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Ministry of Health, Welfare and Sport

The adaptive pathways process: benefits and potential hurdles from a Dutch perspective

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National Institute for Public Health
and the Environment
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Colophon

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Synopsis

The adaptive pathways process: benefits and potential hurdles from a Dutch perspective

Increasingly often, patients are asking for quicker access to new, innovative medicinal products that are not yet licensed or for which reimbursement via the health insurance system is not yet available. In order to meet this demand, the European Medicines Agency (EMA) has developed a new concept for market access of medicinal products, called 'adaptive pathways'. This involves making more effective use of existing flexible marketing authorisation procedures, such as a Conditional Marketing Authorisation. In addition, it is intended that the procedures for marketing authorisation and reimbursement, which currently take place one after the other, should run in parallel as far as possible. Furthermore, patients and healthcare providers will be involved structurally and at an early stage in the processes of marketing authorisation and reimbursement.

The key instrument for making adaptive pathways possible is a brainstorming session organised at an early stage with manufacturers, marketing authorisation and reimbursement authorities, patients and healthcare providers. Together, these parties look at the clinical study design, the development pathway and the licensing and reimbursement route that is envisaged.

The National Institute for Public Health and the Environment (RIVM) is investigating the benefits and potential bottlenecks of the proposed authorisation concept. Research by the RIVM shows that the parties that would be involved with or affected by adaptive pathways in the Dutch situation do see added value in it. They expect that adaptive pathways will make it possible to match medicines better to patients' demands and perhaps do so more cost-effectively.

At the same time, the parties interviewed point out that greater investment must be made in monitoring the safety and quality of medicinal products after they are licensed. This can, for instance, be done through suitable patient records and monitoring systems. In addition, they are of the opinion that bridging the time gap between (international) marketing authorisation and inclusion in the (national) reimbursement system is a very complex issue, which would require extensive agreements and cooperation at international level. Furthermore, they think that the flexible inclusion of medicinal products in the health insurance package demands clear agreements about whether medicines can be withdrawn from the market if they prove not to provide the added value anticipated.

Keywords: medicinal products, marketing authorisation, reimbursement, adaptive pathways, early access

Publiekssamenvatting

The adaptive pathways process: voordelen en knelpunten vanuit het Nederlandse perspectief

Patiënten vragen steeds vaker om versneld toegang te krijgen tot nieuwe, innovatieve geneesmiddelen die nog niet zijn geregistreerd of waarvan de vergoeding via de zorgverzekering nog niet is geregeld. Om aan deze wens tegemoet te komen, heeft de Europese geneesmiddelenautoriteit (EMA) een nieuwe 'zienswijze' voor de markttoelatingsprocedure voorgesteld, adaptive pathways geheten. Dit houdt in dat bestaande flexibele markttoelatingsprocedures, zoals een 'voorlopige markttoelating', effectiever worden ingezet. Daarnaast is het de bedoeling om de procedures van markttoelating en vergoeding, die nu na elkaar komen, zo veel mogelijk parallel te laten lopen. Verder worden patiënten en zorgverleners vroegtijdig en structureel betrokken bij het proces van markttoelating en vergoeding.

Het belangrijkste instrument om adaptive pathways mogelijk te maken is om in een vroegtijdig stadium een brainstormsessie te organiseren met fabrikanten, markttoelatings- en vergoedingsautoriteiten, patiënten en zorgverleners. Samen kijken deze partijen naar de klinische studieopzet, het ontwikkelingstraject en de beoogde registratie- en vergoedingsroute.

Het RIVM onderzocht de voordelen en de knelpunten van het voorgestelde markttoelatingsconcept. Uit onderzoek van het RIVM blijkt dat de Nederlandse partijen die betrokken zijn of beïnvloed worden door adaptive pathways er de meerwaarde van inzien. Zij verwachten dat medicijnen beter op de wensen van de patiënt kunnen worden afgestemd en wellicht goedkoper kunnen worden gerealiseerd.

