The Beneluxa Initiative

Policy brief WHO

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Abstract

While there are improvements in creating innovative therapies, especially for less common/rare diseases, the prices of these kinds of pharmaceuticals are high. This makes it more difficult for national authorities to decide how to price and reimburse these. To make these pharmaceuticals more accessible for patients in small countries, collaboration could be of great help. One of the initiatives that tries to incorporate collaboration to create better and affordable access to high quality treatments is the Beneluxa Initiative. The Beneluxa Initiative is a collaboration between Belgium, the Netherlands, Luxembourg, Austria, and Ireland, that was established in 2015. The goal of the Beneluxa Initiative is to establish sustainable and affordable access to high-quality treatments and promote the responsible use of medicines, focusing mainly on highly priced pharmaceuticals. This is achieved through collaboration in four areas: horizon scanning (HS), information sharing and policy exchange, health technology assessment (HTA), and pricing and reimbursement. There are more European collaborations that perform the same or comparable activities to ensure better healthcare in their countries. One important similarity is that they all focus on more transparency on information surrounding prices and policies between the countries. The Beneluxa Initiative faces challenges due to legal and political differences. However, it offers a promising framework for international healthcare cooperation, with probable strengths in collaboration, transparency, and improved access to medicines.

List of abbreviations

ATMP	Advanced therapy medicinal product
CCC	Cross-country collaborations
DVSV	Dachverband der österreichischen Sozialversicherungen (Austrian Social Insurance)
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPHA	European Public Health Alliance
EU	European Union
EUnetHTA	European Network on Health Technology Assessment
FAAP	Fair and Affordable Pricing
GDP	Gross Domestic Product
HS	Horizon scanning
HTA	Health Technology Assessment
HTAR	European Regulation on health technology assessment
IHSI	International Horizon Scanning Initiative
INAMI	Institut National d'Assurance Maladie-Invalidité (National Health Insurance and Disability Institute)
JNHB	Joint Nordic HTA-Bodies
KCE	Belgian Health Care Knowledge Centre
LBI	Ludwig Boltzmann Institute
MA	Marketing authorisation
NCPE	National Centre for Pharmacoeconomics
OECD	Organization for Economic Cooperation and Development
PAHO	Pan American Health Organizations
QALY	Quality-adjusted life-year
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (National Health Insurance and Disability Institute)
ZIN	Zorginstituut Nederland (National Health Care Institute)

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1. Introduction

All over the world the amount of money spent on medicines is becoming a more worrisome topic. There is an increased need for medicines due to changing lifestyles and patients having higher expectations to be treated. Besides that, overall, more costly medicines are marketed. In high income countries this can lead to funding problems for expensive innovative medicines, thus to less treatment[1]. A field that is highly affected by these funding issues are orphan drugs for rare diseases. While rare diseases are only prevalent in five of 10,000 people, already in 2016 around 6,000 rare diseases existed, affecting 6-8% of the population of the European Union (EU). These rare diseases often have no existing treatments, making them a high unmet medical need. For pharmaceutical companies, rare diseases are commercially not interesting, due to small markets. Therefore, the European Parliament and European Council initiated rules to encourage pharmaceutical companies to develop orphan drugs. Although, since these drugs are only used by a minimal amount of patients, higher costs are unavoidable[2]. While the development of new orphan drugs means that new patients can be treated, this also means that a large part of reimbursement budgets are spent on these drugs[3].

An example of the rising costs for orphan drugs is a study by Eichler et al. They compared costs for medicines per person in the Austrian public statutory health insurance. The results of this study showed that 3.8% of the total drug budget of 2013 (€2.63 billion) was used for orphan drugs, to treat 0.05% of the population. In 2021, even 8.0% of the total drug budget that year (€3.70 billion) was used for orphan drugs, to treat 0.07% of the population[3]. This shows an increase in the budget impact of orphan drugs.

This problem is putting more pressure on healthcare policy makers, emphasising the need for better techniques to procure these orphan drugs[3]. To make these pharmaceuticals more accessible for patients, collaboration of countries could be of significant help. One of the initiatives that tries to incorporate collaboration to create better and affordable access to high quality treatments, originally for orphan drugs, is the Beneluxa Initiative[4].

Motive Beneluxa Initiative

The primary motive behind the Beneluxa Initiative initially was to collaborate on negotiations of pricing and reimbursement of orphan drugs with the pharmaceutical sector[5]. Now their motive is broadly stated as; to research and improve collaboration surrounding pharmaceutical policies on different domains. Their aim is that their collaboration turns out to be beneficial for patients, the pharmaceutical industry, and prescribers[6]. Because of the rising costs of medicines, it is more difficult to provide affordable treatment to patients[1]. Therefore, the aim of the Beneluxa Initiative it for patients to get faster and more affordable access to pharmaceuticals, as well as more knowledge on the added values of new pharmaceuticals. The aim for the pharmaceutical industry is for these collaborations to result in procedures being more predictable and thus have more efficient timelines. Lastly, for prescribers should be able to draft medical guidelines at an earlier timepoint, which can have a positive effect in price negotiations[6].

Objectives

This report will give an overview of insights gained on the collaboration called the Beneluxa Initiative. It will describe the Initiative's history, the organisation, and their vision, which includes ensuring sustainable access to and responsible use of medicines in the participating countries. The report will give details on four collaboration strategies which are used to increase patient access to high-quality

and affordable treatments, as well as to evaluate and regulate pharmaceutical technologies. There will also be an overview of what is already achieved in each area of collaboration.

Furthermore, similar European collaboration structures will be described and compared with the Beneluxa Initiative. Additionally, several opinions and perceptions of different parties on the Beneluxa Initiative and specific cross-country collaborations (CCC) will be given. To conclude, a discussion will be added on the Beneluxa Initiative, CCC, future perspectives, and some strengths and limitations are given.

This report uses grey literature, for which the website of the Beneluxa Initiative was the foundation source. Besides that, other governmental and institutional websites are used. Furthermore, primary literature is used, with PubMed as the main search engine. As well as multiple articles published by the WHO, found on Infarmed. Lastly, some perspectives are added from reflection papers and articles, these were found on the European Public Health Alliance (EPHA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) websites, on PubMed, and on Infarmed.

By presenting a thorough analysis of the Beneluxa Initiative, the aim of this report is to highlight their ways to pursuit improving healthcare outcomes and describing international cooperation in the pharmaceutical sector.

2. About the Beneluxa Initiative

2.1 Participating counties

The Beneluxa Initiative is a collaboration of the following countries: the Kingdom of Belgium, the Kingdom of the Netherlands, the Grand Duchy of Luxembourg, the Republic of Austria, and the Republic of Ireland[4]. These countries are all part of the EU and all have the Euro as currency[7]. The countries' inhabitants and population growth over 2023 can be seen in Table 1, as well as the Gross Domestic Product (GDP) and the % of the GDP that is spent on health. The % of GDP spent on health in Belgium, Netherlands and Austria are almost equal, these are on the upper part of all countries in the Organization for Economic Cooperation and Development (OECD), while Luxembourg and Ireland are on the lower range. All 38 members of the OECD are committed to demographic principles and market economy, making this a reasonable comparison[8].

From a pharmaceutical policy perspective, these countries have some similarities, besides the Beneluxa Initiative. They are all part of the European Medicines Agency (EMA), a decentralised agency of the EU[9]. Firstly, the EMA makes it possible to obtain a marketing authorisation (MA) in all EU and European Economic Area countries, through the centralized procedure[10]. This procedure is optional for most innovative medicines, but it is mandatory for pharmaceuticals used for a selective range of diseases, including orphan medicines[11]. Furthermore, the EMA uses various methods to enable patient access to medicines and promote pharmaceutical innovations. Lastly, the EMA supervises the safety of medicines by pharmacovigilance activities[10].

