



Tithe an
Oireachtais
Houses of the
Oireachtas

AN COMHCHOISTE UM SLÁINTE

Tuarascáil maidir le Drugaí Dílleachta a Mheasúnú

Feabhra 2018

JOINT COMMITTEE ON HEALTH

Report on Evaluating Orphan Drugs

February 2018

[32H016]

Chair's Foreword



Dr. Michael Harty T.D.
(Rural Independent Technical
Group)

Orphan Drugs are defined as medicines that prevent or treat rare diseases. An individual rare disease may affect 1 in 10,000 people. Collectively rare diseases may affect up to 6% to 8% of the population and it is estimated that rare diseases affect 300,000 people in Ireland during their lifetime. For those affected by rare diseases, orphan drugs may provide an opportunity to improve their lives considerably.

Patients with Rare Diseases are extremely vulnerable and disadvantaged across the world.

Owing to the rarity of their condition, a patient will likely see an average of 7.3 physicians over 4.8 years before a diagnosis is made, while due to the chronically debilitating or life-threatening nature of many rare diseases, up to 30% of patients with a rare disease will die before the age of five. Even when patients are diagnosed early and enter the healthcare system, there remain high levels of unmet need, as only 5% of rare diseases currently have a licenced treatment.

These patients suffering from rare diseases deserve the same quality treatment as other patients across Ireland and the European Union. This principle of equity is underpinned in Ireland's National Rare Disease Plan for Ireland 2014-2018: that "Patients resident in Ireland should receive the best possible evidence-based diagnosis and care irrespective of the rarity of their condition."

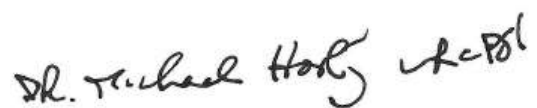
Given the small number of patients affected by rare diseases, a reluctance traditionally existed amongst the pharmaceutical industry to invest in research and develop treatments for rare diseases. In 2000, the EU introduced a series of incentives to stimulate the development of orphan drugs, including fee waivers for regulatory procedures and an extended, 10-year market exclusivity. The EU's intervention has successfully stimulated the development of over 1,500 orphan drugs to date – over 140 of which have subsequently received market authorisation by the EMA for reimbursement across Europe.

Nonetheless, the reimbursement of Orphan Drugs poses a challenge to countries across the EU. Despite their incentive, they remain costly to develop due to the low patient population and low success rate in bringing a drug to market, while they can be difficult to assess

adequately using traditional pricing and reimbursement models that place a high emphasis on clinical data.

As EU Members adapt and refine their own reimbursement models for orphan drugs, it is time Ireland does so too. It is with increasing frequency that orphan drugs are not available in Ireland, despite their availability in Northern Ireland and across the EU. While publicly available comparative data is limited in this regard, it has been suggested that Ireland lags behind most of our closest EU neighbours – significantly so in France and Germany.

While the rationale behind the widening gap in availability of orphan drugs here and elsewhere is complex, the impact on patients is clear. It is therefore incumbent on policymakers to review this process and seek workable solutions, before Ireland inevitably slips in patient outcomes across Europe for rare diseases.



Dr. Michael Harty, T.D.
Chair
Joint Committee on Health
28 February 2018

Table of Contents

| | |
|--------------------------------------------------------------------------------|----|
| Chair’s Foreword..... | 1 |
| Executive Summary..... | 4 |
| Summary of Recommendations..... | 6 |
| 1. Introduction | 9 |
| 1.1 Definition | 9 |
| 1.2 Numbers Affected..... | 9 |
| 1.3 Examples of rare diseases..... | 9 |
| 1.4 The Health (Pricing and Supply of Medical Goods) Act 2013 | 10 |
| 2. Applications Process | 10 |
| 2.1 Key issues | 12 |
| (i) Assessment Criteria | 12 |
| 3. The HSE | 15 |
| 3.1 Duties and Responsibilities | 15 |
| 3.2 Key issues | 15 |
| (i) Communication..... | 15 |
| (ii) Clinical Trials and Compassionate Use..... | 16 |
| (iii) Budget | 17 |
| (iv) Delays..... | 17 |
| (v) Innovation | 18 |
| (vi) QALY | 18 |
| 3 NCPE..... | 20 |
| 4.1 Duties and Responsibilities | 20 |
| 4.2 Key Issues..... | 20 |
| (i) Assessment | 20 |
| (ii) Staffing | 20 |
| 5 EU Collaboration | 21 |
| 5.1 Key Issues..... | 21 |
| 6 Report of the Consultation for a National Rare Disease Plan for Ireland..... | 24 |
| 7 Conclusion..... | 25 |
| Appendices..... | 27 |
| Appendix 1: Membership of the Joint Committee on Health..... | 27 |
| Appendix 2: Stakeholders and Transcripts | 28 |
| Appendix 3 – Terms of Reference of Committee | 29 |

Executive Summary

Orphan drugs refer to medicines, which treat, diagnose or prevent diseases that are life threatening or chronically debilitating, and affect fewer than 5 in 10,000 people.¹

Due to the high costs, the HSE assess each orphan drug before being approved for reimbursement and pricing.

However, advocate groups representing those affected by rare diseases have highlighted a number of on-going issues with the evaluation process. Each EU Member State evaluates orphan drugs separately and as such, the decisions of state members differ. Patient groups also note the length of time from the beginning of an assessment to a decision on reimbursing the cost of the drug. Such delays can have a detrimental effect on the health of patients suffering from rare diseases.

The purpose of this report is to examine the evaluation process and to highlight some of the issues experienced by those in need of orphan drugs.

The Joint Committee on Health held two meetings on the 12 July and 8 November 2017. In attendance were officials from the HSE and representatives of the National Centre for Pharmacoeconomics (NCPE), the Alpha One Foundation and Muscular Dystrophy Ireland. The representation of these two groups does not confine the issue to these two illnesses and there are many other individuals affected by rare diseases and the availability or otherwise of orphan drugs.

The report examines a number of key areas with regard to orphan drugs, such as their assessment and their cost. The Health (Pricing and Supply of Medical Goods) Act 2013 sets out criteria in assessing drugs. This Act does not make any special provision for orphan drugs and as such, the criteria for evaluating orphan drugs and other medicines are identical.