Tegelijkertijd vinden deze partijen ook dat er meer moet worden geïnvesteerd om de veiligheid en kwaliteit van geneesmiddelen te bewaken na de toelating tot de markt. Dat kan bijvoorbeeld door geschikte patiëntenregistraties en monitoringssystemen. Daarnaast signaleren zij dat het erg ingewikkeld is om de kloof tussen de (internationaal ingestoken) markttoelating en (nationaal opgezette) vergoedingssystematiek te overbruggen. Hiervoor is volgens hen veel afstemming en samenwerking op internationaal niveau nodig. Bovendien vergt een flexibele toelating van geneesmiddelen tot het verzekerde pakket er volgens de betrokken partijen ook toe dat er duidelijke afspraken moeten worden gemaakt over of geneesmiddelen van de markt kunnen worden gehaald als zij de verwachte meerwaarde niet kunnen waarmaken.

Kernwoorden: geneesmiddelen, markttoelating, vergoeding, adaptive pathways, vroege toegang

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Summary

This study aims to identify benefits and potential hurdles in the collaboration between stakeholders in the adaptive pathways process, based on a review of relevant literature on early access tools and interviews with Dutch key players in the 'medicines chain'.

The main objective of adaptive pathways is to accelerate patients' access to medicines. In order to achieve a shorter time-to-patient, adaptive pathways aims to integrate the process of marketing authorisation and reimbursement. It explicitly refrains from instituting new legislation, but instead aims to optimise the use of existing early access tools on a case-by-case basis. A main feature of adaptive pathways is early brainstorming sessions during which opportunities to optimise development pathways and accelerate marketing authorisation and reimbursement are explored. These brainstorming sessions are open not only to regulators and manufactures, but also to all stakeholders, including health technology assessment bodies (HTAs), payers, pharmacovigilance agencies, medical professionals and patient representatives.

From the patient's point of view, the effort to provide faster access to promising therapies for seriously ill or dying patients through adaptive pathways is an encouraging development. The parties consulted agree that adaptive pathways opens the door for structural patient involvement in clinical study design, marketing authorisation and reimbursement. The patient organisations consulted are confident that, by structurally involving patients and their organisations in early dialogues, endpoints regarding the quality of life from a patients' perspective will gain more prominence in the assessment of medicinal products. They believe that involving patient organisations in the authorisation and reimbursement processes can also lead to more effective management of the often extremely high expectations of new medicinal products.

On the other hand, the parties interviewed pointed out that early access comes with potential risks for patients. Seriously ill patients waiting on promising therapies, are vulnerable. They are usually more willing to take high risks compared to other patients. To ensure balanced decision-making by vulnerable patients it is necessary, according to the parties consulted, to provide them with transparent information and support by peer groups and medical professionals and to set up independent monitoring programmes, as early access puts more responsibility on the patient's shoulders.

From a system perspective, one of the main barriers to shortening time-to-patient is the time gap between marketing authorisation and reimbursement. Even though adaptive pathways aims to address this issue by involving HTAs and payers in the marketing authorisation process, the question remains whether this barrier can be overcome completely. The reasons behind these reservations are manifold, ranging from different governance levels (Member State vs. EU) to divergent data

needs. National competent authorities for medicinal product authorisation and HTAs have different views on relevant clinical endpoints (patient centred vs. clinical setting) and comparators (placebo vs. active substance) used in clinical trials.

Another system-related theme regularly arising during the interviews was the issue of gatekeeping: what kinds of product merit early access? Once products have entered an adaptive regime, other questions become important, such as: how much should be paid for an 'unfinished' product and how much risk is society willing to accept. In addition to instruments for managing the market entry of medicinal products and monitoring them thereafter, adaptive pathways requires instruments for managing their exit from the market: ways to withdraw reimbursement or marketing authorisation for products that fail to achieve an acceptable benefit-risk ratio and/or the agreed criteria regarding reimbursement. Withdrawing either reimbursement or marketing authorisation requires consensus about who is ultimately responsible. It also requires political support and the support of medical professionals and patients.

Managed entry, use and exit requires a social basis, which can be created by involving parties such as patient organisations, medical professionals, pharmacovigilance agencies, HTAs and payers at an early stage. The early dialogue settings of the adaptive pathways process provide an accessible platform for this, on the condition that these organisations also have the manpower to support the necessary involvement.

