realignment (Table 4); and second, for the leading 10 HTD medicines subject to realignment (Table 5). The medicines were ranked by medicine cost to the HSE in 2015.

We do not have information on the sales or volume of each dosage form and strength of medicines subject to realignment. Hence we present in Tables 4 and 5, for a given medicine, the average, maximum and minimum price declines for the dosage forms and strengths available for a particular medicine.

The 10 leading GMS medicines subject to ex-factory price realignment on 1 August 2016 accounted for 16.7% of total GMS ingredient cost in 2015.¹¹⁶ The downward price realignments, presented in Table 4, varied between 14% and 34% for eight of the 10

¹¹³ Exclusive off-patent medicines: for a non-biologic medicine where a generic medicine is not available for supply; and, for a biologic medicine there is no biosimilar medicine available for supply.

¹¹⁴ Subject to some limited exceptions.

¹¹⁵ These were defined above in footnote 69.

¹¹⁶ HSE (2016a, Table 43, pp. 164-166). The denominator is the total ingredient cost for GMS products which also includes clinical nutritional products and diagnostic products.

medicines, with the exception of tiotropium bromide (7.7%) and denosumab (4.4%). Even the minimum declines exceeded 10% in seven of the 10 medicines.

Table 4: Ex-Factory Price Realignments,^a Leading 10 GMS Patent Protected and Off-Patent Exclusive Medicines,^b 1 August 2016, Ireland.

INN ^c	Brand	Dosage forms & strengths (Number) ^d	Price Average (%)	Declines Max (%)	Min (%)
pregablin	Lyrica	6	23.8	28.6	12.1
salmeterol + fluticasone	Seretide	6	16.9	18.8	11.8
formoterol + budesonide	Symbicort	3	16.5	20.7	10.4
tiotropium bromide	Spiriva	3	7.1	10.3	1.6
denosumab ^f	Xgeva	1	4.4	-	-
olanzapine	Zpadhera	3	14.7	16.0	13.3
aripipazole	Abilify	1	14.0	-	-
duloxetine	Cymbalta, Yentreve	4	28.6	28.7	28.6
levetiracetam	Keppra	6	34.0	37.3	17.1
fentanyl ^e	Durogesic, Instanyl	11	14.2	27.7	3.3

a. Under Clause 5.2 of the Agreement.

b. The 10 leading GMS medicines, by ingredient cost, 2015, subject to price realignment on 1 August 2016.

c. International Nonproprietary Names.

d. The total number listed in the HSE data source.

e. The average decline for Durogesic was 26.0% (N=5); for Instanyl, 4.3% (N=6).

f. Biologic medicine.

Source: HSE (2016a, Table 43, pp. 164-66; Table 2016b).

Turning now to the leading 10 HTD medicines subject to realignment, these accounted for 48% of HSE expenditure on HTD ingredient cost in 2015, with adalimumab alone accounting for 18.5%.¹¹⁷ The price declines for HTD medicines, in comparison with the GMS, are modest, varying, on average, between 0.7% and 6.5% (Table 5). In no case does the average price decrease reach double digits; indeed, if attention is paid to the maximum price decrease in only one case does it exceed 10% and then only by half a percentage point. Price data for two of the top 10 HTD medicines is not available due to confidentiality agreements between the supplier and the HSE.

¹¹⁷ HSE (2016a, Table 49, pp. 179-184). Note the percentage for the top 10 HTD medicines includes all these medicines.

Table 5: Ex-Factory Price Realignment,^a Leading Ten HTD Patent Protected and Off-Patent Exclusive Medicines,^b 1 August 2016, Ireland.

INN ^c	Brand	Dosage forms & strengths (Number) ^d	Price Average (%)	Declines Max (%)	Min (%)
adalimumab ^e	Humira	4	1.3	2.0	0.5
ivacaftor	Kaldeco	-	No pricing information		
fingolimod	Gilenya	3	0.7	1.8	0.1
lenalidomide ^e	Relimid	4	1.4	1.7	1.2
interferon beta 1a ^e	Avonex, Rebif	10	6.5	10.5	3.3
golimumab ^e	Simponi	-	No pricing information		
pegfilgrastim ^e	Neulasta	1	4.7	-	-
certolizumab pegol ^e	Cimzia	1	3.1	-	-
tacrolimus	Advagraf, Propoic	6	2.9	4.3	0.4
imatinib	Gilvec	2	0.4	0.4	0.3

- a. Under Clause 5.2 of the Agreement.
- b. The 10 leading HTD medicines, by ingredient cost, 2015, subject to price realignment on 1 August 2016.
- c. International Nonproprietary Names.
- d. The total number listed in the HSE data source.
- e. Biologic medicine.

Source: HSE (2016a, Table 49, pp. 179-184; 2016b).

The difference between the GMS and HTD schemes may reflect the emphasis in the HTD on newer medicines for which diffusion across the Nominated States may be at a less advanced stage than for older less expensive GMS medicines. In 2014, for example, 98% of HTD expenditure was on medicines which were still patent protected.¹¹⁸ According to the HSE “*in the future, the expectation is that new medicines will in the main be in the*” HTD.¹¹⁹ Indeed, for some of the HTD medicines, in view of their cost, the optimal strategy of suppliers may be to only gradually roll out their introduction across the Nominated States.

A comparison with the 2012-2015 agreement

The Agreement differs in two important respects from the 2012-2015 agreement with respect to the ex-factory pricing of medicines for which there is exclusive supply, irrespective of whether or not the patent is extant: the increased frequency of price

¹¹⁸ Callaghan (2015, p. 15).

¹¹⁹ Cited in Joint Committee on Health & Children (2015, p. 25). The medicines such as ipilimumab and lumacaflor/ivacaflor (which were referred to above) whether approved for reimbursement or not, come within the ambit of the HTD.

realignments over the course of the agreement;¹²⁰ and, the increase by five in the number of Member States included in the basket of Nominated States,¹²¹ including some such as Greece, that typically charge lower prices. The analysis here concentrates on the first difference.

Under the 2012-2015 agreement:

- all patent-protected medicines placed on the market prior to 1 September 2006 and post-patented medicines placed on the market prior to 1 September 2006 without an identical pharmaceutical form for sale,¹²² will be realigned downwards only, to the average price in the Nominated States in which it was available on 1 November 2012; and,
- any medicine introduced after 1 September 2006 will be realigned downwards only, to the average price in the Nominated States in which it was available on 1 January 2013.

The 2012-2015 agreement has one set of realignments (2012 and 2013, depending on whether or not the medicine was introduced before or after 1 September 2006), while the Agreement has four sets of realignments (2016, 2017, 2018, 2019). Hence the additional impact or effect of the Agreement is the three realignments subsequent to the initial realignment in 2016. In assessing the impact of the Agreement in providing savings the initial 2016 realignment should thus be regarded since they are part of the 2012-2015 agreement counterfactual.

According to the DoH one third of the estimated overall savings of €660 million or €205 million is due to the annual realignment of medicines with exclusive supply and the addition of five Member States to the basket of Nominated States (Table 1). On the assumption that the €205 million is spread equally across the four annual price realignments, then the savings in 2016 will be €48 million and €52 million for each of the next three annual

¹²⁰ Clause 7, 2012-2015 agreement.

¹²¹ Greece, Italy, Portugal, Sweden, and Luxembourg.

¹²² Biologics would not have identical pharmaceutical forms since biosimilars are not considered interchangeable under the Health Act 2013.

adjustments.¹²³ However, as argued above, the savings for 2016 would have occurred had the 2012-2015 agreement been replicated in place of the Agreement. Thus additional savings due to price realignment should be €157 million, not €205 million.