The cost of orphan drugs is often extremely high and as resources for funding are finite, it is difficult to fund all that is sought. The report discusses the Quality Adjusted Life Year (QALY) assessment, which is currently in use.

The report also examines the main concerns with the current assessment process and the main difficulties, which may prevent access to orphan drugs. It considers the delays in

¹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

reimbursing the cost for orphan drugs, compassionate access, as well as the role of the HSE and the NCPE.

The Committee recommends considerable change to the evaluation process of orphan drugs. The Committee believes that the current QALY assessment is not effective and that this process neglects to ensure the best outcome for patients.

The Committee also recommends the need of improved patient participation. In situations where an orphan drug is not approved following assessment, the HSE will often engage with the pharmaceutical company in pricing negotiations. However, this stage lacks structure and set timelines. Patient groups have raised concerns that there are no details provided to patients during this process.

Similarly, pharmaceutical companies will allow some patients access to orphan drugs not yet approved under a compassionate access scheme. If the orphan drug is not approved there is ambiguity on whether access to the drug will continue to be provided. The HSE does not engage patients at any stage of this process. The Committee recommends that engagement is initiated early between the HSE, pharmaceutical companies and patients in such scenarios.

The Committee recommends that the Department of Health commence a review of the 2013 Act to identify potential legislative barriers to the reimbursement of orphan drugs and corresponding legislative amendments. The Committee also recommends engagement with patients during the review process and that a report is presented to the Minister of Health.

The Committee also notes that the recommendations related to orphan drugs in the National Rare Disease Plan for Ireland are not yet fully implemented. The Committee recommends that the Department of Health and the HSE establish responsibility for implementing these recommendations and that they be implemented at the earliest possible stage.

Summary of Recommendations

1. The Committee recommends that the evaluation process for orphan drugs be fit for purpose. The Committee recommends that a number of changes are required to achieve this and that further consideration and analysis is required to ensure that the process is beneficial to patients and those in need of orphan drugs.
2. The Committee recommends that a review of the 2013 Act be commenced by the Department of Health, to present a report to the Minister for Health within 6 months of the publication of this report, identifying potential legislative barriers to the reimbursement of orphan drugs and corresponding legislative amendments, as appropriate.
3. The Committee recommends that the Department of Health engage with stakeholders, and in particular with patients during the drafting process of its review. The views of patients are vital to ensuring that the process benefits those in need of orphan drugs.
4. The Committee recommends that the Department of Health, HSE and the Irish Pharmaceutical Healthcare Association (IPHA) agree, at its next review of the Framework Agreement on the Supply of Medicines to Health Services 2016-2020, an explicit process for post-assessment negotiation, detailing set timelines for revised proposals from industry and corresponding response deadlines from the HSE.
5. The Committee recommends the appointment of an independent academic with knowledge of pricing and reimbursement systems and orphan medicines, to conduct a review of the current process and its role in orphan drug availability in Ireland.
6. The Committee recommends that continuous communication between the HSE, patient groups and the pharmaceutical industry is imperative. The Committee acknowledges that further improvements are required. The Committee also acknowledges that a number of factors, such as negotiations and funding shortages, can delay reimbursing the cost of orphan drugs or reaching a decision on reimbursement. However, continuous communication and involvement with patients is beneficial to all stakeholders.
7. The Committee recommends early engagement between the HSE, patients and pharmaceutical companies prior to clinical testing. Such engagement is beneficial in leading to an understanding of the personal circumstances of patients and facilitates agreements around compassionate use.

8. The Committee recommends the establishment of a specific budget for high tech and orphan drugs, which would be separate to individual hospital budgets. It is the Committee's view that caution needs to be exercised when it comes to actual budgets being allocated in this area as there is potential for this being seen as a target and not a budget.
9. The Committee recommends that the QALY process is revised completely and replaced with a new assessment process. Such a process should be specific and appropriate to orphan drugs.
10. The Committee recommends that the State and the HSE has some role in innovation, in collaboration with university structure. It is the Committee's view that unless the State has some involvement over the R&D element of the orphan drug and high tech phenomenon we will constantly be on the back foot with regard to funding. The Committee affirms the need for a sustainable and affordable and perhaps even novel model of funding.
11. The Committee recommends that the NCPE publicise all documents and information that it considers in its assessment of all treatments.
12. The Committee recommends that the Rare Diseases Technology Review Committee commence assessing orphan drugs as soon as possible, so that qualitative data (patient, carer and clinician experience) can support the evaluation of an orphan drug, where clinical certainty concerns exist from quantitative data alone. Such input should be appropriately weighted to have a meaningful impact on the consideration of a medicine.
13. The Committee recommends that further attempts be made to work with other EU states in order to align assessment processes. Such work would allow for a more efficient process, with increased information sharing and quicker assessment times. Such work should be considered a longer-term potential solution and should therefore not preclude the HSE or Department of Health from undertaking immediate activity to enhance the availability of orphan drugs in Ireland, such as the recommendations contained in this report.
14. The Committee recommends that recommendations 30 to 39 of the Report of Consultation for a National Rare Disease Plan for Ireland are fully implemented at the earliest possible stage.

Clear responsibility should be established amongst officials within the HSE and Department of Health for implementing the recommendations in the Rare Disease Plan.

15. The Committee recommends that it schedule a sitting bi-annually to call upon officials within the HSE and Department of Health responsible for the implementation of the Rare Disease Plan to provide detailed updates on their progress to date.

1. Introduction

1.1 Definition

The European Medicines Agency (EMA) defines a medicine as an orphan drug if it meets the following criteria:²

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating,
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that the marketing of the medicine would generate sufficient returns to justify the investment needed for its development,
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

1.2 Numbers Affected

There are between 5,000 and 8,000 distinct rare diseases in existence, affecting more than 6% to 8% of the population of the EU.

There are between 27 million and 36 million people in the EU affected by rare diseases.

In Ireland, the HSE estimates that 300,000 people will develop a rare disease at some stage in their life.³

1.3 Examples of rare diseases

The majority of rare diseases affect fewer than 1 in 100,000 people. Rare diseases may appear at birth or in childhood. Such diseases include spinal muscular atrophy and cystic fibrosis. More than half of rare diseases may appear during adulthood, such as glioma and myeloid leukaemia.