Adaptive pathways presents new opportunities to fast-track innovative medicines, but this has major repercussions on the way the system of assessing, authorising, reimbursing and monitoring the daily use of medicinal products is organised. This system currently involves multiple parties, each of which has legal responsibilities and tasks, and each of which is focused on its own particular 'link' in the 'medicines chain'.

During the interviews with the stakeholders mentioned above it became clear that, even though adaptive pathways itself is not yet a clear concept, it would have some beneficial side-effects. It would increase the readiness to communicate and cooperate more closely among all parties in the Dutch medicines chain. The 'safe harbour' environment of adaptive pathways would foster an increasing willingness to share information, data and expertise. This, in turn, would be supported by a legislative and administrative system that leaves room for experimentation. Conversely, the adaptive pathways pilot also brought to light that it is paramount that all stakeholders share a sense of urgency and are capable of taking an active role in it.

1 Introduction

Recent developments, such as patients' demands for early access to new medicines, growing financial pressure on healthcare systems and the call for a more targeted use of medicines to increase their therapeutic value, are fostering a transition from a traditional approach to marketing authorisation, which implies extensive trials and authorisation for use by broad groups of patients, to an adaptive approach.

This adaptive approach views the clinical development, licensing and reimbursement, and the use and monitoring of pharmaceuticals in clinical practice as a continuum. Collaboration between all stakeholders is crucial in order to both accelerate patients' access to new medicines and maintain a financially viable healthcare system.

Over the past years, several accelerated procedures have been introduced that bring medicinal products to patients at an earlier stage than previously possible, such as the Marketing Authorisation under Exceptional Circumstances, Conditional Marketing Authorisation, Accelerated Assessment and Compassionate Use programmes. In 2014 the adaptive pathways pilot of the European Medicines Agency (EMA) was launched. This pilot aimed not only to bring medicinal products to patients at an earlier stage but also to bring together all stakeholders in the assessment, authorisation, reimbursement and monitoring of medicinal products.

This study focuses on the requirements of good collaboration between those parties involved in the Netherlands. It aims at identifying the benefits and potential hurdles in the collaboration between the stakeholders.

Section 2 discusses the existing early access tools for the authorisation of medicinal products in the EU, and highlights and compares the characteristics of each tool. Section 3 assesses the scope of adaptive pathways. Section 4 provides an overview of the benefits and critical moments in the adaptive pathways approach according to Dutch key players; it highlights the potential opportunities and bottlenecks in the cooperation and alignment between stakeholders and identifies those that might arise at each stage of the pilot. Finally, in Section 5, three major themes are distinguished that require further discussion in order to improve the adaptive pathways process and make it sustainable in the future.

2 Early access tools for the authorisation of medicinal products in the EU

At the start of the 21st century, medical professionals, scientists and the industry increasingly expressed their concerns about the time needed to get effective and innovative medicinal products to the patient. They pointed out that, on average, it took 10 to 15 years to bring a new medicinal product from the laboratory onto the European market. The ever-growing regulatory regime was seen as one of the main constraints (Hoebert et al., 2014; Liberti et al., 2008).

In response to these concerns, the European Commission introduced several accelerated procedures. These fast-track tools are:

- Marketing authorisation under Exceptional Circumstances,
- Accelerated Assessment,
- Conditional Marketing Authorisation,
- Compassionate Use programmes.

These tools will be discussed briefly in the following pages, highlighting their relevant characteristics.

2.1 Marketing authorisation under Exceptional Circumstances

Marketing authorisation under Exceptional Circumstances aims to tackle the problem of promising niche products. In developing these products, applicants are not always able to meet the regulatory requirements for comprehensive evidence of safety and efficacy (Ogbah, 2015). At European level, this problem was first addressed in Directive 75/318/EEC, which introduced a legal provision for marketing authorisation 'under exceptional circumstances'. Subsequent Directives and Regulations¹ reinforced the facility to obtain marketing authorisation without the need to provide comprehensive data. In order to obtain marketing authorisation under Exceptional Circumstances, the applicant has to show that the collection of comprehensive data is impossible, on account of:

- the rarity of the indication, as is the case with orphan diseases,
- the present state of scientific knowledge, which makes it impossible to carry out the trials and provide the required evidence,
- the accepted principles of medical ethics, which do not permit the research needed to provide the required evidence².