There are good grounds for arguing, however, that the savings under the price realignments are likely to be front loaded, skewed towards 2016, rather than 2017-2019. Hence the savings due to the Agreement are likely to be less than €157 million.

Prior to the price realignment of 1 August 2016, the price of patent-protected and off-patent exclusive medicines had not been adjusted since 2012-2013 in accordance with the 2012-2015 agreement. Other things being equal, we would expect that price realignment after three to four years (i.e. on the 1 August 2016) would yield greater savings than annual (i.e. on 1 July 2017, 2018 and 2019) price realignments.

One way of quantifying the impact of this front loading is to assume that the savings of €205 million reflect price changes since 2014, given that no realignments occurred since 2012-2013. If annual realignments had occurred starting in 2014, terminating in 2019, this is equivalent to annual savings of €34.2 million per annum over the six realignments. However, the 2014 and 2015 realignments did not take place under the 2012-2015 agreement. The first realignment was in 2016, which would have reflected not only the 2016 realignment but also the forgone 2014 and 2015 realignments, or €102.5 million in total. On these assumptions the Agreement's savings due to price realignment should be approximately €100 million.

There other evidence to suggest that initial reduction due to price realignment is greater than subsequent realignments. In the 2006-2010 agreement there was provision for realignments in 2008 and 2010. In earlier research the price of all new medicines introduced in 2006, 2007 and 2008 were realigned using the average price in the Nominated States in which they were available in 2008 and 2010.¹²⁴ The evidence suggested that prices dropped by 10% in the initial two year period and to a lesser extent thereafter.

¹²³ Strictly speaking the first realignment is for 11 months while the subsequent three are for a year. Hence instead of four annual savings of €51.25 million, the 2016 saving should be €48 million, each subsequent year €52 million.

¹²⁴ Brick et al (2013a, pp. 21-23).

In sum, the annual realignment of the price of medicines with exclusive supply is likely to lower medicine prices over 2016-2020: under the no agreement counterfactual by €205 million, the 2012-2015 agreement counterfactual by €100 million.

Discussion

The Agreement's annual price realignment is a marked improvement over the 2012-2015 agreement, resulting in considerable additional savings. The change follows earlier research and recommendations that there should be more frequent price alignments than had characterised previous agreements between the State and the IPHA. The addition of some other Member States to the list of Nominated States is also likely to lead to lower prices. In terms of future increased savings one option would be to switch to using the lowest price in the basket of Nominated States rather than the average.¹²⁵

Pricing of Patent-Expired, Non-Exclusive (Excluding Biologic) Medicines

Agreement provisions¹²⁶

Medicines, excluding biologic, for which the patent has expired and for which a "*Generic Medicine*" is "*Available for Supply*":

- on 1 August 2016 each existing such medicine shall be reduced to 50% of the "*Original Ex-Factory Price*" set by the HSE for a new medicine;
- if a medicine becomes a patent-expired, non-exclusive medicine after 1 August 2016, then it shall also be reduced in price by 50% of its "*Original Ex-Factory Price*"; and,

These provisions shall *not* apply to patent protected and off-patent medicines not declared interchangeable subject to annual ex-factory price realignments outlined above or to similar provisions in earlier agreements.

A Generic Medicine is defined in the Agreement as "*medicinal products as defined in Article 10(2)(b) of EC Directive 2001/83/EC in respect of which a Marketing Authorisation has been issued by the HPRA or the European Commission.*"¹²⁷ However, it should be noted that not

¹²⁵ For further discussion of this see Brick et al (2013a, pp. 21-25).

¹²⁶ Clause 7 of the Agreement.

¹²⁷ Clause 1 of the Agreement.

all generic medicines are declared interchangeable by the HPRA, although clearly there is a considerable degree of overlap.¹²⁸

Available for Supply means a medical product that has received the relevant EU or Irish marketing authorisation and “*which is available for sale and supply in the State.*”¹²⁹

The price reductions are from the “Original Ex-Factory Price,” which is defined as “*the ex-factory price at which it [the medicine] was first approved for reimbursement or supply by the HSE, its predecessor(s) or a Relevant Agency.*”¹³⁰ In other words, the 50% price reduction does not use the price of the medicine when the generic enters the market but rather the price of the medicine when it first approved for reimbursement, which is likely to be a decade or more prior to the entry of the generic.

A comparison with the 2012-2015 agreement

Under the 2012-2015 agreement medicines for which the patent had expired where a generic was available the price first fell by 30%-40% of the original ex-factory price before falling further to 50% of the original ex-factory price a year later.¹³¹ In other words, under the 2012-2015 agreement in the first year prices fell by 30%-40% rather than 50% of the original price. Thus the HSE benefits under the Agreement, compared to the 2012-2015 agreement, by the bringing forward by one year the reduction to 50% of the original price.

DoH attributes €115 million savings due to reductions in patent expired medicines for which a generic is available (Table 1). Two separate components are identified by DoH.

First, Clause 6 of the 2012-2015 agreement results in savings of €90 million. As noted above, this clause led to a reduction in the original price of between 30% and 40% when the generic appeared on the market. It is difficult to see how this can be considered as an additional saving due to the Agreement. The reductions existed in the 2012-2015 agreement and hence were part of the counterfactual – what would have happened without

¹²⁸ For further discussion see HPRA (2014).

¹²⁹ Clause 1 of the Agreement.

¹³⁰ Clause 1 of the Agreement.

¹³¹ Clause 6, 2012-2015 agreement. Note for patent expired medicines (with a generic available) whose prices were above 60% of the original price on 1 November 2012, the price shall be reduced to 60% of the original price on 1 November 2012; for medicines due to go off patent from 1 November 2012, the price will be reduced to 70% of the original price and then twelve months later to 50% of the original price.

the Agreement. Hence the €90 million should be discounted as a saving due to the Agreement.

Second, the bringing forward by one year the 50% price reduction results in an estimated savings of €25 million or €4.25 million per annum. This appears, on the face of it, as a genuine additional saving compared to the counterfactual.

In sum, the savings attribute to Agreement's provisions relating to the pricing of the originator's brand or product once a generic appears are €115 million under the no agreement counterfactual and €25 million under the 2012-2015 agreement counterfactual.

Discussion

Under the Health Act 2013 the HSE sets a reference price for generic medicines which have been declared interchangeable by the HPRA. As noted above the reference price is not set by reference to the originator's price, but rather the price charged in other Member States. The available evidence – cited above under 'Increasing generic penetration: the Health Act 2013' - suggests that the price setting mechanism has resulted in a dramatic reduction in expenditure for medicines with a reference price. This raises the issue of the relevance and necessity of Clause 7 of the Agreement.

In the case of the first medicine for which a reference price was set, the DoH (2017) state that:

“The first reference price for atorvastatin products was implemented on 1 November 2013. This represents a major step in ensuring lower prices are paid for these medicines. The new reference prices for atorvastatin products – which are used to control cholesterol – means the HSE now pays 70% less for these products compared to May 2013. The reference price is at 15% of the pre-patent expiry price i.e. the price is 85% lower than the patented price of the original brand (Lipitor).”

In other words, the 50% reduction from the ex-factory price in the Agreement does not appear to be binding for generic medicines which are declared interchangeable and for which a reference price has been set. But how typical is atorvastatin?