The ministry that is responsible for citizen health in Belgium is the Federal Public Service Health, Food Chain Safety and Environment. They organize healthcare, verify food safety conform European standards, stimulate animal and plant health, and attempt to reach overall environmental well-being[12]. The ministry responsible for improving health in the Netherlands is the Ministry of Health, Welfare and Sport. Their primary goals are promotion of high quality and affordable healthcare, healthy nutrition for disease prevention, and of activity by providing good sports facilities[13]. The ministry responsible for forming governmental policies on healthcare in Luxembourg is the Ministry of health and social security. Their primary goal is to provide good healthcare while being able to adapt to the needs of the population[14]. The ministry responsible for healthcare in Austria is the Federal Ministry Republic of Austria for Social Affairs, Health, Care and Consumer Protection. They also supervise a specific department called the Austrian Agency for Health and Food Safety[15]. The ministry responsible for healthcare in Ireland is the Department of Health, their goal is to improve health and wellbeing of the population by offering high quality care[16].

To conclude, these countries all have a governmental party that is responsible for overall health and healthcare. Although, most of the assessments surrounding pricing and reimbursement are performed by agencies, these can be seen in Table 1. These agencies advice the ministries, more on these procedures can be read at *chapter 2.4 vision and areas of corporation*: *Health Technology Assessment*.

Table 1. *Country specifics of participating countries.*

Country	Belgium	Netherlands	Luxembourg	Austria	Ireland
Inhabitants	11.7 million[17]	17.9 million[18]	134.7 thousand[19]	9.2 million[20]	5.1 million[21]
Population growth	0.98% (2022)[17]	0.76% (2023)[18]	1.46% (2023)[19]	0.6% (2023)[20]	0.67% (2023)[21]
Healthcare ministry	Federal Public Service Health, Food Chain Safety and Environment[12]	Ministry of Health, Welfare and Sport[13]	Ministry of health and social security[14]	Federal Ministry Republic of Austria for Social Affairs, Health, Care and Consumer Protection[15]	Department of Health[16]
Healthcare agency[22]	National Institute for Health and Invalidity Insurance	National Health Care Institute	Ministry of Health	Federation of Austrian Social Insurers	National Centre for Pharmacoeconomics
GDP (2022) [23]	€ 554.0 billion	€ 958.5 billion	€ 77.5 billion	€ 447.2 billion	€ 506.3 billion
GDP % on health (2022) [8]	10.9%	11.2%	5.5%	11.4%	6.1%

2.2 History and future collaborations

In 2013, a Hepatitis C treatment named Sovaldi, was released by an American pharmaceutical company. It had a shockingly high price of $84,000 for a 12 week cycle, which can be compared with the costs of an orphan drug, but then for an indication that in the United States alone already more than 3 million patients are affected by[24]. This incident lead ministers all over the world to realise that prices of pharmaceuticals, and budget impacts thereof, were rising. This was also the motivation for the Dutch and Belgian health ministers to discuss initial collaborations in the pharmaceutical sector, back in December 2014[5].

In April 2015, during an informal meeting of European Ministers for Employment, Social Policy, Health and Consumer Affairs, the Belgian and Dutch health ministers proposed collaborating on pharmaceutical policy, particularly regarding price negotiations for, in first instance, orphan medicinal products. Luxembourg joined the initiative, then known as the 'Belgium-Netherlands project', in September 2015, followed by Austria in June 2016. The project was named 'Beneluxa' after these initial members. Ireland joined the Initiative in June 2018, Figure 1 displays a map of the currently participating countries[4].

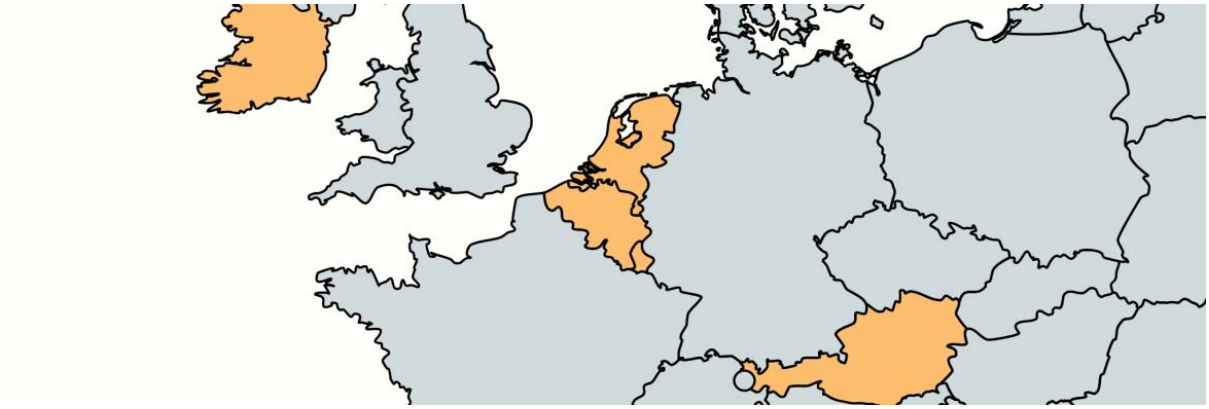

Figure 1. *Map of the participating countries of the Beneluxa Initiative[4].*

To officially join the initiative, the ministers responsible for cross border collaboration on pharmaceutical policy of the different countries all have signed a letter of intent, binding them to the Beneluxa Initiative. For another country to join the Initiative in the future, the minister first must sign this letter of intent. New countries from the EU Member states or other countries can join the initiative under certain conditions. Firstly, all current participating countries should agree with the expansion and the current participating countries should anticipate that the current collaboration initiative is function well enough. Besides this, there are some aspects that should be considered regarding the nature and extent of the collaboration. These include a shared view on access to affordable medicines, a shared view on the value of collaboration, a similar economic position, similarities in pharmaceutical markets and policies, and the country should have tendency to share resources[25].

2.3 Mandate and organisation

At the initialisation of the Beneluxa Initiative, the ministers of the different countries have signed the letter of intent, which gives national experts the mandate to participate in activities of the Beneluxa Initiative. The conditions for collaboration are described in the terms of reference, which were applied in March 2017. After the joining of Ireland in 2018, they were revised [26].

The Beneluxa Initiative has a Steering Committee, which task is to supervise collaboration. They must act on a political mandate that is formed from the letters of intent of the Member States[25]. This Steering Committee consists of a leading chair, two representatives of each country, and a chair of each Domain Task Force[25,26]. There are four Domain Task Forces, consisting of technical experts from the different countries and a chair. The Steering Committee coordinates these. The four domains are: horizon scanning (HS), information sharing and policy exchange, Health Technology Assessment (HTA), and pricing and reimbursement[25]. These domains were officially presented in the first terms of reference and have not been changed since[27]. Their responsibilities are to perform the full collaboration on the specific domain; starting from project launch, executing the project, performing the closure, all follow-up activities, up to delivering reports[25]. At each time there is a certain country conducting the chair and organisational coordinator positions, the Coordinating Country. The other countries deliver national coordinators, they are responsible for daily operations and issues, for preparing meetings, and for external communication[26].

Furthermore, there is a general assembly, which is taking place at least yearly. This includes the Steering Committee and all Domain Task Force members. The main point of this is to inform delegates of members about all the progress that is made by the Beneluxa Initiative. Besides this, it is a way to

inform outside parties like external experts, stakeholders, and other EU member states and countries about the progress of the Beneluxa Initiative[25].