² http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

³ <http://www.hse.ie/eng/services/list/5/rarediseases/>

1.4 The Health (Pricing and Supply of Medical Goods) Act 2013

The Health (Pricing and Supply of Medical Goods) Act 2013⁴ deals with applications received for new medicines from pharmaceutical companies. Schedule 3 of the Act⁵ lists the criteria for making decisions around reimbursement and/ or pricing.

These include

1. The health needs of the public,
2. The cost effectiveness of meeting health needs by supporting the item concerned rather than providing other health services,
3. The availability and suitability of items for supply or reimbursement,
4. The proposed costs, benefits and risks of the item or listed item relative to therapeutically similar items or listed items provided in other health service settings and the level of certainty in relation to the evidence of those costs, benefits and risks,
5. The potential or actual budget impact of the item or listed item,
6. The clinical needs for the item or listed them,
7. The appropriate level of clinical supervisions required in relation to the item to ensure patient safety,
8. 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
9. The resources available to the HSE.

2. Applications Process

The process for dealing with applications for a new medicine is as follows;

- The HSE Corporate Pharmaceutical Unit receives the application from the pharmaceutical company as per Section 18(1) of the Act.
- The Corporate Pharmaceutical Unit of the HSE commissions the NCPE to conduct a health technology review of the new medicine.
- The medicine is subjected to a preliminary rapid review by the NCPE.

⁴ <http://www.irishstatutebook.ie/eli/2013/act/14/enacted/en/html>

⁵ <http://www.irishstatutebook.ie/eli/2013/act/14/schedule/3/enacted/en/html#sched3>

- High-cost products and those with significant budget impact are subjected to formal Pharmacoeconomics assessment.
- Similarly, products where concerns arise in relation to value for money are selected for formal Pharmacoeconomics assessment.
- All such Pharmacoeconomics assessments are carried out in compliance with published HIQA Guidelines.
- Companies submit a dossier for consideration i.e. the company gets the opportunity to put forward its best case for consideration by NCPE.
- Following assessment, a full appraisal report outlining the NCPE conclusions and recommendations is sent to the Corporate Pharmaceutical Unit.
- The appraisal report sets out detailed information on the clinical evidence for the benefits associated with or claimed for the new medicine and the robustness of that evidence.
- Information on cost-effectiveness and the probability of cost effectiveness at a range of thresholds (e.g. €20,000 per Quality Adjusted Life Year (QALY), €45,000/QALY, €100,000/QALY and occasionally at even higher thresholds is also provided.
- In the case of oncology drugs a report is also sent to the National Cancer Control Programme for consideration under the NCCP Therapeutic Review Process.
- The Corporate Pharmaceutical Unit leads on any commercial negotiation with the individual pharmaceutical company.
- The full assessment report, the outputs of any commercial negotiations and any other relevant information is then considered by the HSE Drugs Group, which is the expert body in place to make recommendations to the HSE Leadership Team on New Medicines applications.
- The HSE Leadership Team or Directorate is the final decision making body.
- The Act requires that the HSE provides a formal notice of any proposed decision to the applicant company and requires that the HSE consider any representations received from an applicant company in advance of making a formal (final) decision on pricing and reimbursement.
- Re-assessing. Assessed by the EMA and then individual states.

It should be noted that this process is set out in the Framework Agreement on the Supply of Medicines to Health Services 2016-2020, detailing procedures around communication between the HSE and the pharmaceutical manufacturer as the application undergoes pharmacoeconomic assessment with the NCPE. Post-assessment, a common scenario exists whereby a pharmaceutical company's application is refused by the HSE, triggering

commercial negotiation between both parties. This process lacks defined timelines, reporting structure or deadlines, and has been highlighted by patients and industry alike as a major delaying factor in reaching a final decision with the HSE.

2.1 Key issues

(i) Assessment Criteria

Officials from the HSE stated that the Act does not make separate provision for orphan drugs, and they assess these treatments under the same process and criteria as all other drugs. One criticism of this process is that due to the small number of patients, the value of each orphan drug may be difficult to identify.

Representatives from the NCPE stated that

“As regards the assessment of orphan drugs, in some cases there is a challenge in respect of submitting data to demonstrate their cost-effectiveness because of patient numbers. That is particularly so for ultra-orphan drugs”.

The case studies below illustrate some of the difficulties experienced by patients in need of orphan drugs that are undergoing assessment.

Respreeza and Alpha-1

Alpha-1 antitrypsin deficiency (Alpha-1) is a generic lung disorder, affecting up to 250,000 people in Ireland. The Alpha One Foundation stated that over 350 people are diagnosed with the severe form of Alpha-1 in Ireland. Antitrypsin is a protein that protects the lungs from infection. Those affected by Alpha-1 are deficient in this protein and consequently are highly susceptible to severe lung, liver and skin problems.

Respreeza is a treatment for Alpha-1 that tackles emphysema caused by severe Alpha-1. The Alpha-1 Foundation's studies reported significant benefits to those receiving the Respreeza treatment.

Duchenne Muscular Dystrophy and Translarna

Duchenne Muscular Dystrophy (DMD) is a rare genetic condition that occurs in one in every 3,500 males. It is caused by a mutation that results in a deficiency of the protein Dystrophin. The consequences of this deficiency are severe muscle weakness, cardiac and respiratory problems and a life expectancy of 27 years.

Translarna, also known as ataluren, is suitable for children with a diagnosis of DMD, who are over 5 years old and are able to walk at least 10 steps unaided. There are currently five patients in Ireland with DMD who are either eligible or will be eligible for Translarna once they reach the age of 5 years old.

Assessment of Respreeza and Translarna

The HSE did not approve Respreeza or Translarna for reimbursement as neither drug was deemed cost effective. The HSE confirmed that the treatments showed marginal clinical improvements at a very high price and quoted that the budget impact for Translarna would be in excess of €3 million.

The HSE also emphasised that they carried out assessments in line with the criteria set out in the legislation. Both drugs have shown benefits to patient on clinical trials. However, both drugs have high costs and the HSE did not consider them as cost effective. In such cases, the HSE engages with the suppliers to negotiate pricing however, in both of these situations no agreement was reached⁶.