We can address this issue further using an alternative method of determining the decline in price due to reference pricing in relation to the original price. The results are presented in Table 6 for the fifteen leading GMS medicines, ranked by ingredient cost in 2013,¹³² which appeared on the initial list of medicines that the DoH/HSE wished to be prioritised by the HPRA because they were considered as offering the greatest savings.¹³³ These 15 medicines in 2013 accounted for 18.9% of GMS ingredient cost and nine of the leading 20 GMS products. The priority review was to be undertaken in the latter part of 2013 and the first quarter of 2014.

For 2005 and 2015 for the sample of 15 leading medicines we estimate the average GMS cost per medicine: the total ingredient cost divided by the total number of prescriptions.¹³⁴ We take 2005, when, as far as we are aware, there were no generic medicines available for each of the 15 medicines, as indicative of the original price of the medicine. This estimate will, of course, be biased downward as the medicine may have been available at a higher price prior to 2005. However, the earliest year in the HSE data source is 2005.

At the other extreme we use 2015. This is the latest year for which such data is available from the HSE data source. Furthermore since the initial list of medicines to be reviewed with respect to interchangeability by the HPRA and a reference price set by the HSE would have taken place in 2013 and 2014, 2015 is the first year for which annual data would be able to capture the impact of reference pricing.

There are a number of points that can be made in relation to Table 6. First, in the case of atorvastatin the 85% reduction in the reference price compared to the original ex-factory price highlighted in the quote from the DoH (2017) is very close to the 87.7% reduction recorded in the table, which gives considerable confidence in the reliability of the tabular results.¹³⁵

¹³² HSE (2014, Table 46, pp. 192-194). The source ranks the top 100 GMS medicines, which accounted for 75% of GMS ingredient cost.

¹³³ HPRA (2014, p. 8). Virtually all interchangeable medicines fall under GMS.

¹³⁴ For example, for in 2005 the GMS paid €36,471,497 for 50,527,982 prescriptions resulting in an average cost of €35.55.

¹³⁵ Reference prices are regularly reviewed and this may explain why in 2015 the reduction is 87.7% rather than 85%.

Table 6: Original and Reference Price, Average Ingredient Cost per Prescription, Leading 15 GMS Interchangeable Medicines,^a 2005 & 2015, Ireland.

INN ^b	Average Ingredient Cost per Prescription 2005 Original Price (1)	Average Ingredient Cost per Prescription 2015 Reference Price (2)	Average Ingredient Cost Reduction ^c (%) (3)
atrovastatin	€37.55	€4.61	87.7
esomeprazole	€41.59	€7.86	81.1
olanzapine	€117.39	€31.32	73.3
omeprazole	€49.03	€7.75	84.2
rosuvastatin	€29.95	€8.56	71.4
lansoprazole	€38.73	€6.52	83.2
quetiapine ^d	€60.58	€18.76	69.0
pantoprazole	€33.84	€6.52	80.7
clopidogrel	€54.45	€7.58	86.1
pravastatin	€41.55	€5.27	87.3
perindopril	€20.03	€5.98	70.1
risperidone	€63.33	€30.97	51.1
ramipril	€16.32	€3.62	77.8
valsartan	€24.06	€6.08	74.7
losartan	€27.40	€6.72	75.5

a. The 15 leading GMS medicines, by ingredient cost, 2013, included in the initial list of medicines selected by the DoH/HSE for the HPRA to add to the list of interchangeable medicines. We were not able to find data for lercanidipine for 2005 or 2006 and hence omitted it from consideration. The HSE data source only provided data for the leading 100 medicines.

b. International Nonproprietary Names.

c. $Col\ 3 = 1 - ((Col(2)/Col(1)))$.

d. 2006 was used, since quetiapine was not listed in the data source for 2005.

Source: HPRA (2014, Table 2, p. 8); HSE (2006, Table 19.2, pp. 73-75; 2007, Table 19.2, pp. 74-76; 2014, Table 46, pp. 192-194; 2016a, Table 42, pp. 161-163 & Table 43, pp. 164-166).

Second, the reduction in the price of interchangeable medicines with a reference price is always, without exception, more than 50% of the original ex-factory price. In five of the 15 cases the decline is 80% or greater, in 14 of the 15 the decline is 69% or greater. In other words, under the reference pricing regime introduced under the Health Act 2013, prices of interchangeable medicines fall by more than 50%. This suggests that for these medicines the provisions of the Agreement are irrelevant.

Nevertheless, there may be a class (es) of medicines for which the Agreement provisions are relevant and savings can be attributed.

First, generic medicines considered, for medical reasons, to be unsuitable for classification as interchangeable. However, if this is the case then it would seem unlikely that generic

suppliers of medicines would enter the market in the first place, since market penetration and returns would likely be quite low. Nevertheless, for whatever reasons, some generic medicines may have been launched that fall into this category.

Secondly, the HSE may not request the HPRA to review all medicines that are suitable for classification as interchangeable. However, this does not appear to be the case, with the list of interchangeable medicines growing by the day. Indeed, the DoH (2017) stated that *“It is expected that 80% by value of the off-patent market for prescribed medicines will be subject to reference pricing by end Quarter 1 2015.”* Nevertheless there may be some low volume off patent medicines or low volume dosage forms/strengths of medicines that could be certified as interchangeable but where the resources needed by the HPRA and the HSE may not justify the inclusion of such medicines on the Interchangeable List.¹³⁶

Third, there is likely to be a lag between, on the one hand, the generic being available for supply (and hence triggering the 50% price reduction of the originator brand), and, on the other, the HPRA adding the active ingredient to the Interchangeable List and the HSE setting a reference price. During the lag between the generic being available for supply and the setting of the reference price, bringing forward the 50% reduction results in savings attributed to the Agreement.¹³⁷

Fourth, under reference pricing if the medical practitioner writes *“Do Not Substitute”* across a GMS prescription for an interchangeable medicine then the brand named on the prescription must be dispensed. Typically such prescriptions will be for the originator’s brand which may have developed a certain amount of brand loyalty; the greater the degree of product differentiation the more important will be such no substitution prescriptions.

The important point for present purposes is that the brand is reimbursed not at the reference price, but the brand specific price. The maximum for which is set under the Agreement. However, as we have seen in the discussion of price realignments for medicines for which there is exclusive supply, prices under the various State/IPHA agreements mean

¹³⁶ It appears that for some medicines added to the Interchangeable List not all dosage forms and strengths are accorded a reference price.

¹³⁷ Of course, account would need to be taken of the fact that originator’s product would likely have already fallen from the original ex-factory price due to various realignments. See Table 4 for the record of realignment for leading GMS medicines.

that by the time a reference price has been set the originator's price has already fallen substantially in relation to the original or initial price (Table 4).

In any event we have limited data on the market share of "Do Not Substitute" prescriptions. In aggregate terms, in early 2016, the DoH (2016b, p. 26) reported that over 70% of the off-patent market, by volume, was accounted for by generics. At the level of individual medicines, in October 2015, generics accounted for 95% by volume of donepezil,¹³⁸ for memantine, over 85% of the tablet and around 55% of the oral solution.¹³⁹ This does not mean, of course, that the remaining non-generic medicines fall into the "Do Not Substitute" category. The patient, for example, may decide to pay for the original brand.

In sum, the available evidence suggests that the major savings on generic medicines are due to reference pricing not the Agreement. This raises considerable doubts as to the relevance of Clause 7 of the Agreement, especially with respect to the straight reduction to 50%. Nevertheless, notwithstanding these doubts, there are enough lags and other factors to suggest that attributing €15 million to the Agreement is likely to be credible under the 2012-2015 agreement counterfactual.