2.4 Vision and areas of cooperation

Vision

The goal of the Beneluxa Initiative is to provide sustainable and affordable access to high quality treatments, as well as promote responsible use of medicines across participating countries[4]. This is primarily focussed on highly priced pharmaceuticals[25]. This is being realized by performing collaboration in the four domains mentioned above: HS, information sharing and policy exchange, HTA, and pricing and reimbursement [4,25].

Horizon scanning

HS involves systematically identifying new and emerging health technologies, including pharmaceuticals, which could significantly affect health, healthcare services, and society in general. This can be done by actively searching to find new information the earliest as possible, or by different stakeholders or researchers notifying the interested parties of the emerging technologies[28].

HS is performed using specific techniques, which are often confidential to the specific HS experts that are performing them. Although, all these techniques involve the identification of useful information sources and determining the frequency of scanning these sources. There are also databases that are specialized in HS that are monitored[28].

HS is a part in the entire process of HTA activities, which ranges from the biomedical research until clinical use. HS is taking place before the actual marketing access, as can be seen in Figure 2. By performing HS at that timepoint, information on emerging technologies is gathered before widespread adoption. This is safeguarding patients form ineffective or even dangerous treatments, while also promoting more innovative and cost-effective treatments. This is also giving policy makers the chance to revise guidelines in time, if this is needed for adoption of the technology. Furthermore, earlier evaluations leads to researchers planning ahead on the clinical development of these technologies[28].

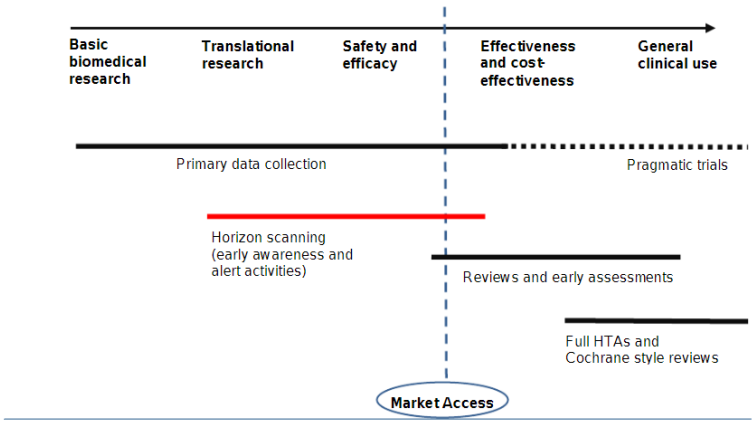

Figure 2. *Timeline of HTA activities, including Horizon scanning[28].*

To summarize, HS is a technique to gain insights in near-future marketing of new, innovative technologies, including pharmaceuticals. This technique itself is performed as one of the

collaborations between the countries of the Beneluxa Initiative. Furthermore, the approaches for performing the HS techniques are also shared between the Beneluxa countries [4,25].

In 2017, a report was published in which the Belgian Health Care Knowledge Centre (KCE) lead a Beneluxa HS task force to develop procedures for HS, as well as a model for joint HS. This report concluded that a joint HS procedure, with a central HS unit collaborating with national HS experts, would lead to more efficient resource use due to minimization of duplicate work, and to maximization of knowledge exchange by experts. Some conditions that were stated as important in this report were; prior agreement on joint HS activities, adaptation of national policies to the joint HS and vice versa, national dedication to contribute to the HS activities, and regular evaluation[29].

Based on these insights, a new joint initiative named the International Horizon Scanning Initiative (IHSI) was presented in October 2019[30]. This initiative was operational in 2022 and countries are able to join it without joining the Beneluxa Initiative[31]. The IHSI is founded to make the HS even more efficient. Their aims are to promote more transparency and earlier insights on prices, policies, and research data, all to strive for lower prices, less disruptive innovations, and more effective policy adjustments, also regarding HTA[32]. The IHSI HS system consists firstly of a database, which serves as IHSI's collection of upcoming pharmaceutical products. Additionally, there are High Impact Reports in which specific data from the database is analysed and assessed to bring attention to pharmaceuticals with potential to make a significant impact[33].

In 2022, a study by Vogler was published that reported that HS procedures improved slightly from 2014 to 2019 but were still not commonly used. Of the 44 countries that participated in the questionnaire, only six countries reported to commonly use HS for pharmaceuticals and four countries reported using some HS techniques. Furthermore, the IHSI that was started after performing these questionnaires is, in this study, reported to be a promising tool to facilitate decisions regarding the necessity of conducting a HTA and initiating price negotiations[34].

HS Domain Task Force reports

The HS Domain Task Force publishes reports on some of the possible HTA and health system challenges, with the goal to inform policy makers, payers, healthcare organizations, and the general public on time about possible difficulties and successes surrounding upcoming, non-marketed, pharmaceuticals[35,36]. Two diseases that they published such a report on are Alzheimer's Disease and Haemophilia.

In January 2022, the Domain Task Force that was working on HS published a report on pharmaceutical developments on Alzheimer's Disease. Information was gathered form clinical trials that were published between Q2 and Q4 of 2021 on 20 pharmaceuticals that were expected to enter the market between 2022 and 2027. These pharmaceuticals were all in different phases of development, with different estimated MA dates. At the point of publication of this report most of them were uncertain and some of them unlikely to receive a MA. The estimated costs of these pharmaceuticals have a wide range, from <€1,000 up until €100,000 per patient per year, which differs based on the form of treatment. From the gathered trial information, the HS Domain Task Force was able to detect new clinical trials measures, like new diagnostic criteria and new outcome measures, as well as new biomarkers that were used. Two HTA challenges that were found are the gap between requirements of the regulatory and HTA data and the need for real-world data for long-term outcomes[35].

In June 2022, the HS Domain Task Force published a report regarding to all pharmaceutical developments for the disease Haemophilia. Information was gathered from clinical trials and academic papers that were published up to Q4 of 2021, which is when the report was completed. It included 14

pharmaceuticals that were expected to enter the market between 2021 and 2025. These pharmaceuticals were all in different phases of development, with different estimated MA dates. At the point of publication of this report, most of them were likely and some of them uncertain to receive a MA. The estimated costs of these pharmaceuticals are all at the high-cost range, starting at €25,000 and even up to >€100,000 per patient per year, since it mostly includes advanced therapy medicinal products (ATMP). From the gathered trial information, the HS Task Force was able to detect that the clinical trials were mostly done on severe haemophiliac patients and were only including adults. New biomarkers are being developed, as measurement besides the standard outcome measures. Although, for Haemophilia there are no standards for conducting trials, making the performance of a HTA more challenging. Additionally, the low prevalence of this disease makes it more difficult to measure drug impact, emphasizing the need for long term safety and efficacy studies [36].

Information sharing and policy exchange

Another point of collaboration is information sharing and policy exchange. Beneluxa's vision is that by performing this over a longer time, this could affect policy initiatives on pricing and reimbursement in a positive way[4]. There have been multiple meetings and webinars in the past, in which certain topics were discussed. The first information sharing based meeting was in 2017 on patient registries, the Beneluxa countries met together with Hungary and the United Kingdom. The main outcome was the need for identification of existing patient registries, and everything needed therein, to be able to find an appropriate registry for possible collaborations. Moreover, both technical and political challenges associated with establishing a joint registry were identified[37]. In 2018 the Beneluxa published a report containing patient registries of it member countries at that time, thus excluding Ireland[38]. Table 2 shows an overview of all the webinars that took place surrounding information sharing and policy exchange and what the goal and topics of the webinars were[37].