The Alpha One Foundation and Muscular Dystrophy Ireland gave details of the personal impact on patients awaiting the assessment of orphan drugs. There are a number of issues raised in relation to the assessment. Firstly, orphan drugs are assessed under the same criteria as all other drugs. Secondly, the high costs of orphan drugs make it difficult to provide funding. Finally, the time taken to assess and then attempt to negotiate pricing for orphan drugs is detrimental to those in need.

The Committee acknowledge the difficulty in approving orphan drugs for reimbursement under the current set of guidelines and assessment procedures. It also notes that the HSE reimbursed a number of orphan drugs following negotiations with pharmaceutical companies. The HSE have made a large amount in savings following negotiations and these savings allow more funding for other orphan drugs.

⁶ In October 2017, Respreeza was made unavailable in Ireland although in December 2017, it was announced that the supplier would continue to provide the treatment to those previously receiving it.

However, this process only adds to the delay in approving the drugs.

The Committee also note that even when orphan drugs are approved there may be further issues in providing funding for them.

1. The Committee recommends that the evaluation process for orphan drugs be fit for purpose. The Committee recommends that a number of changes are required to achieve this and that further consideration and analysis is required to ensure that the process is beneficial to patients and those in need of orphan drugs.
2. The Committee recommends that a review of the 2013 Act be commenced by the Department of Health, to present a report to the Minister for Health within 6 months of the publication of this report, identifying potential legislative barriers to the reimbursement of orphan drugs and corresponding legislative amendments, as appropriate.
3. The Committee recommends that the Department of Health engage with stakeholders, and in particular with patients during the drafting process of its review. The views of patients are vital to ensuring that the process benefits those in need of orphan drugs.
4. The Committee recommends that the Department of Health, HSE and IPHA agree, at its next review of the Framework Agreement on the Supply of Medicines to Health Services 2016-2020, an explicit process for post-assessment negotiation, detailing set timelines for revised proposals from industry and corresponding response deadlines from the HSE.
5. The Committee recommends the appointment of an independent academic with knowledge of pricing and reimbursement systems and orphan medicines, to conduct a review of the current process and its role in orphan drug availability in Ireland.

3. The HSE

3.1 Duties and Responsibilities

The HSE is responsible for the reimbursement of medicines under a number of statutory schemes, such as the GMS (Medical Card Scheme), the Long Term Illness scheme and the Drugs Payment Scheme.

Initially the HSE commissions the NCPE to evaluate each new drug. The HSE will then review this assessment and based on the recommendation, it may approve the drug for reimbursement and/ or pricing. One of the main criteria is the Quality Adjusted Life Year (QALY) assessment. This is a scientific based assessment that looks at the benefits of the drug to a person's life.

If a new medicine is not considered as cost efficient the HSE will often engage with pharmaceutical companies to negotiate pricing. This process is confidential and as such it is difficult to communicate detailed information to patients.

3.2 Key issues

(i) Communication

The representatives from Alpha One Foundation and Muscular Dystrophy Ireland both highlighted concerns regarding communication from the HSE particularly in relation to meeting dates and meeting outcomes. The representatives also emphasised the urgency of decision making as patient's health deteriorated.

The representatives stated their opinion that the HSE was not engaging enough with patient groups. Officials from the HSE stated that there was a new facility for patient groups to contribute to the assessment process and in 2016 approximately 40% of assessment included patient submissions. The officials also referenced improvements in facilitating stakeholder involvement. However, they acknowledged that this is an ongoing process and communication can improve.

(ii) Clinical Trials and Compassionate Use

Many pharmaceutical companies will provide temporary free access to an orphan drug to individuals in a member state where the drug is not available. Patients can avail of this process through “compassionate use” programmes or clinical trials. In Ireland, this arrangement is between the pharmaceutical company and the individual patients. These programmes are temporary and when a drug is not approved for reimbursement, there is ambiguity on whether access to the treatment will continue.

The Helsinki Protocol⁷ sets out guidelines for dealing with patients on clinical trials and compassionate use programmes. Access to the treatment will often continue to be provided to patients as part of compassionate access.

However, these protocols are not legally binding but are considered as ethical principles. Officials from the HSE confirmed that most pharmaceutical companies manage patients participating in clinical testing programmes very well but some companies take a different approach and wish to conclude their compassionate use programmes.

Officials from the HSE stated that pharmaceutical companies manage this process with patients and that it has no role in managing continued compassionate care.

While not legally binding, the Helsinki protocol states

“In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.”

Officials from the HSE responded that as the HSE is not involved in the programme at any point, it is not able to intervene at the compassionate use stage.

The National Rare Diseases Plan⁸ advised early dialogue between the HSE and companies who are running clinical trials with Irish patients. Patient groups reported that patients are often unaware of whether the HSE would approve each orphan drug and the length of time to finalise a decision. Early and continuous dialogue between all groups would reduce ambiguity and create a more transparent process.

⁷ <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

⁸ <http://health.gov.ie/blog/publications/national-rare-disease-plan-for-ireland/>

(iii) Budget

The HSE expenditure on medicines is approximately €2 billion per annum. This is approximately 14% of the total health budget.

However, there are no specific funds allocated to orphan drugs. The allocation of financial resources for one drug will affect funding in other areas.

The Committee recommends that High Tech and Orphan Drugs, as they are both initiated in secondary care, should have a single allocation. It is the Committee's view that caution needs to be exercised when it comes to actual budgets being allocated in this area as there is potential for this being seen as a target and not a budget.

The Rare Diseases Plan (see section 6), advises that the HSE carry out a preliminary economic evaluation of current activity and costs for orphan medicine and technologies for rare disease patients across all hospitals settings. It also advises that funding for orphan drugs should be considered in a separate budget and not through individual hospital budgets.

(iv) Delays

The representatives of the NCPE stated that they complete rapid reviews of orphan drugs in 6 weeks. They also confirmed that in most cases a full assessment is completed within 6 months.

The officials from the HSE stated that delays could occur "when the clinical benefits by the trial studies are marginal but the prices charged are substantial." Negotiations between the HSE and pharmaceutical companies will then proceed and these discussions will prolong the overall assessment and reimbursement process.