Pricing of Patent-Expired, Non-Exclusive Biologic Medicines

Agreement provisions¹⁴⁰

Biologic medicines¹⁴¹ for which a biosimilar¹⁴² medicine is "Available for Supply" (i.e. a patent-expired non-exclusive biologic medicine):

- on 1 August 2016 shall be reduced to 80% of the "Original Ex-factory Price." In other words, the biologic medicine will be priced to the State at a discount of 20% of the initial or original ex-factory price.

¹³⁸ For details see: <http://www.hse.ie/eng/staff/PCRS/circulars/donepezilrefpricefeb16.pdf>. Accessed 23 May 2017.

¹³⁹ For details see: <http://www.hse.ie/eng/staff/PCRS/circulars/memantinerefpriceApril16.pdf>. Accessed 23 May 2017.

¹⁴⁰ Clause 8 of the Agreement.

¹⁴¹ A biologic medicine is defined in Clause 1 of the Agreement as "Medicines which are biological medicinal products as defined in Annex 1 of Directive 2001/83/EEC in respect of which a Marketing Authorisation has been issued by the HPRA or the European Commission."

¹⁴² A biosimilar medicine is defined in Clause 1 of the Agreement as "biological medicinal products which contain a version of the active substance of a Biologic Medicine and which are similar to other Biologic Medicines in terms of quality characteristics, biological activity, safety and efficacy and in respect of which a Marketing Authorisation has been issued by the HPRA or the European Commission."

- after 1 August 2016 it shall be reduced “to 80% of the ex-factory price of that Biologic Medicine as of the 31st July 2016.”¹⁴³
- the supplier shall also pay the HSE a rebate of 12.5% of the value at the reduced price, irrespective of whether or not the patent-expired non-exclusive biologic medicine became available before or after 1 August 2016.¹⁴⁴

Patent-expired, non-exclusive biologic medicines are priced, directly and indirectly, at a discount of 30% to the original ex-factory price or the ex-factory price on 31 July 2016.¹⁴⁵

“Available for Supply” and “Original Ex-factory Price” were defined above.

A couple of points can be made concerning the pricing of patent-expired, non-exclusive biologic medicines as compared with the pricing of patent-expired non-exclusive non-biologic medicines.

First, when a biosimilar medicine becomes available after 1 August 2016 the percentage price reduction for the corresponding biologic medicine is 30% from the price of the medicine *on 31 July 2016, not the original ex-factory price*. However, the decline in price for biologic medicines from the original ex-factory price – as seen in Table 5 - appears to quite modest.

Second, instead of a straight price reduction of 30%, the price of biologic for which a biosimilar becomes available for supply is achieved in part by a rebate. Prices in Ireland are used to set prices in a number of other Member States and beyond. Typically such prices do not include discounts and rebates. This may be the reason for the rebate rather than a straight price reduction.

A comparison with the 2012-2015 agreement

Under the 2012-2015 agreement there was no provision for price reductions on biosimilars. Price reductions only applied to “*patent expired medicines where the identical pharmaceutical form of that medicine, approved by the Irish Medicines Board or European*

¹⁴³ Clause 8.1.2 of the Agreement.

¹⁴⁴ Clause 8.1.3 of the Agreement.

¹⁴⁵ If the original price is €100, then the first reduction is to €80. 12.5% of €80 is €10, resulting in a price, including the rebate, of €70.

*Commission, is available for prescription in the Schemes ...*¹⁴⁶ Biosimilars are explicitly excluded from such a definition.¹⁴⁷

DoH attribute €55 million savings due to reductions in patent expired biologic medicines for which a biosimilar is available (Table 1). Savings of at least this magnitude, at first glance, are credible. It has been estimated, for example, that over 2019-2020 six biologics will lose patent protection with sales in 2015 of €170 million: 30% is €51 million.¹⁴⁸

In sum, the €55 million savings is consistent with both the no agreement and 2012-2015 agreement counterfactual.

Discussion

There are, however, serious concerns that the policy framework for the successful introduction, use and dissemination of biosimilars, in contrast to generics, is not in place. Hence the savings envisaged as a result of the Agreement may not be realised in full. This lacuna is acknowledged by policymakers. Steps are being taken to address this problem.

Suppliers of biosimilars will only enter the market, triggering the provisions of the Agreement, if they expect to make a positive return on their investment. To date the indications are that biosimilars have achieved extremely low market shares in Ireland.

This is illustrated by the example of entanercept. In 2015 it accounted for €52.5 million or 11.1% of HTD ingredient cost.¹⁴⁹ Sales of the biosimilar, Benepali, in the final two months of 2016 amounted to three packets, while the biologic brand, Enbrel, sold 10,000 packages.¹⁵⁰ Such a low market share is consistent with other evidence regarding biosimilar market penetration in Ireland.¹⁵¹

Despite guidance from the HPRA (2014) and the NIMC (2016), there is little incentive for the medical practitioner to prescribe a biosimilar by name. Time and effort is required to inform the patient of the proposed change from the biologic original brand. Unlike generic, there is

¹⁴⁶ Clause 6, 2012-2015 agreement.

¹⁴⁷ HSE (2016c).

¹⁴⁸ The estimates are reported in Harris (2017). See also HSE (2016c).

¹⁴⁹ HSE (2016a, Table 49, pp. 182-184).

¹⁵⁰ Coyle (2017). The corresponding numbers for insulin glargine were 18 and 12,172, respectively.

¹⁵¹ See, for example, IMS Health (2016).

no legal framework that permits the pharmacist to substitute a biosimilar.¹⁵² The patient has little or no incentive to switch to a biosimilar, since the HTD and GMS cover the cost of the medicine in full. There is no copayment – as occurs for a generic – if the patient prefers a brand that is more expensive than the reference price.

Recognising these problems, which have been highlighted by the suppliers of biosimilars,¹⁵³ the Minister for Health has promised a consultation paper in 2017 Q1 on the development of a National Biosimilar Policy, although the paper has, as yet, to be published. Issues to be considered include whether or not there should be pharmacy level substitution as occurs with generics. No doubt the consultation paper will draw on the success of the use of biosimilars in other jurisdictions. In particular the success of the use biosimilar for infliximab at University Hospital Southampton¹⁵⁴ and in Norway and Denmark where the infliximab biosimilar reached market penetration levels as of April 2016 in excess of 90%.¹⁵⁵

Rebate on Sales

Agreement provisions¹⁵⁶

Each supplier shall provide rebate to the HSE on the value of all medicines reimbursed by the HSE and relevant agencies including State-funded hospitals. The rebate is set at 5.25% for sales between 1 June 2016 to 31 July 2018; 5.5% for the period 1 August 2018 to 31 July 2020.

The rebate does not apply to sales of patent expired and non-exclusive medicines, irrespective of whether or not they are biologic medicines.

¹⁵² A Bill was introduced on 31 May 2016 to amend the Health Act 2013 to make biosimilars and biologics interchangeable medicines. The bill, was entitled, Health (Pricing and Supply of Medical Goods) (Amendment) Bill 2016. However, the Minister for Health felt while he agreed with the objective of the legislation, it would not in fact achieve its objective (Harris, 2017).

¹⁵³ HEA (2015).

¹⁵⁴ For details see, for example, <http://pharmaphorum.com/news/uk-hospital-saving-80-000-per-month-using-biosimilar-conference/#> and <https://www.ecco-ibd.eu/index.php/publications/congress-abstract-s/abstracts-2016/item/dop029-outcomes-of-a-managed-switching-programme-changing-ibd-patients-established-on-originator-infliximab-to-biosimilar-infliximab.html>. Accessed 23 May 2107.