Table 2. *Overview of Beneluxa webinars surrounding information sharing and policy exchange[37].*

Topic (year)	**Webinar goal**	**Topics**
Biosimilars (2018)	Discussion	Effectively promote biosimilar uptake
	Presentation of results	Mapping operation on the status of biosimilars
Managed entree agreements (2019)	Information exchange	Experience and practice of managed entree agreements
Transparency (2020)	Discussion	-Aspects of transparency -Improve transparency and access to medicines

Health Technology Assessment

HTA involves a systematic and multidisciplinary evaluation of the characteristics of health technologies and interventions, including their direct and indirect effects. This indicates that decisions in policy making surrounding healthcare are supported by research to these technologies[39].

The Beneluxa countries have national HTA procedures for pharmaceuticals, overseen by national agencies. In Belgium it is the responsibility of the National Health Insurance and Disability Institute (INAMI-RIZIV, Institut national d'assurance maladie-invalidité in French, Rijksinstituut voor Ziekte- en Invaliditeitsverzekering in Dutch) to conduct HTA and recommend on reimbursement. Reimbursement is granted if a pharmaceutical is found to have good efficacy, safety, easy use, and an added therapeutic value and a positive cost-effectiveness over existing treatment. Otherwise, the prise should be below

the comparable alternative. Based on this, an independent commission recommends on the price and reimbursement to the Minister of Social affairs, who is responsible for all final choices[40].

In the Netherlands it is the responsibility of the National Health Care Institute (ZIN, Zorginstituut Nederland in Dutch) to conduct HTA and recommend on reimbursement. A dossier on necessity, effectiveness, cost-effectiveness, and feasibility of the pharmaceutical is submitted to the ZIN. An important aspect for the procedure in the Netherlands is the influence of other groups, since experts from the ZIN write a report to gain advice from a scientific advisory board, health insurers, physicians, and patients. For the second version of the report, only the scientific advisory board gives advice, along with advice on social impact of the appraisal committee in the case that an extensive budget of social impact is expected. Based on the advice from all different groups, the ZIN recommends on reimbursement to the Minister of Health, Welfare and Sport, who is responsible for all final choices[40,41].

In Austria, the responsible institution for HTA is the Austrian Social Insurance (DVSV, Dachverband der österreichischen Sozialversicherungen in German). The DVSV oversees, among other things, the health insurance in Austria and it publishes the Erstattungskodex/EKO, a list of reimbursed outpatient pharmaceuticals[40,42]. The department overseeing specifically the pharmaceutical sector is the Vertragspartner Medikamente[42]. Drugs are evaluated based on pharmacological, medical-therapeutic, and economic grounds. Furthermore, it should comply with the General Austrian Social Insurance Act and the code of reimbursement. An advisory board that consists of multiple parties recommends on reimbursement and usage criteria, based on which the DVSV makes decisions[40,42].

In Ireland it is the responsibility of the National Centre for Pharmacoeconomics (NCPE) to conduct HTA and recommend on reimbursement. This is done on the cost-effectiveness and a budget impact analysis of the reimbursement of a pharmaceutical. This recommendation is done to the Health Service Executive, after which a Drug Committee executes a review, followed by a decision from a senior leadership of the Health Service Executive[40].

Lastly, in Luxembourg there is no formal process for HTA of pharmaceuticals. Luxembourg however does perform relative effectiveness assessments and economic evaluations for reimbursement and pricing decisions on pharmaceuticals, which are performed by the Ministry of Health[43].

The most significant differences between the HTA processes of the Beneluxa Initiative countries, according to an article by O'Mahony published in 2019, can be seen in Table 3. Differences in intertemporal discounting can be leading to a fundamental division on what is defined as a reasonable price. The countries also differ in terms of sources for perspectives of analysis, how to weigh health gains, and on cost-effectiveness thresholds[44].

Table 3. *Comparison of differences between the Beneluxa Initiative countries' HTA procedures[44].*

	Belgium	**The Netherlands**	**Austria**	**Ireland**
Intertemporal discounting	Differential discounting: 3% and 1.5%	Differential discounting: 4% and 1.5%	5%	5%
perspective of analysis	health system perspective	broader societal perspective	No perspective stated	health system perspective
weighting of health gains	Not specifically stated	variations in disease severity	Not specifically stated	No special weightings
cost-effectiveness thresholds	€45,000 per quality-adjusted life-year (QALY)	€20,000–80,000 per QALY, based on disease severity	No clear threshold	No clear threshold

As part of the Beneluxa Initiative, the countries' healthcare agencies strive to have corresponding timelines, methodologies, and content of the HTA procedures[40]. This is aimed to eventually lead to joint assessment procedures, for which primary knowledge gained in the European Network on Health Technology Assessment (EUnetHTA) is used[45]. EUnetHTA is an initiative of the European Commission and Council of Ministers that was initiated in 2004. Several joint actions already showed effective results to cross-border collaborations of national HTA organisations. Furthermore, a HTA working structure was established[46]. This is the basis for the four HTA based collaboration methods that the Beneluxa Initiative is currently studying. Firstly, the re-use of (parts of) HTA reports of the other countries. Secondly, the writing of HTA reports collectively with authors from several countries, which is then usable in all these countries. Furthermore, the mutual recognition of HTA reports that are conducted by one of the countries. Lastly, the participation as external referee in national MA procedures by the countries' HTA institutes[45].

Achievements

Table 4 shows a timeline of the HTA collaborations done by countries of the Beneluxa Initiative and for which pharmaceuticals these were performed. The Beneluxa Initiative made some notes on this timeline, published on their website, at a council, and in an article form. Starting with the most important progression in 2018, the exchange of national HTA activities between the countries. As of 2019, legal reasons made it not yet possible to adopt any HTA reports of other countries, but quite some partial re-use of HTA reports was done, with the aim to learn more about future adoption of full HTA reports[45]. In 2022, Beneluxa countries made a statement at the Employment, Social Policy, Health and Consumer Affairs council about the difficulties of conducting HTA collaborations[30]. Their statement mainly focussed on the need for better retrieving of HTA data, by sharing more existing data, but also by gathering more specific data in clinical trials, which is needed for HTA activities. Another focus point was the need for earlier conversations between companies and HTA agencies, to develop clearer guidelines for MA applications and HTA data gathering. In 2023, Utrecht University and the Beneluxa Initiative collaborated to analyse previously conducted HTAs, the outcome of this is in *chapter 4 opinions and perceptions*[30].

Table 4. *A timeline of all HTA activities performed by the Beneluxa Initiative[30,45].*
Including joint pricing or reimbursement: highlighted in grey.

Name pharmaceutical	**Active substance**	**Therapeutic area**	**Year**	**Type of HTA-collaboration**
LOJUXTA	Lomitapide	Hyper-cholesterolemia	2015	Re-use of Dutch work by Belgium
ORKAMBI	Lumacaftor / Ivacaftor	Cystic fibrosis	2016 (1st submission)	-Joint writing by Belgium & the Netherlands -ZIN acted as external referee for RIZIV-INAMI -Luxembourg used the final report
PRALUENT	Alirocumab	Dyslipidemias	2016	ZIN acted as external referee for RIZIV-INAMI
ORKAMBI	Lumacaftor / Ivacaftor	Cystic fibrosis	2017 (2nd submission)	-Joint writing by Belgium & the Netherlands -ZIN acted as external referee for RIZIV-INAMI -Luxembourg and Austria used the final report