Once a marketing authorisation under Exceptional Circumstances has been granted, the applicant may be subject to specific obligations such as additional efficacy or safety studies. The authorisation can also require detailed pharmacovigilance activities, a risk management plan,

¹ Article 14 (8) of Regulation (EC) No. 726/2004, Article 22 of Directive 2001/83/EC (which covers the legal provision for medicinal products that undergo national procedures) and Annex I, Part II of Directive 2001/83/EC.

² An independent ethics committee may be consulted by the EMA to verify the ethical issues.

limitations to prescription (in-/outpatient) or conditions of use, transparency in the product information (i.e. the accompanying patient information leaflet must state that the information available for the product in question is incomplete in specified areas).

The Exceptional Circumstances designation is valid for five years on a renewable basis, but it is subject to an annual re-assessment of the benefit–risk ratio by the Committee for Medicinal Products for Human Use (CHMP). If it is expected that the applicant will be able to complete the dossier confirming a positive benefit/risk balance in the future, the product will be given Conditional Marketing Authorisation.

2.2 Accelerated Assessment

The Accelerated Assessment procedure, introduced in 2005³, aims to speed up access by patients to new medicines that are of 'major public health interest'. Applicants can request Accelerated Assessment provided they are able to demonstrate that their products are of major public health interest. There is no single definition of what constitutes major public health interest, and this should be asserted by the applicant on a case-by-case basis. A justification for the early introduction of the product, including the major benefits expected, should be submitted. The following key items would normally be included in a request for Accelerated Assessment:

- The relevant unmet medical needs⁴ and the available methods of prevention, diagnosis or treatment.
- The extent to which the medicinal product is expected to have a major impact on medical practice, its major added value, and/or how it addresses the principal unmet needs.
- An outline of the main available evidence (e.g. number of clinical trials, key results) on which the applicant bases the claim that the product is of major public health interest.

Based on the request and the justifications presented by the applicant, combined with the recommendations of the Rapporteurs, the CHMP decides whether to allow Accelerated Assessment. If so, the CHMP will conduct the assessment in not more than 150 days. If it identifies major objections during the assessment, however, the CHMP can revert to the normal timetable for the centralized assessment procedure, which allows a maximum assessment period of 210 days.

2.3 Conditional Marketing Authorisation

Conditional Marketing Authorisation, first introduced in 2006⁵, aims to make medicinal products available to patients before the completion of a full application dossier, in order to meet unmet medical needs of patients and/or public health needs. This means that Conditional

³ Regulation (EC) No 726/2004.

⁴ Unmet medical need: a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the European Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

⁵ The legal basis for a Conditional Marketing Authorisation is Article 14 (7) of Regulation (EC) No 726/2004. The provisions for the granting of such an authorisation are laid down in Regulation (EC) No 507/2006.

Marketing Authorisation is available only to medicinal products that can be used to treat, prevent or diagnose seriously debilitating or life-threatening diseases, orphan diseases or in response to acute public health threats. In these cases it may be necessary to grant marketing authorisation on the basis of less comprehensive clinical data than is normally required.

The CHMP can postpone the obligation to provide comprehensive clinical data on safety and efficacy only if all the following requirements are met:

- The risk/benefit balance of the medicinal product is positive.
- It is likely that the applicant will be in a position to provide comprehensive clinical data in the future.
- Unmet medical needs will be met.
- The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The holder of a Conditional Marketing Authorisation will be required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit/risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

A Conditional Marketing Authorisation is a temporary authorisation. It is valid for one year, on a renewable basis. It is subject to specific obligations, as mentioned above, which the competent authorities review annually. Once the missing data have been obtained, it is possible to replace a Conditional Marketing Authorisation with a regular marketing authorisation. The obligation to acquire additional data, and the opportunity to gain a regular marketing authorisation set a Conditional Marketing Authorisation apart from a Marketing authorisation under Exceptional Circumstances.