¹⁵⁵ See, for example, Welch (2016).

¹⁵⁶ Clauses 9, 7.1.3, and 8.1.4 of the Agreement.

A comparison with the 2012-2015 agreement

The rebate provisions of the Agreement marked an important break from the earlier 2012-2015 agreement in two respects.¹⁵⁷ First, the rebate is extended to all Relevant Agencies which includes hospitals. Under the 2012-2015 agreement the rebate only applied to community drug schemes.¹⁵⁸ There was no rebate on medicine sales to hospitals. Second, the magnitude of the rebate was increased from the 4% rebate in the 2012-2015 agreement.¹⁵⁹ The 4% rebate has been a longstanding feature of the agreements between the State and IPHA (and its earlier incarnations), first appearing in the 1969-71 agreement.¹⁶⁰

DoH attributes €225 million savings due to rebates on sales (Table 1). These savings are divided into three components:

- €70 million due to the rebate on sales to hospitals of 5.25% rising to 5.5%;
- €40 million due to extra rebate on community drug schemes of 1.25% rising to 1.5%;
and,
- €115 million due to the 4% rebate on community drug scheme sales.

Rebates are the most important single source of savings attributed by DoH to the Agreement, accounting for more than a third of the overall figure of €600 million.

While the savings due to the extension of rebates to hospitals and the increase in the rebate on community drug schemes are clearly additional, relative to the counterfactual of the 2012-2015 agreement, the same cannot be said of the 4% rebate on community drug scheme sales. As noted above the 4% rebate goes back to the first agreement between the State and the representative body that was the predecessor of the IPHA - just under fifty years ago. It is thus hard to argue that the savings due to the 4% rebate on community drug scheme sales should be considered additional.

¹⁵⁷ On the other hand under clause 6.1 the 2012-2015 agreement there was no rebate on patent expired medicines available for prescription.

¹⁵⁸ Clause 9, 2012-2015 agreement.

¹⁵⁹ Clause 9, 2012-2015 agreement. The 4% rebate did not apply to patent expired medicines where the identical pharmaceutical form of the medicine was available in Ireland. This exemption was not included in the Agreement.

¹⁶⁰ Clause 7, 1969-71 agreement. Note this agreement was between the Pharmaceutical and Allied Industries Association and the DoH.

In sum, the Agreement clauses relating to rebates will likely result in savings of €110 million under the 2012-2015 agreement counterfactual, €225 million under the no agreement counterfactual.

Discussion

In the previous section it was argued that the rebate on the price of a biologic for which a biosimilar becomes available for supply may be used in part because it is a form of disguised price reduction that does not affect the posted or list price which is used by other Member States to set prices. A similar argument also could be applied to hospital rebates and the increase in community drug schemes rebates that featured in the Agreement. However, the longstanding 4% rebate dates back to 1969 when, at least for Ireland, there was no reference to the prices charged in other jurisdictions. Other factors must have caused the rebate.¹⁶¹ Hence it appears that the motivation for rebates may have changed over time.

Continuity of Supply¹⁶²

Under the Agreement suppliers must notify the HSE of discontinuation of a medicine: at least twelve months where there is “*no reimbursable therapeutic alternative for approved indications;*” and, at least three months “*where there is a reimbursable therapeutic alternative for approved indications.*”¹⁶³ Similar provisions existed in the 2012-2015 agreement.¹⁶⁴

IMPLICATIONS

Overall Savings Due to the Agreement

The critical issue in estimating the likely savings from the Agreement is the appropriate counterfactual. In other words, but for the Agreement, how would the pricing of medicines,

¹⁶¹ It may, for example, be a simple and straightforward method of reducing medicine expenditure.

¹⁶² Clause 11 of the Agreement.

¹⁶³ Clause 11.2(b) of the Agreement. Where a supplier transfers a Marketing Authorisation to another supplier that is likely to materially change supply arrangements the supplier shall notify the HSE at least three months before the transfer and inform the new holder of the terms of the Agreement.

¹⁶⁴ Clause 10, 2012-2015 agreement. One difference between the Agreement and the 2012-2015 agreement was that the latter contained the following clause, “10.5 Where a supplier is in breach of this Clause [10], it will be required to either source and supply alternative equivalent products at the same price as the unavailable product or reimburse the HSE any difference in cost arising from the shortage.”

including rebates, be determined? What is required is a credible counterfactual benchmark against which to estimate the savings flowing from the Agreement.

The €600 million savings billed by the Minister for Health as a result of the Agreement over 2016-2020 were benchmarked against a counterfactual characterised with:

- no agreement between the State and the IPHA, despite the fact such agreements have existed since 1969; and,
- no use of the powers of the Health Act 2013 to mitigate the lack of an agreement, despite the fact that the State threatened to use these powers during the negotiations leading to the Agreement.

This benchmark is the no agreement counterfactual.

An alternative counterfactual benchmark is the status quo. In other words, the 2012-2015 agreement is replicated starting in 2016 and its three year term extended for one year to 2020.

The choice of counterfactual is not some academic esoteric issue. It matters. Under the no agreement counterfactual the estimate savings are, of course, €600 million, while under the status quo counterfactual the savings are less than half of this amount, €290 million (Table 7). However, as noted above, both of these estimates are subject to a number of qualifications and caveats. Nevertheless, notwithstanding these the conclusion concerning the different magnitudes of the two counterfactuals remains unaltered.

The issue thus becomes which counterfactual is more appropriate for estimating the savings due to the Agreement. It is suggested that there are five sets of reasons for preferring the status quo option.

First, in other instances where counterfactuals are employed for analogous purposes – from merger analysis to NCPE evaluations – the counterfactual is the status quo. This does not mean, of course, that in some cases an alternative credible counterfactual might be appropriate. However, as discussed below under point five the no agreement counterfactual does not appear to be credible.

Table 7: Estimates of State/IPHA Agreement’s Savings, Two Counterfactuals, Public Purchases, 2016-2020

Source of Savings (Clause of Agreement or 2012-2015 agreement)	Cumulative Savings 2016-2020 (€m)	
	Counterfactual	
	No Agreement ^a	Status Quo ^b
Original Price of New Medicine (Clause 6 & Assessment Principles)	None	None
Annual Ex-Factory Price Alignments on Patent Protected and Exclusive Off-Patented Medicines (Clauses 5, 7.1.3 & 8.1.4) ^c	205	100
Pricing of Patent-Expired, Non-Exclusive (Excluding Biologic) Medicines (Clause 7)		
Existing Clause 6 (of 2012-2015 agreement)	90	-
Price Reduction Straight to 50% ^d	25	25
Pricing of Patent-Expired, Non-Exclusive Biologic Medicines (Clause 8) Biologics less 30%	55	55
Rebate on Sales (Clause 9)		
Clause 9 (of the 2012-2015 agreement) ^e	115	-
Hospital Rebate (5.25% rising to 5.5%) ^f	70	70
Extra Rebate (1.25% rising to 1.5%) ^f	40	40
Total	600	290

- a. The counterfactual assumes no agreement between the State/IPHA and that the State does not mitigate this by employing the powers of the Health Act 2013.
- b. The counterfactual is the 2012-2015 agreement extended by one year.
- c. “Extended Reference Basket & Price Realignments” in the DoH documentation.
- d. “Clause 7 (previous Clause 6) straight to 50%” in DoH documentation. Instead of 30% in year 1 and 50% in year 2, the 50% reduction occurs in year 1 under the Agreement.
- e. “PCRS Rebate” in DoH documentation. DoH confirmed that this referred to the 4% rebate in the 2012-2015 agreement and continued in the Agreement.
- f. The first increase occurred from 1 June 2016 to 31 July 2018; the second from 1 August 2018 to 31 July 2018.