Name pharmaceutical	Active substance	Therapeutic area	Year	Type of HTA-collaboration
VYNDAQEL	Tafamidis	Amyloidosis	2017	-ZIN acted as external referee for RIZIV-INAMI -Luxembourg used the final report
OCALIVA	Obeticholic acid	Primary biliary cholangitis	2017/2018	-Partial joint writing by Belgium & the Netherlands, broken up by company -Initial draft used by Belgium & the Netherlands for national reports
SPINRAZA	Nusinersen	Spinal muscular atrophy	2018	-RIZIV-INAMI used assessment report by ZIN -Other HTA organisations used the final report -Joint negotiation with Belgium & the Netherlands -> successful
XERMELO	Telotristat	Carcinoid syndrome diarrhea	2018	-RIZIV-INAMI used assessment report by ZIN
RAVICTI	Phenylbutyrate	Urea cycle disorders	2018	-RIZIV-INAMI used assessment report by ZIN
TAGRISSO	Osimertinib	Non-small-cell lung carcinoma	2018	-RIZIV-INAMI used assessment report by LBI
VERZENIOS	Abemaciclib	Breast cancer	2018	-RIZIV-INAMI used assessment report by LBI
ZOLGENSMA	Onasemnogene abeparvovec	Spinal Muscular Atrophy	2020/2021	-Joint writing by Belgium, the Netherlands and Ireland - DSVS acted as external referee for RIZIV-INAMI -Joint negotiation with Belgium, the Netherlands and Ireland -> successful
ZYNTEGLO	Betibeglogene autotemcel	Beta thalassemia	2021	-Joint writing by Belgium & the Netherlands -NCPE acted as external referee for RIZIV-INAMI -Joint negotiation with Belgium & the Netherlands -> manufacturer withdrew application for reimbursement
LIBMELDY	Atidarsagene autotemcel	Metachromatic leukodystrophy	2022/2023	-Joint writing by Belgium & Ireland, the Netherlands as co-author -DSVS acted as external referee
HEMGENIX	Etranacogene dezaparvovec	haemophilia B	2023	-Joint writing by Belgium & the Netherlands

LBI: Ludwig Boltzmann Institute (Austria)

In March 2023, Beneluxa decided to attempt perform joint evaluations for four pharmaceuticals, based on the Dutch Horizon Scan 2023-2024. The drugs in Table 5 were selected from this, based on the anticipated therapeutic outcomes. The Beneluxa stated to contact the companies for discussions about joint submissions[30].

Table 5. *Drug candidates for joint evaluations[30].*

Name pharmaceutical	**Therapeutic area**
Fezolinetant	Menopause symptoms
Leriglitazone	X-linked adrenoleukodystrophy
Phenylbutyrate/tauroursodeoxycholic acid	Amyotrophic lateral sclerosis
Vamorolone	Duchenne's disease

Pricing and reimbursement

The fourth area of collaboration is regarding pricing and reimbursement. This mostly includes joint negotiations (not including pooled procurement) with the pharmaceutical industry of prices of pharmaceuticals. Collaboration in this area will also require more transparency on medicine pricing between the countries[47]. More efficient assessments, pricing, and reimbursement are reached by knowledge and expertise sharing. This positively affects the payers position, since more knowledge is gained on products, usage, market, and joint price negotiations are performed[25].

Several joint pilots on HTA and pricing and reimbursement were conducted, of which the topic are overlapping. In 2018, the Beneluxa Initiative published the report "Guidance Joint Assessment & Joint Negotiations", with the following information on this conduction[48].

> The requirements for the conducted pilot are as following; All parties join a pilot voluntary. They include 2 or more Beneluxa countries, excluding Luxembourg since they only participate as observer instead of an active participant. Moreover, all pilots start with joint HTA, which can then lead into joint negotiations if a pharmaceutical is found to have an added value. Lastly, all the steps in the pilot are conducted by all the participating countries together. Contrary to the reimbursement decisions, which are made separately by the countries[48].
>
> The selection of products for the pilots are done on a case-by-case basis. Pharmaceuticals for diseases with high unmet medical needs, that are anticipated to have high added values, and that already have good (non-)clinical evidence, have priority. Furthermore, the selected pharmaceutical should comply with national legislations of participating countries. No reimbursement procedures can be ongoing in any of the participating countries before entering the pilot. Lastly, the manufacturer should have plans to market in all Beneluxa countries, so not only the participating countries[48]. An entry to the pilot can either be company driven or Beneluxa driven[48].
>
> For the timing of the procedure, important parts are that it already starts with an orientation meeting, around 6 months before the planned reimbursement application. So that the joint HTA can be started once the Committee for Medicinal Products for Human Use of the EMA gives a positive opinion. The joint negotiations should start around 1 month after the finalized HTA. After the completion of the negotiations, the reimbursement decisions can be made in all countries[48].

By participating in these pilots, multiple parties are benefited. With as the most important points, earlier access to medicines for patients, more sustainable and affordable healthcare for society, better informed decisions for the Beneluxa Initiative due to joint expertise, and lower workload for companies[48].

Table 4 above also includes joint negotiations that (successfully) took place in the Beneluxa Initiative. The first successful collaboration to reach an agreement on pricing and reimbursement was for Spinraza (a spinal muscular Atrophy drug) in July 2018, in the Netherlands and Belgium. This was seen as a benefit for the patients, as well as for collaboration regarding pharmaceutical policy and price negotiations[30].

3. Comparable collaborations

Access to medicines is becoming more of a struggle all over the world, therefore initiatives exist that aim for better collaboration between countries[49]. Some existing European pharmaceutical collaborations are for example the Pharmaceutical Pricing and Reimbursement Information network and the Piperska group, these are mainly focussed on sharing information and experience[49].

There are also some CCC performing pooled procurement methods, pooled procurement is an agreement by purchasing authorities on combining financial and other resources. This is done to increase purchasing power and to enhance efficiency[50].

These collaborations exist all over the world. A non-European example is the Pan American Health Organizations (PAHO) in American countries for vaccines, syringes and supplies. This was followed up by PAHO's Strategic Fund, for the procurement of essential medicines[49].

3.1 Comparable European collaborations

In Europe, the EC approved the Joint Procurement Agreement in 2014, this was regarding emergency supplies like vaccines, but excluding orphan and oncology drugs[49]. After this event, there were major changes in terms of ensuring access to medicines in Europe. Firstly, procurement became more important in general. Secondly, multiple European national governments joined forces to make medicines more affordable. The Beneluxa initiative is one of these voluntary joined forces, other European collaborations are the Baltic Procurement Initiative, the Nordic Pharmaceutical Forum, the Valletta Declaration, and the Fair and Affordable Pricing (FAAP). The timeline of the establishment of these collaborations can be seen in Figure 3 [51].

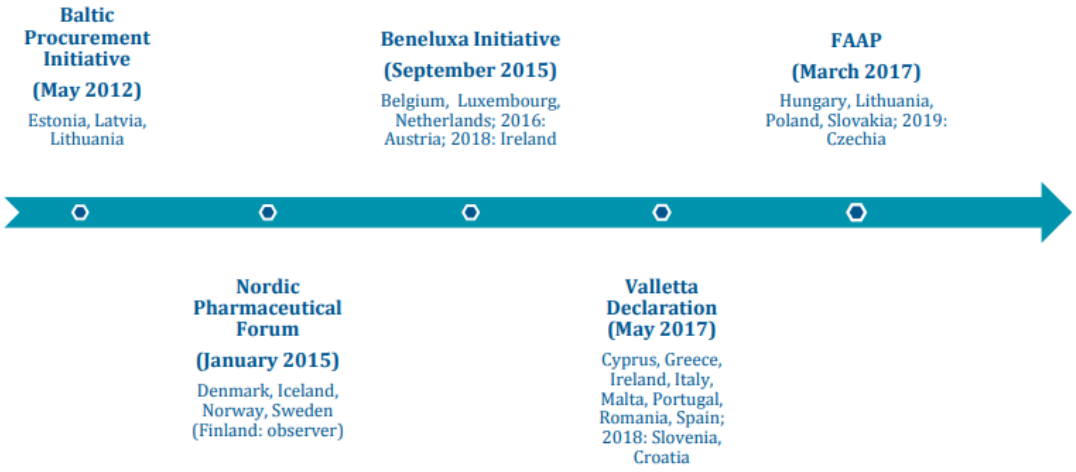

Figure 3. *Timeline of establishment of different European collaborations*[51].