The officials from the HSE confirmed that in 2017, there was a delay between approval and reimbursement in the case of products for the treatment of cystic fibrosis, cancer, heart failure and a number of other conditions

(v) Innovation

Considering the strain that the cost of providing these new medicines has on our services and health budget, the State and the HSE has some role in innovation, in collaboration with university structure. It is the Committee's view that unless the State has some involvement over the R&D element of the orphan drug and high tech phenomenon we will constantly be on the back foot with regard to funding. We need a sustainable, affordable, and perhaps even novel model of funding.

(vi) QALY

The Quality Adjusted Life Year (QALY) is calculated for all drugs to ensure that the costs are representative of their benefits. Those drugs which are considered to have €45,000 per QALY or less are considered to be cost effective.

If a drug does not meet a QALY/ €45,000, it is the HSE decision on whether to approve the drug for re-imbursement with regard to the criteria set out in the Act. The HSE will also meet with the pharmaceutical company in order to negotiate the price.

Some suggest that the QALY threshold of €45,000 is too low. If the QALY threshold was increased to €100,000, it may lead to further medicines being approved. However, it would also lead to paying higher costs for each medicine. As stated earlier, in cases where drugs are above the current QALY threshold of over €45,000 the HSE will attempt to negotiate further savings with the suppliers.

The main issue with regard to QALY is whether the set thresholds adequately provide fair assessment on the benefits of each drug. It is noted that there is a balance required in providing funds. Increasing funds and the QALY threshold may increase the price of each drug but not necessarily provide a wider range of drugs.

It is also noted that some drugs may pass as cost effective but obtaining the necessary funds for the drug may take time and, as such, the reimbursement for the drug would be delayed. Authorizing more orphan drugs as cost effective will not necessarily increase the number of drugs reimbursed.

As the QALY is based heavily on the quantitative data derived from clinical studies, assessing an orphan drug's clinical effectiveness based on this approach alone can be challenging, given their often-limited clinical trial data due to small patient populations.

The Committee do not believe that the current QALY is appropriate for orphan drugs. It recommends that a new process is establish that is specific to orphan drugs and that this process provides the best possible outcome for orphan drug patients.

6. The Committee recommends that continuous communication between the HSE, patient groups and the pharmaceutical industry is imperative. The Committee acknowledges that further improvements are required. The Committee also acknowledges that a number of factors, such as negotiations and funding shortages, can delay reimbursing the cost of orphan drugs or reaching a decision on reimbursement. However, continuous communication and involvement with patients is beneficial to all stakeholders
7. The Committee recommends early engagement between the HSE, patients and pharmaceutical companies prior to clinical testing. Such engagement is beneficial in leading to an understanding of the personal circumstances of patients and facilitates agreements around compassionate use.
8. The Committee recommends the establishment of a specific budget for high tech and orphan drugs, which would be separate to individual hospital budgets. It is the Committee's view that caution needs to be exercised when it comes to actual budgets being allocated in this area as there is potential for this being seen as a target and not a budget.
9. The Committee recommends that the QALY process is revised completely and replaced with a new assessment process. Such a process should be specific and appropriate to orphan drugs.
10. The Committee recommends that the State and the HSE has some role in innovation, in collaboration with university structure. It is the Committee's view that unless the State has some involvement over the R&D element of the orphan drug and high tech phenomenon we will constantly be on the back foot with regard to funding. The Committee affirm the need for a sustainable and affordable and perhaps even novel model of funding.

4. NCPE

4.1 Duties and Responsibilities

The NCPE facilitates healthcare decisions on the reimbursement of technologies, usually pharmaceuticals, by applying clinical and scientific evidence in a systematic framework, in order to maximize population wellness.

The NCPE assessment considers the clinical effectiveness and health related quality of life benefits and all relevant costs including potential savings from reduced healthcare resource use (e.g. hospitalisation), which a new treatment may provide, and whether the price requested by the manufacturer is justified.

The NCPE will then advise the HSE in relation to the cost effectiveness, value for money, and budget impact associated with the specific pharmaceutical product.

The NCPE has a standardized process and criteria for the evaluation of pharmaceutical products including orphan drugs.

4.2 Key Issues

(i) Assessment

The representatives from Muscular Dystrophy Ireland confirmed that they were updated during the NCPE assessment process as there are set time-lines in which to assess each medicine and to report back to stakeholders. However, the representatives highlighted their concerns that they are unaware of what actual studies the NCPE based their assessment on. They referred to NICE⁹ in the United Kingdom who publish a list of documents it receives and considers for assessment.

(ii) Staffing

The representatives from the NCPE stated that staffing comprised of nine whole-time equivalents and that they required an additional nine more staff. The representatives confirmed that completing assessments on time was more difficult due to the staff shortages.

⁹ The National Institute of Health Care Excellence (NICE) provide guidance to the NHS (UK) regarding orphan drugs.

The main cause for the difficulty in employing staff was finding individuals with the required level of experience and knowledge.

11. The Committee recommends that the NCPE publicise all documents and information that it considers in its assessment of all treatments.
12. The Committee recommends that the Rare Diseases Technology Review Committee commence assessing orphan drugs as soon as possible, so that qualitative data (patient, carer and clinician experience) can support the evaluation of an orphan drug, where clinical certainty concerns exist from quantitative data alone. Such input should be appropriately weighted to have a meaningful impact on the consideration of a medicine.

5. EU Collaboration

5.1 Key Issues

The EU offers incentives to encourage companies to research and develop medicines to treat rare diseases. To access these incentives, companies can apply for orphan designation for their medicine, provided certain criteria are met.

The European Medicines Agency (EMA) assesses these medicines. Once approved, the medicines are available to Member State markets. However, each individual Member State and its relevant national authorities will then assess the medicine before deciding whether or not to approve access to their market and reimburse the cost to patients.

The assessment of each national authority differs. Germany has a record of approving a high number of orphan drugs. The officials from the HSE told the Committee that Germany has a unique situation. Firstly, once the EMA approve the drugs, they are immediately available to the German market. Pharmaceutical companies will have free pricing for the first year of availability. After this, the German health authority and the pharmaceutical companies will negotiate pricing but the large population in Germany allows a strong negotiating position.

As such, German patients will have greater access to a wider range of orphan drugs. However, officials from the HSE point out that this comes at a price, and Ireland would not have sufficient resources to adopt this position.

In response to queries relating to EU member states harmonising an assessment process, the officials from the HSE stated that resources for each State will differ and therefore it would be difficult to achieve harmonisation. .