Source: Based on information provided by the DoH and text.

Second, the no agreement counterfactual attributes savings to the Agreement which are the result, in part at least, of other policy initiatives taken independently of the Agreement (e.g. reference pricing which encourages generic firms to come to market sooner rather than

later triggering price reductions) or the result of gains made in earlier agreements. Indeed, the 4% rebate goes back to 1969.

Third, the DoH press release announcing the Agreement is consistent with the view that the counterfactual is the status quo, not no agreement. The DoH (2016a) states, for example, *“The pricing provisions in this agreement represent a significant improvement on those contained in the previous agreement.”* In the ‘Notes to Editors’, the press release points out the key pricing elements in the Agreement, which highlight the improvements as compared with the 2012-2015 agreement.

Fourth, the Minister for Health stressed that the savings from the Agreement will be used to fund new medicines. It seems reasonable to assume that for budget purposes the HSE projects forward based on the status quo. Any additional savings due to the Agreement are then a windfall gain that can be used for new medicines.

Fifth, it could be argued that the Health Act 2013 provided the HSE with a plausible alternative price setting mechanism in the event of a failure of the State and IPHA to reach an agreement. However, in this case the appropriate counterfactual is not the no agreement counterfactual set out above. Rather it is the set of pricing rules (or some variant thereof) that the HSE threatened to unilaterally impose in May 2016 during the State/IPHA negotiations.

Pricing of New Medicines

Setting the scene

Despite the undoubted benefits of the Agreement in terms of savings, it does nothing to control the price of new medicines. As noted above expensive new medicines tend to be included in the HTD scheme. The evidence cited above suggests that the HTD has not only grown substantially, but also that its outturn consistently exceeds its allocation.¹⁶⁵ Furthermore, *“[I]n a no-policy change scenario, there is no sign of cost pressure abating on this scheme given the prospective pipeline of new innovative drugs.”*¹⁶⁶

¹⁶⁵ Callaghan (2015, p. 15) with respect to outturn and allocation.

¹⁶⁶ Callaghan (2015, p. 15).

In the discussion above under ‘Future Policy on Pricing New Medicine’ it was suggested that the HSE consider reviewing the appropriate cost-effectiveness threshold for a QALY and other related issues in setting the price for a new medicine. Subsequently, after consultation and consistent with the provisions of the Health Act 2013, the HSE could issue guidance on the pricing of a new medicine. This should, for example, set a cost per QALY cost-effectiveness threshold and a set of strict conditions, if any, under which this threshold can be exceeded. This guidance would, of course, inform the thresholds used in the NCPE’s pharmacoeconomic evaluation for the HSE.

The evidence cited above under ‘Preparations for negotiations with IPHA’ for the UK suggests that a €45,000/QALY is on the high side and that a much lower threshold is appropriate. In part the latter threshold is based on more effective healthcare alternatives forgone due to the funding of medicines, which is consistent with the 2013 remarks cited of the HSE Director-General Designate. Furthermore a recent evaluation of the UK Cancer Drugs Fund, set up to fund medicines that did not meet UK cost-effectiveness thresholds, found that the Fund *“has not delivered meaningful benefits to patients or society.”*¹⁶⁷

At the present time the process for setting prices for new medicines, especially for those with a cost per QALY above €45,000, lacks predictability and transparency, despite the publication of the helpful summaries of the NCPE evaluations which inform the HSE listing decision. This decision-making process, as noted above, can lead to situations in which those who shout or lobby the loudest and most ably are rewarded. It puts the HSE in an invidious position.

Guidance and clarity raises the possibility of shielding the HSE at least partially from the pressure to add expensive new medicines to the Reimbursement List, while at the same time increasing transparency and predictability. The pressure on the HSE to approve expensive new medicines is unlikely to abate, given: the current incentives created by the healthcare system; and, the unrealistic expectations raised concerning the funding for new medicines based on €600 million of savings attributed to the Agreement. In reality the savings are less than half that amount.

¹⁶⁷ Aggarwal et al (2017, p. 1).

The latter point concerning expectations is usefully illustrated with respect to the decision to fund Orkambi in May 2017, despite its high QALY and budget impact.¹⁶⁸ In defending the decision the representative body Cystic Fibrosis Ireland argued that the Government's estimate of the savings due to the Agreement provided the necessary resources for the medicine to be added to the Reimbursement List.¹⁶⁹ The IPHA (2017) made a similar argument in welcoming the decision to fund Orkambi. To the extent that the no agreement counterfactual substantially overstates the savings due to the Agreement the expectations of patients are not aligned with the funds available for new medicines.

Exit vs voice

In some areas of healthcare in Ireland patients can exercise exit over voice.¹⁷⁰ Exit in this context means that a patient instead of choosing to change and improve the quality of the public healthcare system from within opts instead for private health insurance.^{171,172} Such a choice of exit over voice results in better service for the private patient as long waiting lists are avoided. The patient receives "*faster access to the public acute hospital sector*" and other instances of queue jumping.¹⁷³

However, for new medicines there is no private health insurance. The only option is public provision through access to the various community drug schemes, including the HTD. Hence in terms of access to new medicines patients will tend to use voice over exit. In other words, there will be intense lobbying – voice - of the political system to ensure access.¹⁷⁴

Such lobbying is likely to lead to a misallocation of resources, especially since those with private health insurance tend come disproportionately from higher socio-economic groups.

¹⁶⁸ See footnote 93 for a discussion on the background concerning the Orkambi decision.

¹⁶⁹ Watt (2017) used the €750 million figure rather than €600 million. See footnote 4 above for details.

¹⁷⁰ This distinction is based on a distinction drawn by Hirschman (1970).

¹⁷¹ Around 45% of the population has private health insurance in Ireland, with a concentration in the better off socio-economic groups. For further details see Health Insurance Authority/MillwardBrown (2016).

¹⁷² Another example of exit over voice concerns the situations where a patient/consumer receives unsatisfactory service or treatment from a medical practitioner such as GP or a pharmacist. The patient/consumer can either switch to another medical practitioner (exit) or complain to the medical practitioner's professional regulatory body (voice). See Madden & O'Donovan (2015) with respect to complaints about doctors.

¹⁷³ Connolly and Wren (2016, p. 2).

¹⁷⁴ A number of factors are likely to facilitate voice: it is often easy to identify those individuals likely to benefit from a particular new medicine; the numbers are often small; and, there incentives are aligned in wanting access to the medicine.

In other words, at the margin, extra resources will be spent on access to high cost – in terms of cost per QALY – new medicines as opposed to other interventions in the healthcare system that might well lead to better returns.

Such a view is consistent with the 2013 letter from the Director-General Designate of the HSE to the Minister for Health (cited above) which stated that *“a positive reimbursement decision [to fund ivacaftor] might ultimately have implications (opportunity costs) for other social services which might be provided (including health services). Some of those other health services would be highly cost effective to support.”*

Furthermore there is evidence of long waiting times in Ireland for hip replacement, knee replacement and cataract removal all of which have QALY’s well below €45,000.¹⁷⁵ While the media might be replete with organisations motivated by a desire to access to a new medicine, much less attention is paid to those subject to long waiting times for hip and knee replacements or cataracts.

This is not surprising. Some persons requiring a hip or knee replacement or a cataract would have jumped the queue through private health insurance. Those persons at or near the top of the waiting list can expect rapid treatment and hence have little incentive to exercise voice. Furthermore of those left on the waiting list there are problems of coordination while a solution is not always in sight – at least compared to the decision to add a medicine to the Reimbursement List.