Baltic Procurement Initiative

Firstly, the Baltic Procurement Initiative, this is a collaboration between Estonia, Latvia and Lithuania, which started out as a task force in 2010 and was officially established in 2012. Their focus point is joint procurement of vaccines, which may extend to joint procurement of medicines in the future. This procurement process is lead by one of the countries, that legally procures products for the other countries, for which only the lead countries' legislations are in place. Each procurement is on a voluntary basis for each country and the lead country is decided on a case-by-case basis. As of October 2021, three successful joint procurements had taken place[49,51]. To assure better access to healthcare,

another collaboration point is lending of medicines and medical devices to prevent shortages. Lastly, the Baltic Procurement Initiative actively exchanges information.

Nordic Pharmaceutical Forum

The Nordic Pharmaceutical Forum is a collaboration between Denmark, Iceland, Norway and Sweden, with Finland as an observer, that was established in 2015[49]. They joined forces to enhance their position towards the industry and apply more price pressure[52]. Their focus points are ensuring a better pharmaceutical supply and promotion of information sharing. To reach this, they collaboratively perform price negotiations and procurement of medicines, this is both focussed on old pharmaceuticals and on innovative, often more expensive, pharmaceuticals[51]. Besides these activities, the Nordic Pharmaceutical Forum collaborates on HS, sustainability, manufacturing, logistics and supply security[52]. They have successfully performed a joint negotiation in 2020. They also have engaged in a lot of knowledge sharing, one major collaboration this brought on was the development of standard terms for new ATMPs throughout these countries. Lastly, they performed 2 successful joint procurements[53].

Valletta Declaration

The Valletta Declaration is a collaboration that was primarily between Malta, Italy, Cyprus, Greece, Portugal and Spain, established in 2017. In 2018, Ireland, Romania, Slovenia, and Croatia joined. The main goal is to improve access to medicines for patients, with a focus on innovative medicines and therapies. Their points of collaboration are, among others, HS, creating methods to perform joint HTA and to perform joint negotiations. For this last point, the products have been identified and some products are under consideration. Beside these, knowledge sharing is a collaboration point, which is connected to the identification of good practices surrounding pricing and reimbursement, for which they aim to have transparency on prices between the countries[51]. Thus, first steps are made for these points, although they also encountered hesitation from the industry.

Fair and Affordable Pricing

The FAAP is a collaboration which was established in 2017. After their first memorandum of understanding expired, they signed a new one in 2019 that is now still in place. The countries that are currently in the FAAP are the Czech Republic, Hungary, Lithuania, Poland and Slovakia[51]. The main goals of the FAAP are improvement of access to affordable pharmaceuticals and development of methods to collaborate, focussed on high priced medicines. They share knowledge on pricing and reimbursement, this is already done successfully in several expert meetings. Furthermore, they started on researching methods to collaborate on HTA and there are plans to perform pilots for joint negotiations in the future[51,54].

Joint Nordic HTA-Bodies

Another collaboration was established in 2018, named Finose, including Finland, Norway and Sweden. Denmark joined this in 2023 and Iceland in 2024, after which they decided to change some points about their collaboration, as well as their name. This collaboration now exists as the Joint Nordic HTA-Bodies (JNHB)[55]. Their main goal is to collaboratively provide efficient and transparent HTA of medicinal products. They aim to perform knowledge sharing between the different countries' HTA bodies. Furthermore, they will perform joint assessments, which will be shared with price negotiators. This should lead to higher quality and less time-consuming procedures. There are no plans to make joint decisions on recommendations or reimbursement, this will be done nationally[56].

Comparisons

Table 6 presents an overview of the different collaborative areas of the Beneluxa Initiative and pooled procurement and in which CCC these are performed. Although, the contents of these collaborations are not the same in each CCC. As can be seen in Table 6, each CCC performs some form of information sharing and policy exchange, to most collaborations this is mostly contained to knowledge sharing. Collaboration on pricing and reimbursement is primarily done by performing joint negotiations in all the compatible CCC.

Table 6. *Overview of different collaborations in European CCC.*

	Beneluxa Initiative	**Baltic Procurement Initiative**	**Nordic Pharmaceutical Forum**	**Valletta Declaration**	**FAAP**	**JNHB**
HS	✓	**X**	✓	✓	**X**	**X**
Information sharing and policy exchange	✓	✓	✓	✓	✓	✓
HTA	✓	**X**	**X**	✓	✓	✓
Pricing and reimbursement	✓	**X**	✓	✓	✓	✓
Pooled procurement	**X**	✓	✓	**X**	**X**	**X**

The biggest differences between the Baltic Procurement Initiative and the Beneluxa Initiative are mainly that Baltic Procurement Initiative focusses on performing pooled procurement and is currently only collaborating on vaccines. Additionally, they specifically use one countries' legislation for procurement, while during the Beneluxa Initiative's collaborations, all legislations of all countries stay applicable. Lastly, lending of medicines and medical devices is not something the Beneluxa Initiative performs.

The Nordic Pharmaceutical Forum and the Beneluxa Initiative both perform HS, practice information sharing and policy exchange, and perform joint pricing and reimbursement, mostly in the form of joint negotiations. The biggest differences between these CCC are that the Nordic Pharmaceutical Forum also performs pooled procurement and that they have an added focus on real world logistics, e.g. ensuring better security of supply.

The Valletta Declaration has the same collaboration points as the Beneluxa Initiative, with empathises on the importance of transparency between countries. Although, the developments in the collaboration of the Valletta Declaration are less evolved than the Beneluxa Initiative's.

The goals of the FAAP are similar to the goals of the Beneluxa Initiative and their working plans are also comparable, except for inclusion of HS. Although, they have not performed any collaborative assessments or negotiations yet. The last update on the achievements page of the FAAP website was on an information sharing workshop that took place in 2020[54].

The plans of the JNHB are similar to the collaborations of the Beneluxa Initiative. Although, since the JNHB is a new collaboration in this specific composition, there are no results in terms of collaboration yet. A similarity that both CCC emphasize, is that after joint negotiations are performed, the Beneluxa Initiative countries and the JNHB countries both make their own reimbursement decisions.

3.2 Cooperations between cross-country collaborations

The following cooperations are performed between the Beneluxa Initiative and other CCC. Firstly, in June 2021 the Beneluxa Initiative and the Nordic Pharmaceutical Forum published a joint statement on their plans to perform examinations to issues surrounding pricing and reimbursement. They stated the importance of performing cost-effectiveness analysis to achieve the most health benefits inside the budgets. Furthermore, they stated the importance of on time availability of clinical evidence, so value assessment decisions can be made based on this evidence. The Beneluxa Initiative and the Nordic Pharmaceutical Forum aim to perform research to the timing of all cost-effectiveness assessments and to the value-framework for medicine assessment[30].

In December 2022, the Beneluxa Initiative published a statement reaching out to other CCC. They described a workshop on negotiations about new pharmaceuticals that took place in June 2022. They reported that representatives from nine countries discussed their experiences on negotiation of new pharmaceuticals and possibilities for inter-organisation knowledge sharing, surrounding challenges of the negotiation process. With this statement, the Beneluxa Initiative reached out to other CCC to actively partake in more discussions surrounding these topics[30].

4. Opinions and perceptions of different parties on cross-country collaborations

There are few statements or interviews published surrounding the Beneluxa Initiative. Although, there is one organisation that published two reflection papers: the EPHA, an international non-profit organization that focusses on improving health in Europe through policies[57]. Furthermore, there is one study published that directly focussed on perspectives of different stakeholders on the Beneluxa Initiative itself. Lastly, some research groups have published studies to specific collaboration techniques and on CCC, which sometimes include their perceptions on these topics. The following chapter shows these different standpoints on the Beneluxa Initiative specifically and on CCC in general.