Due to the variety of assessment processes and resources in each Member State, it is common for orphan drugs to be available in some EU states and not others.

The officials from the HSE noted that the Department of Health had engaged in discussions with other EU states with the intention of collaborating with other countries nations with similar populations.

However, they also stated that any EU wide harmonisation was difficult as the resources and requirements of each EU state differed greatly.

One EU Member worth considering for its approach to orphan drugs is that of Scotland, which saw an significant increase in orphan drug availability over a relatively short period of time, through the creation of bespoke pathways for these treatments.

In Scotland, a high proportion of medicines for end-of-life and rare conditions were not being recommended for reimbursement by the Scottish Medicines Consortium, giving rise to concern amongst patients and the pharmaceutical industry that clinically effective medicines (that were often the only treatment option) were being rejected solely on the basis of cost. In 2013, a Task and Finish Group reviewed the pricing and reimbursement process and made several recommendations to enhance access to these medicines¹⁰ – all of which were accepted by the Scottish Government.

This 'New Approach' (2014) included a revised process for assessing orphan, ultra-orphan¹¹ and end-of-life medicines, the creation of a Patient and Clinician Engagement platform to allow first-hand evidence be taken into account, and a decision-making framework for ultra-orphan medicines that was not based on the QALY.

¹⁰ http://www.parliament.scot/S4_HealthandSportCommittee/Reports/her-13-08w.pdf

¹¹ In England and Wales, ultra-rare diseases are considered as those with a prevalence of less than 1 per 50,000 population

In January 2013, the Scottish Government also created a Rare Conditions Medicines Fund for orphan drugs where the rare disease affects fewer than 1 in 2,000 people, which was then replaced in October 2014 by the New Medicines Fund.

A December 2016 independent review found an increase in acceptance rates for orphan and cancer medicines from 48% in 2011-2013 to 75% in 2014-2016 for orphan, ultra-orphan and end-of-life medicines¹². The review recommended several reforms to improve access further – all of which were accepted immediately by Cabinet Secretary for Health Shona Robison.

13. The Committee recommends that further attempts be made to work with other EU states in order to align assessment processes. Such work would allow for a more efficient process, with increased information sharing and quicker assessment times. Such work should be considered a longer-term potential solution and should therefore not preclude the HSE or Department of Health from undertaking immediate activity to enhance the availability of orphan drugs in Ireland, such as the recommendations contained in this report.

¹² <https://beta.gov.scot/publications/review-access-new-medicines/.../00511595.pdf>

6. Report of the Consultation for a National Rare Disease Plan for Ireland

This report was launched in May 2014¹³. However, recommendations 30 to 39 inclusive are not yet fully implemented.

1. The HSE develop a Working Group to bring forward appropriate decision criteria for the **reimbursement of orphan medicines and technologies**. The approach should include an assessment system similar to that for cancer therapies established under the National Cancer Control Programme and link with the CAVOMP at European level.
2. The HSE undertake a **preliminary economic evaluation** of current activity and costs for orphan medicine and technologies for rare disease patients across all hospitals settings.
3. Applications for the use of orphan medicines and technologies in hospitals are dealt with in the **context of a national budget**, rather than through individual hospital budgets, and that the HSE take account of this.
4. The HSE develop a publicly available **annual report documenting the use of both existing and new-to-market orphan medicines and technologies** in Ireland and a summary of applications received and decisions relating to those applications.
5. The existing **horizon scanning between pharmaceutical companies and the HSE**, including clinical value assessment authorities, continue and be enhanced to improve information available regarding orphan medicines in the pipeline and the future needs for these medicines.
6. The capacity to prescribe all orphan medicines and technologies for **ultra-rare conditions be limited to specialist teams** designated through the Centres of Expertise.
7. The HSE apply a set of **guidelines on the prescribing** of orphan medicines and technologies in Ireland. The HSE should evaluate clinical outcomes regarding use of orphan medicines.
8. Clinicians should provide data necessary to the **monitoring of prescription patterns** and pharmacovigilance, to ensure patient safety and high-quality healthcare.
9. Early dialogue between the HSE and companies who are running **clinical trials in Ireland** with Irish patients where license approval is imminent.
10. Sponsors could be offered an incentive to run trials in Ireland **increasing access to innovation** for Irish patients.

¹³ <http://health.gov.ie/blog/publications/national-rare-disease-plan-for-ireland/>

14. The Committee recommends that recommendations 30 to 39 of the Report of Consultation for a National Rare Disease Plan for Ireland are fully implemented at the earliest possible stage. Clear responsibility should be established amongst officials within the HSE and Department of Health for implementing the recommendations in the Rare Disease Plan.
15. The Committee recommends that it schedule a sitting bi-annually to call upon officials within the HSE and Department of Health responsible for the implementation of the Rare Disease Plan to provide detailed updates on their progress to date.

7. Conclusion

In order for patients in Ireland to avail of orphan drugs, each medicine must go through a number of tests and assessments. The EMA must first assess and approve the drug to allow access to the European markets.

Following this, each EU Member State assesses the drug under its own assessment process. This creates ambiguity for patients, as drugs will become available in some EU states but not others. Respreeza and Translarna are two examples of this, as both are not approved in Ireland but are available in some other EU States.

The Health (Pricing and Supply of Medical Goods) Act 2013 established criteria for the assessment process of all medicines in Ireland. One of the main features of this process is that there are no specific provisions for orphan drugs. As such, orphan drugs may be at a disadvantage in passing the assessment process.

The HSE is responsible for approving each drug for reimbursement. There were a number of key issues raised including communication with patient groups, clinical trials and compassionate use, resources for orphan drugs and the QALY assessment.

The NCPE carries out an assessment of each drug and makes recommendations on the cost effectiveness of the medicine to the HSE. The main assessment criterion is the QALY, which attempts to value the benefit of each drug. There is some debate as to whether this process is the best method for evaluating orphan drugs.

At the Committee meetings, members discussed a number of options for EU collaboration in relation to orphan drugs. The officials from the HSE stated that there was much difficulty in this as different States had different assessment processes due to varying resources in each State. However, if a number of States could align their assessment processes, it may result in the sharing of assessment resources and information. Such collaboration may then result in faster assessment times and a more standardised EU assessment process.