Hence in order to correct the biases inherent in the current method of determining whether or not new medicines should be added to the Reimbursement List, the HSE should consider developing guidance, paying particular attention to cost-effectiveness thresholds and when they might be exceeded, after consultation, in order to ensure greater predictability and transparency.¹⁷⁶

¹⁷⁵ O’Mahony and Coughlan (2016, p. 8).

¹⁷⁶ An issue which is beyond the remit of this paper concerns the independence of the HSE. At the present time the HSE reports to the Minister for Health and all the leading HSE executive members are State employees. The current structure of the HSE represents a move to make the HSE more accountable to the Minister for Health. The Board of the HSE was recently abolished and its CEO replaced in pursuit of this objective (DoH, 2012). It is intended to abolish the HSE at some point in the future. Making decisions on issues such as adding new medicines to the Reimbursement List are often delegated by the State to independent

Using Evidence to Inform Policy

Lunn and Ruane (2013, p. 1) in answering the question of when and how evidence can inform policy state,

“There is a sense in which the answer to this question is obvious. Whatever, the policy domain, few would dispute that decision-makers are inclined to make better decisions when they have the relevant factual information, understand the underlying processes involved, and possess reliable estimates of the likely outcomes associated with the options under consideration.”

DPER and IGEES, as noted above, were created in part to provide the relevant factual information and present reliable estimates.

In the present case suppose it is accepted that the status quo rather than the no agreement is the appropriate counterfactual benchmark. Instead of savings of €600 million attributed to the Agreement the sum is €290 million. How would that affect public policy?

While it is difficult to be precise, the Minister for Health and other signatories representing the State may have decided that savings of €290 million were insufficient. The representatives of the State may have pushed for further concessions from the IPHA. Rebates may have been increased. Realignments might have used the lowest price among the Nominated States to set the ex-factory price. The cost per QALY threshold could be set well below €45,000.

Given the asymmetry in access to information it is difficult for those outside the negotiations to be able to assess the claims and counterclaims. Often when more information becomes available subsequent to decisions having already been made entrenched positions have been adopted. Far better the basis on which estimates such as the €600 million are made should be published prior to decisions being made so that the legislators and civil society can assess and debate the issues.¹⁷⁷ Better policy and value for money should result.

regularly bodies (Gorecki, 2011). If the HSE is abolished then some thought might be given to the creation of such an independent body.

¹⁷⁷ For example, as part of DPER/IGEES healthcare papers referred to above.

Notwithstanding the lack of documentation concerning the savings flowing from the Agreement a forum does exist within which the Agreement can be assessed. The Joint Committee on Health has shown an interest in the cost of prescription medicines. It published a report in 2015 on the issue, with recommendations relating to “*the inclusion of key performance indicators for drug price savings under a new Agreement.*”¹⁷⁸ It would therefore be an appropriate place within which the magnitude of the savings flowing from the Agreement could be thoroughly examined.¹⁷⁹

¹⁷⁸ Joint Committee on Health & Children, Houses of the Oireachtas (2015, p. 24).

¹⁷⁹ The committee has not, to date, dealt with the issue of the savings flowing from the Agreement. In a recent examination of the future of healthcare in Ireland by a committee of the Dail, although reference is made to the Agreement, the report does not address the effectiveness of the Agreement in terms of cost savings nor does it suggest methods of dealing with the ongoing budgetary pressures occasioned by the flow of new medicines beyond some general recommendations. Nevertheless, the committee makes a recommendation that is consistent with discussion above in ‘Pricing of New Medicines.’ See Committee on the Future of Healthcare (2017, pp. 99-101).

REFERENCES

- Aggarwal A, T Fojo, C Chamberlain, C Davis, and R Sullivan R. (2017) "Do Patient Access Schemes for High Cost Cancer Drugs Deliver Value to Society? – Lessons from the NHS Cancer drugs Fund." *Annals of Oncology*. 27 April. doi:10.1093/annonc/mdx110.
- Barry, Michael (2014) "Economic Evaluation and Access to Medicines in the Irish Healthcare Setting." November. This may be accessed at: <http://studylib.net/doc/14719988/current-challenges-of-affordability-of-healthcare-in-ireland>
- Barry, Michael (2015) "National Medicines Management Programme (MMP) – Update." Presentation at 3rd National Medicines Forum, Royal College of Physicians of Ireland, Dublin 30 April.
- Brick, Aoife, Paul K Gorecki and Anne Nolan (2013a) *Ireland: Pharmaceutical Prices, Prescribing Practices and the Use of Generics in a Comparative Context*. Research Series No. 32. Dublin: Economic and Social Research Institute.
- Brick, Aoife, Paul K Gorecki and Anne Nolan (2013b) "Usage of Generics in Ireland: Recent Trends and Policy Developments." *Journal of Generic Medicines*. Vol. 10, No. 2, pp. 72 -85.
- Callaghan, Niamh (2015) *Primary Care Reimbursement Service*. Staff Paper. Dublin: DPER.
- Committee on the Future of Healthcare (2017) *Report*. Dublin: Houses of the Oireachtas.
- Competition and Consumer Protection Commission (2014) *Guidelines for Merger Analysis*. Dublin: the Commission.
- Connolly, Sheelah and Maev-Ann Wren (2016) "The 2011 proposal for Universal Health Insurance in Ireland: Potential implications for healthcare expenditure." *Health Policy*. <http://dx.doi.org/10.1016/j.healthpol.2016.05.010>
- Coyle, Dominic (2016) "Drug pricing deal will not deliver if 'generics' fail to sell." *Irish Times*, 6th February. This may be accessed at: <http://www.irishtimes.com/business/health-pharma/drug-pricing-deal-will-not-deliver-if-generics-fail-to-sell-1.2964714>
- Cullen, Paul (2017) "Decision to provide CF drugs made without funding agreement." *Irish Times*. 14 April. This may be accessed at: <http://www.irishtimes.com/news/health/decision-to-provide-cf-drugs-made-without-funding-agreement-1.3047911>
- Department of Health (DoH) (2012) *Future Health. A Strategic Framework for Reform of the Health Service 2012-2015*. Dublin: the Department.
- Department of Health (DoH)(2016a) "State to Make Major Savings Under New Drug Pricing Deal. Press Release. 20 July. Dublin: the Department.
- Department of Health (DoH) (2016b) *Departmental Brief for Minister*. May. Dublin: the Department.
- Department of Public Expenditure and Reform (DPER) (2016) *Brief for Incoming Minister for Public Expenditure and Reform*. May. Dublin: DPER.