European Public Health Alliance's reflection of the Beneluxa Initiative

The EPHA published two reflection papers surrounding the Beneluxa Initiative itself. The first one was published in September 2017, which was co-funded by the Health Programme of the EU. This publication focussed on a specific negotiation that happened between the Beneluxa Initiative and the pharmaceutical company Vertex in May 2017 on Orkambi. Vertex made an offer to the Netherlands and Belgium together, which was rejected by their governments after gaining advice from their advisory HTA agencies. EPHA reasoned that after the rejection of Vertex's offer, it became clear that the Beneluxa Initiative has some impactful advantages. Some important aspects that were found after this case, according to the EPHA are, firstly, the flexibility of not all countries being obliged to participate in each collaboration. Secondly, they address the achievement of the obstacles these countries overcome with such a collaboration, e.g. on legal grounds. Thirdly, they see the breakthrough around Orkambi as a groundbreaking start for future pharmaceuticals. Furthermore, EPHA mentions the importance of HTA processes, using them to rationalise decisions like in the Orkambi case. Lastly, this case proves that governments actually prioritise therapeutic benefits for patients, instead of having a primary focus on lower prices[5].

While this paper stated the Beneluxa Initiative as promising, EPHA published another reflection paper in December 2019, which was also co-funded by the Health Programme of the EU. This paper emphasized that an important achievement of the Beneluxa Initiative is its tight collaboration mainly due to on the information exchange. This might even be a threat to pharmaceutical companies, taking away their advantages in negotiations. The EPHA argues that joint negotiations themselves are not as effective since they are a legal challenge and with the abundant information exchange platforms like the IHSI, joint negotiations are also less needed. They conclude with the statement that the Beneluxa Initiative probably will not exist in 5 years, although having set a great example for CCC by focussing on information exchange[58].

Stakeholder perspectives on the Beneluxa Initiative

For an article that was published in December 2022, 15 semi-structured interviews were conducted with stakeholders about opportunities and challenges of the Beneluxa Initiative. The aim was to compare opinions from policy makers and the pharmaceutical industry. The writers concluded that mainly the understanding of the Beneluxa Initiative's procedures differs between these groups, which is according to the industry due to lack of transparency on procedures. On the other hand, the industry did recognize the positive results that happened due to the collaboration. Some of the responses mentioned that there are more opportunities surrounding CCC, with the following suggestions; enhanced communication with stakeholders, a stronger legislative structure, and adjustment of pharmaceutical companies to working with multiple countries at once[59].

Prospects of performing joint price negotiations

There are also publications on specific tasks of the Beneluxa Initiative. O'Mahony from the Centre for Health Policy and Management from the Trinity College in Dublin published specifically on collaborative bargaining on prices, based on the fact that the countries have their own HTA processes[44]. This article is a reaction to Irelands' minister for Health, who said the Beneluxa Initiative would be "ensuring that medicines can be sourced at a price that is affordable and sustainable in the context of the ever competing demands for resources rights [sic] across our health service" after Ireland joined the Beneluxa Initiative[44,60]. The goal of this article was to clarify reasons for political involvement hindering collective actions. It explained that different HTA methods between countries makes it more difficult to perform joint negotiations, as well as joint full adoption of HTA assessments. Since the countries are prone to have different conclusions on HTA, full co-adoption could be leading to weaker HTA controls and to longer assessments to reach a suitable solution. O'Mahoney argued that an even bigger issue are the differences in political influences in the countries, since they directly influence the reimbursement decisions. A positive prospect for the Beneluxa Initiative is the conduction of partial mutual HTA, if focussed on sharing of information. Additionally, recommendations for applying cost-effectiveness thresholds in all countries and basing decision processes more on finding a balance regarding true opportunity costs[44].

Feasibility study of joint Health Technology Assessment

Another interesting insight is a study conducted by members of the Beneluxa Initiative itself in collaboration with the Utrecht University on the feasibility of joint HTA. They compared the past HTA procedures of the Beneluxa Initiative's countries, based on national assessments of drugs between 2016 and 2020[30]. In this study, 444 indications were included and compared on assessment for Austria, Belgium, Ireland, and the Netherlands. A low overlap of 10% was found in which pharmaceutical were assessed by all countries, which is due to the different inclusion and exclusion criteria of the national HTA procedures. A higher amount of indications overlap was found between any two or three countries. Then, the added benefit conclusions were compared of Belgium, Ireland, and the Netherlands, these were comparable in 62-74% of the assessments. The differences were mainly due to unclear or missing evidence, which could possibly be fixed by enhancing information sharing. Their conclusion is therefore that these differences in added benefit conclusions are not to be blamed on HTA differences. The writers mention that this conclusion differs with quite some other studies comparing HTA between different countries, that mostly state the HTA of countries to differ more. Their explanations for this different outcome are that the Beneluxa countries have similarities in advancement of HTA systems. Additionally, this study filtered indications first based on if they were assessed in these countries, afterwards comparing the added benefit conclusions, which is giving a better insight in agreement levels[30,61].

Feasibility study of a joint Horizon Scanning system

The KCE lead a HS taskforce in 2017 that compared HS systems in different countries and aimed to develop a system for performing joint HS. This report included a feasibility study of the joint HS system in Belgium, after which companies and medical societies were questioned on their experiences and opinions on the tested system. For this test, three of the six pharmaceutical companies that were invited for the feasibility study participated. All the participating companies were positive about this HS system and any possible international cooperations it could lead to. Some companies stated that the forms they had to fill out were quite elaborate, which was time consuming and sometimes the data that was asked for was not available in this stage of drug development. Two medical societies were questioned on some novel treatments in this feasibility study. The experts from these societies

were overall positive about HS, although they suggested to also focus more on identifying diseases that have a big medical need and a lack of research[29].

European Federation of Pharmaceutical Industries and Associations' opinion on cross-country collaborations

The EFPIA is an organisation that speaks for the research based pharmaceutical industry in Europe[62]. They published a report in 2019 in which they assess four CCC methods: HS, HTA, information sharing (including purchasing and joint pricing negotiations), and joint public procurement.

Joint HS processes, according to the EFPIA, should be aimed to reduce duplication of work by countries. They also state that transparency in cooperation with the industry is important since companies are a mayor source of information during HS processes.

For HTA, the EFPIA states that this is best to be performed at the national level, to safeguard the countries economic, legal, and ethical believes. Although, they also state that they are in favour of the way that patients are guaranteed the fastest access to new medicines. In their opinion, the elimination of joint HTA means excluding any duplication of assessment by for example the national procedures and the collaborations, thus providing earlier access. Furthermore, they emphasise that all participation of the industry in (pilot) CCC should be voluntary, and declining should have no consequences on possibilities for national HTA.

The EFPIA stated that information sharing can have benefits, but it should give legal predictability to the industry and all sensitive information like prices and clinical outcome data should stay confidential. Furthermore, the data should only be exchanged between countries with similar healthcare systems.

For joint pricing negotiations, EFPIA is in favour of using this for better access to medicines and for promotion of innovation. Although, they are against using this technique for short-term lowering of prices since this might harm long-term innovations.

The EFPIA thinks it is important that companies should not be pressured in joint public procurement. In the case that they engage and it is not reached, national level engagement should still be possible, since early patient access is the most important outcome[63]. Joint public procurement is not performed by the Beneluxa Initiative.