2.4 **Compassionate Use programmes**

In contrast to the other early access tools, Compassionate Use (CU) programmes are not part of the marketing authorisation process. CU programmes allow for the use of an unauthorised medicine outside a clinical study on individual patients under strictly controlled conditions and make medicines available on a named-patient basis or to specific cohorts of patients. CU programmes cannot replace clinical trials, although safety data may be collected. Access to CU programmes is restricted. Patients can only gain access through their physician and with consent of the manufacturer. The costs of CU programmes are usually not covered by national health insurance schemes.

CU programmes are governed by national legislation, to make medicines available on a named-patient basis or to specific cohorts of patients. In the Netherlands, this is laid down in the *Geneesmiddelenwet* (Article 40, paragraph 3f). The authority to approve CU programmes falls under the jurisdiction of the Dutch Medicines Evaluation Board (CBG-MEB).

In addition, article 83 of Regulation (EC) No 726/2004 provides an option for Member States to ask the CHMP to provide an opinion to all EU Member States on how to administer, distribute and use certain medicines for compassionate use. This advice complements national legislation, which means that the final approval has to be given by the national Competent Authority. In order for the CHMP to issue advice on a CU programme, the medicinal product has to be either the subject of an application for a centralised marketing authorisation or undergoing clinical trials.

2.5 Conclusion

All four early access tools aim to bring promising new medicinal products to patients more quickly than is normally possible. Table 1 shows the main characteristics of each procedure.

Table 1. Main characteristics of early access tools for the authorisation of medicinal products in the EU

Exceptional Circumstances	Accelerated Assessment	Conditional Marketing Authorisation	Compassionate Use programmes
Unmet medical need	Unmet medical need	Unmet medical need	Unmet medical need / unable to join Randomised Clinical Trial (RCT)
Comprehensive data not possible	Comprehensive data normally available	Comprehensive data expected after authorisation	Product is the subject of a centralised authorisation application or undergoing RCTs in the EU
To remain such indefinitely	Assessment time shortened (150 instead of 210 days)	Switch to 'full' marketing authorisation after data collection	Temporary programme, pending authorisation
Normal validity of marketing authorisation	Normal validity of marketing authorisation	Valid for 1 year only	N/A
Annual re-assessment	N/A	Annual renewal	N/A
Possible in all registration procedures	Only in centralised procedure	Only in centralised procedure	National competence / EU advice

3 Adaptive pathways: a new approach to marketing authorisation

Providing patients with early access to new medicinal products increases uncertainty about the benefit/risk profiles of those products. This requires a different approach by regulators: more focus on active surveillance, post-marketing authorisation clinical trials and a continuous evaluation of the benefit/risk balance of the product (Breckenridge et al., 2012; Arnardottir et al., 2011). Various parties have presented ideas about the structure and preconditions of adaptive licensing and life-cycle approaches (Eichler et al., 2012; De Jong et al., 2012; Breckenridge et al., 2011).

The adaptive pathways pilot of the EMA, which was launched in 2014, offers a more flexible approach to marketing authorisation, in which stepwise approval stages replace the current one-off marketing authorisation. The EMA explicitly refrains from instituting new regulatory tools, but aims to provide an increasing awareness and an optimised use of all existing tools and the flexibility within the existing regulatory framework (see Section 2). The type of marketing authorisation obtained (full, conditional, under Exceptional Circumstances), including any potential restrictions or conditions, will be determined on a case-by-case basis, depending on the level of clinical evidence ultimately obtained (EMA, 2014a).

Rather than being a new regulatory tool, adaptive pathways should be regarded as an opportunity for early brainstorming discussions among all stakeholders, including regulators, companies, health technology assessment bodies (HTAs) and patient representatives. The aim of these discussions is to explore ways to optimise development pathways and accelerate patient access to medicines. To achieve this acceleration, the adaptive pathways pilot also looks for ways to reduce the time lag between marketing authorisation and reimbursement. Therefore, the early involvement of both HTAs and payers is key.

Because of the nature of the adaptive pathways pilot (early brainstorming discussions) only those products that fulfil an unmet medical need and are in an early stage of clinical development are included in the scheme. Early stage in this context means all stages prior to the initiation of confirmatory studies, i.e. during or prior to phase II (EMA, 2014b). The early stage inclusion in the pilot enables a more meaningful contribution from all stakeholders to the planning of development, licensing, monitoring, reimbursement and utilisation pathways.