The officials from the HSE confirmed that some initial talks between the Department of Health and other States had begun and the Committee is strongly in favour of attempting to create some common process between states.

The Committee notes that the Report of the Consultation for a National Rare Disease Plan for Ireland made a number of recommendations, which reference many of the points in this report. These recommendations are not yet fully implemented and the Committee strongly recommends that these be put into effect.

The Committee strongly recommend that the current assessment process is altered considerably. This change includes revising the QALY process and improving patient engagement.

Appendices

Appendix 1: Membership of the Joint Committee on Health

Deputies:

- Bernard Durkan (Fine Gael)
- Dr Michael Harty [Chairman] (Rural Independent Technical Group)
- Billy Kelleher (Fianna Fáil)
- Alan Kelly (Labour)
- Kate O'Connell (Fine Gael)
- Margaret Murphy O'Mahony (Fianna Fáil)
- Louise O'Reilly (Sinn Féin)

Senators:

- Colm Burke (Fine Gael)
- John Dolan (Civil Engagement Technical Group)
- Rónán Mullen (Independent)
- Dr Keith Swanick (Fianna Fáil)

Appendix 2: Stakeholders and Transcripts

The Joint Committee (hereinafter referred to as the “Committee”) held 2 days of hearings in July and November of 2017 to engage with relevant stakeholders to discuss orphan drugs. The table below identifies all stakeholders who made presentations to the Committee, the date of their presentations and the session during which they made their presentation.

Figure 1: Joint Committee hearings – stakeholders / witnesses present

12 July 2017

Session 1

- Mr John Hennessy, HSE
- Mr Shaun Flanagan, HSE
- Professor Michael Barry, NCPE

Session 2

- Ms Geraldine Kelly, Alpha One Foundation
- Professor Gerry McElvaney, Alpha One Foundation
- Ms Clair Kelly, Muscular Dystrophy Ireland
- Mr Richard Lodge, Muscular Dystrophy Ireland

8 November 2017

- Mr John Hennessy, HSE
- Mr Shaun Flanagan, HSE
- Professor Michael Barry, NCPE
- Dr Lesley Tilson, NCPE

See hyperlink to the transcripts of the Meetings of [12 July](#),¹⁴ and [8 November](#)¹⁵ 2017

¹⁴ Meeting of the Oireachtas Joint Committee on Jobs, Enterprise and Innovation ([12 July 2017]). Available at:<http://oireachtasdebates.oireachtas.ie/Debates%20Authoring/DebatesWebPack.nsf/committeetakes/HEJ2017071200002?opendocument#D00100>

¹⁵ Meeting of the Oireachtas Joint Committee on Jobs, Enterprise and Innovation (8 November 2017). Available at:
<http://oireachtasdebates.oireachtas.ie/Debates%20Authoring/DebatesWebPack.nsf/committeetakes/HEJ2017110800002?opendocument#C00100>

Appendix 3 – Terms of Reference of Committee

A) Functions of the Committee [derived from Standing Orders – DSO 84A and SSO 70A]

(1) The Committee shall consider and report to the relevant House(s) on-

- (a) such aspects of the expenditure, administration and policy of a Government Department or Departments and associated public bodies as the Committee may select, and
- (b) European Union matters within the remit of the relevant Department or Departments.

(2) The Select Committee appointed by Dáil Éireann is joined with a Select Committee appointed by Seanad Éireann (to form a Joint Committee) for the purposes of the functions set out in this Standing Order, other than at paragraph (3), and to report thereon to both Houses of the Oireachtas.

(3) Without prejudice to the generality of paragraph (1), the Select Committee shall consider, in respect of the relevant Department or Departments, such—

- (a) Bills,
- (b) proposals contained in any motion, including any motion within the meaning of DSO 187,
- (c) Estimates for Public Services, and
- (d) other matters

as shall be referred to the Select Committee by the Dáil, and

- (e) Annual Output Statements including performance, efficiency and effectiveness in the use of public moneys, and
- (f) such Value for Money and Policy Reviews as the Select Committee may select.

(4) Without prejudice to the generality of paragraph (1), the Joint Committee may consider the following matters in respect of the relevant Department or Departments and associated public bodies:

- (a) matters of policy and governance for which the Minister is officially responsible,
- (b) public affairs administered by the Department,
- (c) policy issues arising from Value for Money and Policy Reviews conducted or commissioned by the Department,
- (d) Government policy and governance in respect of bodies under the aegis of the Department,
- (e) policy and governance issues concerning bodies which are partly or wholly funded by the State or which are established or appointed by a member of the Government or the Oireachtas,
- (f) the general scheme or draft heads of any Bill
- (g) any post-enactment report laid before either House or both Houses by a member of the Government or Minister of State on any Bill enacted by the Houses of the Oireachtas,
- (h) statutory instruments, including those laid or laid in draft before either House or both Houses and those made under the European Communities Acts 1972 to 2009,
- (i) strategy statements laid before either or both Houses of the Oireachtas pursuant to the Public Service Management Act 1997,
- (j) annual reports or annual reports and accounts, required by law, and laid before either or both Houses of the Oireachtas, of the Department or bodies referred to in subparagraphs (d) and (e) and the overall performance and operational results, statements of strategy and corporate plans of such bodies, and
- (k) such other matters as may be referred to it by the Dáil from time to time.

(5) Without prejudice to the generality of paragraph (1), the Joint Committee shall consider, in respect of the relevant Department or Departments—

- (a) EU draft legislative acts standing referred to the Committee under DSO 114 and SSO 107, including the compliance of such acts with the principle of subsidiarity,

- (b) other proposals for EU legislation and related policy issues, including programmes and guidelines prepared by the European Commission as a basis of possible legislative action,
- (c) non-legislative documents published by any EU institution in relation to EU policy matters, and
- (d) matters listed for consideration on the agenda for meetings of the relevant EU Council of Ministers and the outcome of such meetings.

(6) Where the Select Committee appointed by Dáil Éireann has been joined with a Select Committee appointed by Seanad Éireann, the Chairman of the Dáil Select Committee shall also be the Chairman of the Joint Committee.