- Department of Health. (2017) "Reference Pricing." <http://health.gov.ie/future-health/reforming-primary-care-2/reference-pricing/>
- Dillion, Andrew, (2015) "Carrying NICE over the threshold." *Blog*. 19 February. London: National Institute for Health and Care Excellence. <https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold>
- European Commission (2009) *Report on the Pharmaceutical Sector Inquiry*. Luxembourg: Office for Official Publications of the European Communities.
- European Commission (2016) *Country Report Ireland 2016*. Commission Staff Working Document. SWD(2016) 77 Final. Brussels: the Commission.
- Gorecki, Paul K (2011) "Economic Regulation: Recentralisation of Power or Improved Quality of Regulation." *Economic and Social Review*, Vol. 42, No. 2. Summer, pp. 177-211.
- Gorecki, Paul K, Anne Nolan, Aoife Brick & Sean Lyons (2012) *Delivery of Pharmaceuticals in Ireland. Getting a Bigger Bang for the Buck*. Research Series No. 24 Dublin: Economic and Social Research Institute.
- Harris, Simon (2016) "Opening Statement by Minister Simon Harris TD – Joint Committee on Health" 29th September. It may be accessed at: <http://health.gov.ie/blog/speeches/opening-statement-by-minister-simon-harris-td-joint-committee-on-health/>
- Harris, Simon (2017) "Speech by Minister Simon Harris at the Healthcare Enterprise Alliance Breakfast Briefing." 8th February. Royal College of Physicians, Dublin. It may be accessed at: <http://health.gov.ie/blog/speeches/speech-by-minister-simon-harris-at-the-healthcare-enterprise-alliance-breakfast-briefing/>
- Health Insurance Authority/Millward Brown (2016) *A Review of Private health Insurance in Ireland*. Dublin: the Health Insurance Authority.
- Health Products Regulatory Authority (HPRA) (2014) *Guide to Interchangeable Medicines*. Dublin: HPRA.
- Health Products Regulatory Authority (HPRA) (2015) *Guide to Biosimilars for Healthcare Professionals and Patients*. Dublin: HPRA.
- Health Service Executive, Primary Care Reimbursement Service (2006). *Statistical Analysis of Claims and Payments 2005*. Dublin: HSE.
- Health Service Executive, Primary Care Reimbursement Service (2007). *Statistical Analysis of Claims and Payments 2006*. Dublin: HSE.
- Health Service Executive, Primary Care Reimbursement Service (2010). *Statistical Analysis of Claims and Payments 2009*. Dublin: HSE.
- Health Service Executive, Primary Care Reimbursement Service (2014). *Statistical Analysis of Claims and Payments 2013*. Dublin: HSE.
- Health Service Executive (HSE) (2013) "Notice of Decision Under Section 24 of the Health (Pricing and Supply of Medical Goods) Act 2013." 30 September. Dublin: HSE. <http://www.hse.ie/eng/services/news/atorvastatinrefpricing.pdf>
- Health Service Executive, Primary Care Reimbursement Service (2016a). *Statistical Analysis of Claims and Payments 2015*. Dublin: HSE.

- Health Service Executive (2016b) "IPHA Price Changes." Dublin: HSE. These may be accessed at: <http://www.hse.ie/eng/about/Who/cpu/iphaPricechanges.pdf>
- Health Service Executive (2016c) "Biosimilar Medicines in the Irish healthcare setting." Dublin: HSE. This may be accessed at: <http://hse.ie/eng/about/Who/clinical/natclinprog/medicinemanagementprogramme/yourmedicines/positionpapers/biosimilarmedicines.pdf>
- Health Service Executive (2017) "HSE statement on negotiations with Vertex re Orkambi, Kalydeco and other treatments for Irish Cystic Fibrosis Patients." Press Release. 12 April. This may be accessed at: <http://www.hse.ie/eng/services/news/media/pressrel/HSE-statement-on-negotiations-with-Vertex-re-Orkambi-Kalydeco-and-other-treatments-for-Irish-Cystic-Fibrosis-Patients.html>
- Hennessy, John (2015) *Opening Statement to Joint Committee on Health & Children*. 12 March. Dublin: HSE This may be accessed at: <http://www.oireachtas.ie/parliament/media/committees/healthandchildren/health2015/HSE-Opening-Statement.doc>
- Hirschman, Albert (1970). *Exit, Voice and Loyalty. Responses to Decline in Firms, Organizations, and States*. Cambridge, Mass: Harvard University Press.
- IMS Health (2016) *The Impact of Biosimilar Competition*. London: IMS Health.
- International Monetary Fund (IMF) (2013) *Ninth Review Under the Extended Arrangement. IMF Country*. Report No. 13/93. April. Washington DC: IMF.
- Irish Fiscal Advisory Council (IFAC) (2015) *Controlling the health budget: Annual Budget Implementation in the Public Health Area*. Analytical Note No 8. Dublin: IFAC.
- Irish Pharmaceutical Health Association (IPHA). (2016) "IPHA Statement: New Agreement on Medicines Pricing to Allow State Fund New Medicines for Patients in Ireland." Press Release. 20 July. Dublin: IPHA.
- Irish Pharmaceutical Health Association (IPHA). (2017) "IPHA welcomes decision to reimburse Cystic Fibrosis medicines." Press Release. 11 April. Dublin: IPHA.
- Joint Committee on Health & Children, Houses of the Oireachtas (2015) *Report on the Cost of Prescription Drugs in Ireland*. 31HHCN022. Dublin: Houses of the Oireachtas.
- Lunn, Pete and Frances Ruane (2013) "When and How Can Evidence Inform Policy?" In Lunn, Pete and Frances Ruane (eds) *Using Evidence to Inform Policy*. Dublin: Gill & Macmillan, pp. 1-22.
- Madden, Deirdre and Orla O'Donovan (2015) *Qualitative Review of Complaints Received by the Medical Council 2008-2012 and Doctors' Responses*. Dublin: Medical Council.
- McCullagh, Laura and Michael Barry (2016) "The Pharmacoeconomic Evaluation Process in Ireland." *PharmacoEconomics*. Published online 29 July 2016.
- McDonagh, Michelle (2017) "Improving access to medicines." *Irish Times*. 23 May.
- Mitchell, Susan (2016a) "Revealed: Irish Spending on Drugs Highest in Europe." *Sunday Business Post*, 14 February, pp. 1-2.
- Mitchell, Susan (2016b) "Deal or No Deal on Drugs." *Sunday Business Post*. 31 July 2016.

- National Medicines Information Centre (NIMC) (2015) "Update on Biosimilar Medicines." *Bulletin*, Vol. 21, No. 5, December.
- O'Mahony, James and Diarmuid Coughlan (2016) "The Irish Cost-Effectiveness Thresholds: Does it Support Rational Rationing or Might it Lead to Unintended Harm to Ireland's Health System." *PharmacoEconomics*. Vol. 34, Issue 1, January, pp. 5-11.
- pwc (2016) *The value of community pharmacy – detailed report*. London: Pharmaceutical Services Negotiating Committee.
- Toumi, Mondher, Cecile Remuzat, Anne-Lise Vataire & Duccio Urbinati (2013) *External Reference Pricing of Medicinal Products: Simulation-Based Considerations for Cross-Country Coordination. Final Report*. Brussels: European Commission.
- Volger, Sabine, Lena Lepuschutz, Peter Schneider & Verena Stuhlinger (2015) *Study on Enhanced Cross-Country Coordination in the Area of Pharmaceutical Product Pricing. Final Report*. Luxembourg: Publication Office of the European Union.
- Wall, Martin & Sarah Bardon (2016) "HSE to unilaterally cut prices it pays for drugs." *Irish Times*, 17 May. This may be accessed at: <http://www.irishtimes.com/news/ireland/irish-news/hse-to-unilaterally-cut-prices-it-pays-for-drugs-1.2650666>
- Watt, Philip (2017) "It was right to provide CF drug Orkambi." Letter to the Editor. *Irish Times*. 8 May. This may be accessed at: <http://www.irishtimes.com/opinion/letters/it-was-right-to-provide-cf-drug-orkambi-1.3073158>
- Welch, Anna Rose (2016) "The Norwegian Biosimilar Phenomenon: From Biosimilar to 'Biogeneric.'" *Biosimilar Development*, 26 July. This may be accessed at: <https://www.biosimilardevelopment.com/doc/the-norwegian-biosimilar-phenomenon-from-biosimilar-to-biogeneric-0001>