Stakeholder perspectives on cross-country collaborations

In 2019, a study was performed to assess the different CCC, mainly focussed on their (prospective) results and challenges. This was based on semi-structured interviews with employees from these different collaborations. Overall, they were positive about the collaborations, while the results are difficult to measure this early, they mentioned some promising points like information sharing and initiation of assessments. Some important facilitating factors that were mentioned in the interviews were trust, technical experts, political commitment, and enthusiasm and commitment. On the other hand, some challenges were mentioned including language, different national policies, legal differences, and reluctance of the pharmaceutical industry to joint negotiations. Some important lessons that were already learned are the importance of political will and commitment, enough funding is needed to reach cooperation and invest in experts' time, and communication is difficult; misunderstandings can happen due to differences in knowledge levels or language[64].

5. Discussion

The Beneluxa Initiative aims to build a strong collaboration on multiple aspects with the goal to create more affordable and better access to medicines for patients. This initiative has already accomplished some interesting collaborations, nonetheless, they also encountered challenges.

Accomplishments Beneluxa Initiative

The Beneluxa Initiative already built a stronger collaboration since the founding in 2015. While the participating countries all vary in terms of healthcare systems and pharmaceutical policies, they still found ways to collaborate.

One of the collaborations of the Beneluxa Initiative is information sharing and policy exchange. An accomplishment of the Beneluxa Initiative in this field, is the current level of knowledge sharing. Beneluxa's emphasis on this principle reduces the information monopoly of the pharmaceutical industry. This transparency is meant to lead to fairer pricing of pharmaceuticals and more informed healthcare decisions, for healthcare providers, policy makers, and patients. The focus on collaboration of the Beneluxa Initiative encourages the adoption of innovative solutions and efficient practices across the countries. This might lead to improvement of the overall quality of healthcare services and access to medicines, which are the main goals of the Beneluxa Initiative.

For their collaboration surrounding HS, a major accomplishment is the founding of the IHSI, since this is seen as a promising and effective HS platform. There is a large amount of partners already connected to this platform and the network is still expanding, already representing over 74 million citizens' healthcare interests[65].

Additionally, for the other points of collaboration, HTA and pricing and reimbursement, the Beneluxa Initiative has successfully built ways to cooperate. Mainly the techniques for joint assessments and negotiations are already applied, while they are also still being monitored to improve in the future. This can be seen as an accomplishment on staying up to date with the evolving and innovative pharmaceutical field.

On the other hand, a challenge of the Beneluxa Initiative is that it is a collaboration among multiple countries with different healthcare systems, political views, and overall priorities. This complexity might negatively affect the different HTA processes and the implementation of joint initiatives. Furthermore, joint negotiations might result in problems surrounding differences in national legislations and policies, which might slow down the processes or even make it impossible. However, the reimbursement decisions are made by the countries individually, so any national legislations surrounding this have no impact on the processes.

Another challenge is the Beneluxa Initiative's goal to be as transparent as possible, which is contradictory to one of their main accomplishments. Knowledge sharing has already led to joint HTA and joint negotiations and it is prone to result in fairer pricing of pharmaceuticals. Although, this is in some ways conflicting with the interests of the pharmaceutical industry, thus it might result in pharmaceutical companies resisting engagement in joint negotiations. When knowledge is shared between countries, they can lose pricing strategies and competitive advantages, which are reasons for prices to drop and thus profit margins for the companies to be smaller. An important note on this contradictory challenge is that the emphasis of both the Beneluxa Initiative and the pharmaceutical industry is on the importance of giving patients the fastest access to new medicines.

Cross-country collaborations

The biggest difference in collaboration activities between the Beneluxa Initiative and other European CCC, is that the Beneluxa Initiative does not perform any form of pooled procurement. Some potential reasons for this are that pooled procurements are higher risk, since they might lead to overall less interest of suppliers. Furthermore, the potential impact of failed tender calls can be significant, and countries may be less likely to meet their contractual obligations[49].

A difficult point for CCC in general is the legal differences between countries, since these make it more complicated to perform joint procedures. Especially around something as impactful as medicines, the countries can have different legislations and political views, making CCC more difficult.

For all the CCC described in *chapter 3 Comparable collaborations*, only a few successful joint assessments, negotiations, and procurements have been done. Although this might seem as if there is not a huge progression, most of the collaborations only exist for less than 10 years. Therefore, these first successful collaborations can also be seen as impactful first steps to creating more united fronts on ensuring better access to more affordable medicines.

Future perspectives

In EPHA's reflection paper, that was published in December 2019, they mention that there will be no Beneluxa Initiative like this in 5 years[58]. Now, almost 5 years later, it still exists with the same Domain Task Forces. Although, a returning point that is found in the literature is the likely shift to a stronger focus on information sharing.

A future perspective of the Beneluxa Initiative might be the inclusion of more countries. This might provide a broader base for sharing knowledge, leading to more effective negotiations and improved access to medicines.

Collaborating with other CCC and international organizations might support the impact of the Beneluxa Initiative and might even be of an advance for the pharmaceutical sector worldwide. An important event suggesting this might happen was the publication of the workshop results on inter-organisation knowledge sharing surrounding challenges of the negotiation process, to reach out to other CCC. This can be seen in *chapter 3.2 Statements collaborations.*

Another future perspective that might have positive effects, is more consideration of legal and political differences of the countries. This might help the collaboration processes to run more effective and therefore faster.

An interesting occurrence that might be of use for the Beneluxa Initiative was the 5th Pharmaceutical pricing and reimbursement information conference, that took place in April 2024. The participants discussed some of the important points that need to be addressed in the future to ensure access to affordable medicines. During this meeting, the importance of information exchange and collaboration were emphasized most. Although, another point was the futureproofing of pharmaceutical policies to improve access to medicines, they mentioned fair pricing concepts, environmental influence, crisis preparing, and more patient involvement to be important[66,67]. These points might be interesting for the Beneluxa Initiative to incorporate in their working structure in the future.

In 2025, a new European Regulation on HTA (HTAR) will be in place. This will be a framework for joint clinical assessments, scientific consolations, and identification of upcoming heath technologies. The goal of the HTAR is to improve HTA across the EU and to establish a transparent framework, reducing

duplicate work. The HTAR comes with set rules for these procedures[68]. Although, since these are also aims of the Beneluxa Initiative, the HTAR might provide faster improvements.

Strengths and limitations

A limitation of this study is that the information that is found might be incomplete, since the Beneluxa Initiative's website is a bit unorganized in where to find which information. For example, the achievements of the four Domain Task Forces are not added to the sections were the recording of this started. Organising these unorganized points might make it more clear for the public what the Beneluxa Initiative performs and what it has achieved. Therefore, a strength of this study is the HTA achievements overview, in *Table 4 of chapter 2.4 Vision and areas of cooperation*, information is combined in a format that the Beneluxa Initiative started but discontinued after 2017.

Another limitation is the lack of opinions of different stakeholders on the Beneluxa Initiative, which would have been useful for *chapter 4 Opinions and perceptions of different parties on cross-country collaborations*. Furthermore, the one study that focussed on opinions on the Beneluxa Initiative, it was not possible to receive the individual responses and the questionnaire, which could have been interesting to include in this study. On the other hand, it was possible to find the opinions of different associations, like the EPHA and EFPIA, which are valuable additions to this study.

Another strength of this study is the combination of grey literature with primary literature to give a comprehensive overview of the Beneluxa Initiative. This is important in this study to include valuable information of for example the Beneluxa Initiative's website, while staying objective.

Conclusion

The Beneluxa Initiative presents a promising system for international cooperation surrounding healthcare, it has some promising strengths in terms of collaboration, transparency, and improved access to medicines. However, it also has some limitations related to legal and political differences. These challenges should be considered more in their collaborations, to maintain or even enhance the initiative's success and gain a broader impact on healthcare systems.

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