Other criteria for the selection of products for the adaptive pathways pilot are an iterative development plan and the use of real-world data on safety and efficacy to supplement clinical trials. The iterative development plan can follow two registration scenarios (Figures 1 & 2):

- a. Starting with a marketing authorisation for a well defined subpopulation, expanding the population and finally achieving full authorisation ('widening of the indication' scenario).
- b. Obtaining a Conditional Marketing Authorisation, whether based on surrogate endpoints or not, and conducting confirmatory studies afterwards ('prospectively planned reduction of uncertainty' scenario).

Widening of the indication Scenario

(Final target indication in blue and red)

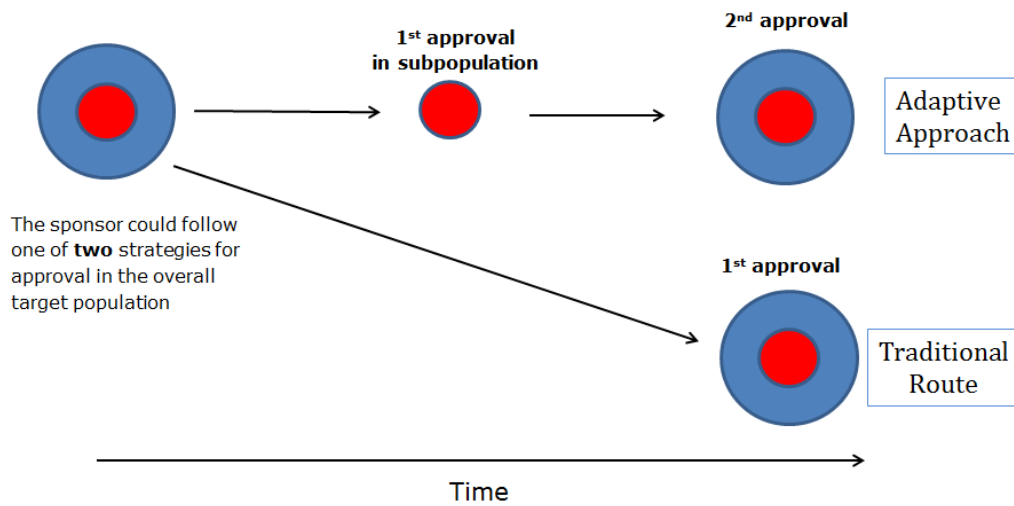


Figure 1. Adaptive pathway registration scenario 1: widening of the indication (EMA, 2014a)

Prospectively planned Reduction of uncertainty Scenario

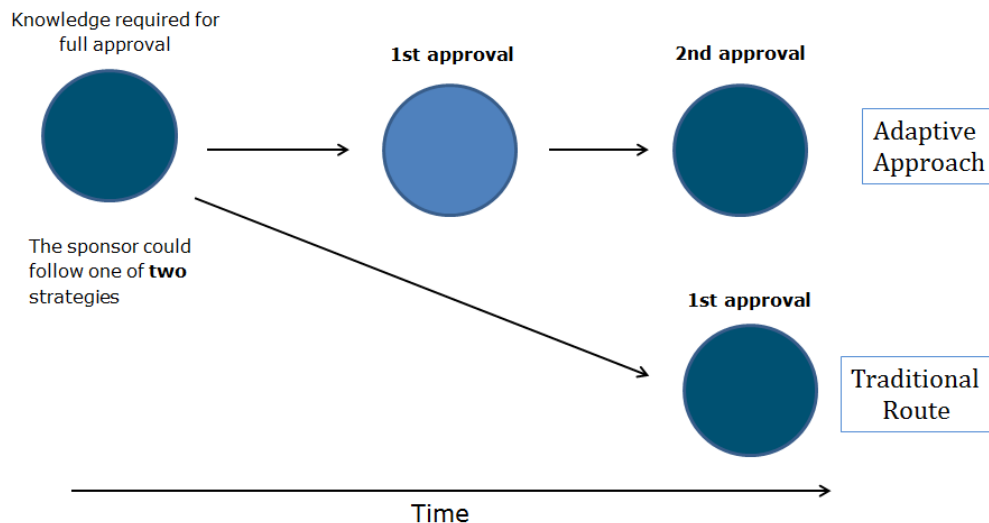


Figure 2. Adaptive pathway registration scenario 2: Conditional approval and confirmatory studies (EMA, 2014a)