(7) The following may attend meetings of the Joint Committee, for the purposes of the functions set out in paragraph (5) and may take part in proceedings without having a right to vote or to move motions and amendments:

- (a) members of the European Parliament elected from constituencies in Ireland, including Northern Ireland,
- (b) members of the Irish delegation to the Parliamentary Assembly of the Council of Europe, and
- (c) at the invitation of the Committee, other members of the European Parliament.

(8) The Joint Committee may, in respect of any Ombudsman charged with oversight of public services within the policy remit of the relevant Department or Departments, consider—

- (a) such motions relating to the appointment of an Ombudsman as may be referred to the Committee, and
- (b) such Ombudsman reports laid before either or both Houses of the Oireachtas as the Committee may select: Provided that the provisions of DSO 111F apply where the Committee has not considered the Ombudsman report, or a portion or portions thereof, within two months (excluding Christmas, Easter or summer recess periods) of the report being laid before either or both Houses of the Oireachtas.

B) Powers of the Committee [derived from Standing Orders – DSO 85, 114 and 116 and SSO 71, 107 and 109]

The Joint Committee has:-

- (1) power to take oral and written evidence and to print and publish from time to time minutes of such evidence taken in public before the Committee together with such related documents as the Committee thinks fit;
- (2) power to invite and accept oral presentations and written submissions from interested persons or bodies;
- (3) power to appoint sub-Committees and to refer to such sub-Committees any matter comprehended by its orders of reference and to delegate any of its powers to such sub-Committees, including power to report directly to the Dáil and to the Seanad;
- (4) power to draft recommendations for legislative change and for new legislation;
- (4A) power to examine any statutory instrument, including those laid or laid in draft before either House or both Houses and those made under the European Communities Acts 1972 to 2009, and to recommend, where it considers that such action is warranted, whether the instrument should be annulled or amended;
- (4B) for the purposes of paragraph (4A), power to require any Government Department or instrument-making authority concerned to submit a Memorandum to the Committee explaining any statutory instrument under consideration or to attend a meeting of the Committee for the purpose of explaining any such statutory instrument: Provided that such Department or authority may decline to attend for stated reasons given in writing to the Committee, which may report thereon to the Dáil;
- (5) power to require that a member of the Government or Minister of State shall attend before the Committee to discuss policy for which he or she is officially responsible: Provided that a member of the Government or Minister of State may decline to attend for stated reasons given in writing to the Committee, which may report thereon to the Dáil and Seanad: and provided further that a member of the Government or Minister of State may request to attend a meeting of the Committee to enable him or her to discuss such policy;
- (6) power to require that a member of the Government or Minister of State shall attend before the Committee to discuss proposed primary or secondary legislation (prior to

such legislation being published) for which he or she is officially responsible:

Provided that a member of the Government or Minister of State may decline to attend for stated reasons given in writing to the Committee, which may report thereon to the Dáil and Seanad: and provided further that a member of the Government or Minister of State may request to attend a meeting of the Committee to enable him or her to discuss such proposed legislation;

- (6A) power to require that a member of the Government or Minister of State shall attend before the Committee and provide, in private session if so requested by the member of the Government or Minister of State, oral briefings in advance of meetings of the relevant EU Council of Ministers to enable the Committee to make known its views: Provided that the Committee may also require such attendance following such meetings;
- (6B) power to require that the Chairperson designate of a body or agency under the aegis of a Department shall, prior to his or her appointment, attend before the Committee to discuss his or her strategic priorities for the role;
- (6C) power to require that a member of the Government or Minister of State who is officially responsible for the implementation of an Act shall attend before a Committee in relation to the consideration of a report under DSO 164A and SSO 157A;
- (7) subject to any constraints otherwise prescribed by law, power to require that principal office-holders in bodies in the State which are partly or wholly funded by the State or which are established or appointed by members of the Government or by the Oireachtas shall attend meetings of the Committee, as appropriate, to discuss issues for which they are officially responsible: Provided that such an office-holder may decline to attend for stated reasons given in writing to the Committee, which may report thereon to the relevant House(s);
- (8) power to engage, subject to the consent of the Houses of the Oireachtas Commission, the services of persons with specialist or technical knowledge, to assist it or any of its sub-Committees in considering particular matters; and
- (9) power to undertake travel, subject to—
 - (a) such recommendations as may be made by the Working Group of Committee Chairmen under DSO 108(4)(a) and SSO 104(2) (a); and

- (b) the consent of the Houses of the Oireachtas Commission, and normal accounting *procedures*.

In accordance with Articles 6 and 8 of Protocol No. 2 to the Treaty on European Union and the Treaty on the Functioning of the European Union (Protocol on the Application of the Principles of Subsidiarity and Proportionality) as applied by sections 7(3) and 7(4) of the European Union Act 2009, the Committee has the power-

- (a) to consider whether any act of an institution of the European Union infringes the principle of subsidiarity [DSO 116; SSO 109]; and
- (b) to form a reasoned opinion that a draft legislative act (within the meaning of Article 3 of the said Protocol) does not comply with the principle of subsidiarity [DSO 114 and SSO 107].

C: Scope and context of activities of the Committee

In addition to the powers and functions that are given to Committees when they are established, all Oireachtas Committees must operate within the scope and context of activities in Dáil Standing Order 84 and Seanad Standing Order 70 as set out below.

- A Committee may only consider such matters, engage in such activities, exercise such powers and discharge such functions as are specifically authorised under its orders of reference and under Standing Orders;
- Such matters, activities, powers and functions shall be relevant to, and shall arise only in the context of, the preparation of a report to the relevant House(s).
- A Committee shall not consider any matter which is being considered, or of which notice has been given of a proposal to consider, by the Committee of Public Accounts pursuant to DSO 186 and/or the Comptroller and Auditor General (Amendment) Act 1993;
- A Committee shall not consider any matter which is being considered, or of which notice has been given of a proposal to consider, by the Joint Committee on Public Petitions in the exercise of its functions under DSO 111A(1); and
- A Committee shall refrain from inquiring into in public session or publishing confidential information regarding any matter if so requested, for stated reasons given in writing, by—
 - (i) a member of the Government or a Minister of State, or
 - (ii) the principal office-holder of a body under the aegis of a Department or which is partly or wholly funded by the State or established or appointed by a member of the Government or by the Oireachtas:

Provided that the Chairman may appeal any such request made to the Ceann Comhairle, whose decision shall be final.