4 Adaptive pathways: opportunities, critical moments and spin-off according to Dutch key players

In the Netherlands, the system for monitoring and assessing the development, marketing authorisation, reimbursement and daily use of medicinal products involves multiple parties. Each of these parties has legal responsibilities and tasks. Figure 3 provides a schematic overview of the position of each party in the marketing authorisation process.

In order to evaluate new opportunities and potential bottlenecks of adaptive pathways and its current spin-off, we consulted a number of key players in areas that adaptive pathways aims to bring together. Besides the members of the official Dutch medicines chain, as shown in Figure 3 (Significant, 2014; Janssen et al, 2013), such as the National Health Care Institute (ZIN), the Dutch Patient Federation (NPCF) and the Dutch Association of Medical Oncology (NVMO) were consulted. The next section outlines the position, responsibilities and tasks of the key players consulted, and Appendix 1 provides an overview.

Given the variety and number of organisations of patients and medical professionals, the NPCF and the NVMO were considered a *pars pro toto* for patient organisations and medical professionals. Consulting these parties was especially important in order to gain insight into the views, responsibilities and tasks of the parties concerned with the reimbursement and use of medicinal products.

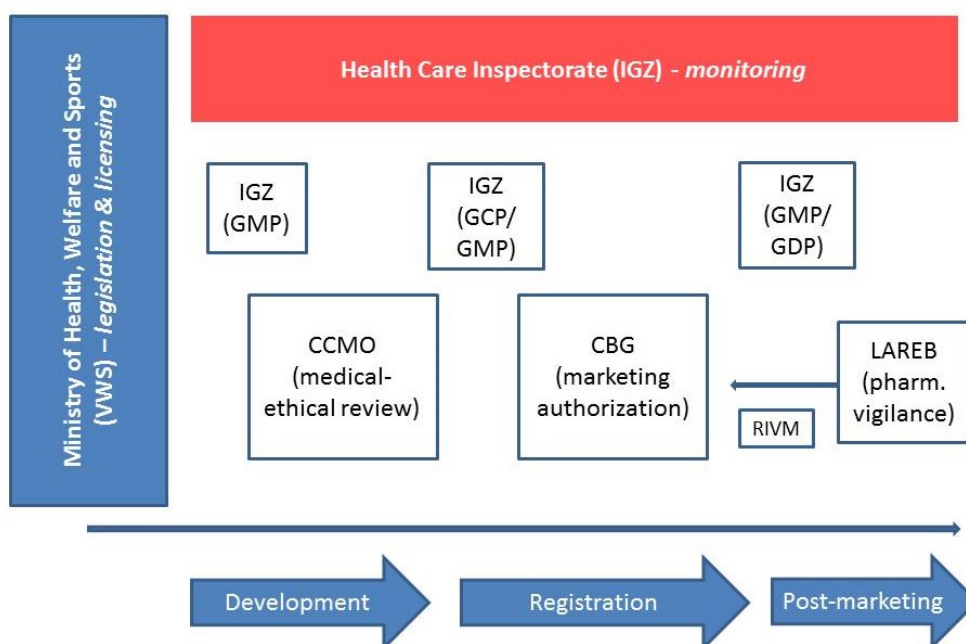


Figure 3. The Dutch medicines chain (source: <http://www.opgmk.nl/>)

4.1 Parties consulted: position, responsibilities and tasks

Central Committee on Research Involving Human Subjects (CCMO)

In the Netherlands, the Medical Research Involving Human Subjects Act (WMO) and the Embryo Act govern biomedical research involving human subjects. The Central Committee on Research Involving Human Subjects (CCMO) protects subjects taking part in medical research by reviewing the research protocol based on statutory provisions, while taking into account the interests of medical progress.

The CCMO oversees the operations of the accredited Medical Ethical Reviewing Committees (MERCs) in the Netherlands and acts as a reviewing committee for specific fields of research, such as gene and cell therapy, xenotransplantation, substances that fall under the Opium Act, vaccine development and interference DNA. The CCMO acts as the Competent Authority for the (marginal) review of research on a medicinal product. If the CCMO is the reviewing committee then the Ministry of Health, Welfare and Sport (VWS) carries out the marginal review (CCMO, 2015).

Health Care Inspectorate (IGZ)

The Health Care Inspectorate (IGZ) promotes public health through effective enforcement of the quality of health services, prevention measures and medical products. With regard to the development, production and marketing of medicinal products, the IGZ has the following tasks and responsibilities (IGZ, 2015):

- Manufacturers, distributors and importers of medicines intended for human use must hold a Manufacturing or Wholesale Authorisation. The Inspectorate enforces this legal obligation in the Netherlands.
- The Inspectorate conducts inspections to ensure compliance with the Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) guidelines. Manufacturers based in countries outside the European Union are also subject to inspection on the authority of the European Medicines Agency (EMA) and the Dutch Medicines Evaluation Board (CBG-MEB). In addition, these inspections assess individual products for compliance with the terms and conditions of their (European) marketing authorisation.
- On request, the Inspectorate will also advise the Medicines Evaluation Board regarding licensed manufacturers (for the purposes of 'site clearance'). The manufacturers of active pharmaceutical ingredients do not need a Manufacturing Authorisation. Nevertheless, GMP inspections of these companies will be conducted at the request of the EMA, CBG-MEB, EDQM or the manufacturers themselves.
- The Inspectorate oversees the pharmacovigilance activities of pharmaceutical companies (more specifically, holders of the drug registration and marketing authorisation for the Netherlands).

Medicines Evaluation Board (CBG-MEB)

The Medicines Evaluation Board (CBG-MEB) assesses and guards the efficacy, safety and quality of both human and veterinary medicinal

products. The CBG-MEB is an autonomous administrative body, associated with the government of the Netherlands, consisting of doctors, pharmacists and scientists. A medicinal product may not be brought onto the market in the Netherlands until it has been granted a marketing authorisation. The CBG-MEB evaluates a medicinal product based on criteria stated in the Medicines Act and determines the conditions for its approval on the Dutch market (CBG-MEB, 2015).

Netherlands Pharmacovigilance Centre (LAREB)

The Netherlands Pharmacovigilance Centre (LAREB) collects and analyses reports of adverse reactions to pharmaceuticals and vaccines in order to guard the safety of medicines and vaccines in the Netherlands. Healthcare professionals, patients and manufacturers can report an adverse reaction. LAREB sends anonymous copies of the reports to the CBG-MEB, the European Medicines Agency and the World Health Organization (LAREB, 2015).

National Health Care Institute (ZIN)

The National Health Care Institute (ZIN) has three distinct roles. First of all, it acts as the a health technology assessment body. In that capacity, it advises the Minister for Health, Welfare and Sport on the content and composition of the insured package according to statutory, care-related and social criteria. Second, it is responsible for the implementation of the Health Insurance Act for specific groups of citizens, such as conscientious objectors, people living abroad, illegal immigrants, defaulters and people who are not insured. Furthermore, the Institute promotes the development of quality standards and helps to implement those standards (ZIN, 2015).

Dutch Patients and Consumer Federation (NPCF)

The Dutch Patients and Consumer Federation (NPCF) represents over 160 patient and health care consumer organisations. It aims to strengthen the position of patients both in the consultation room and in the health care system as a whole, for example by promoting patient involvement. It also provides information to help individual patients make choices in health care (NPCF, 2015).

Dutch Association of Medical Oncology (NVMO)

The Dutch Association of Medical Oncology (NVMO) functions as the official organisation for internist-oncologists in the Netherlands. It aims to uphold the quality of medical oncology and to provide the best possible access to oncological care. The Association has devoted special attention to budgetary problems that inhibit the use of new medicinal products by establishing a committee to advise internist-oncologists on the use of new, innovative medicinal products (NVMO, 2015).

Ministry of Health, Welfare and Sport (VWS)

The Ministry of Health, Welfare and Sport (VWS) is responsible for issuing and enforcing legislation with regard to health care and making health policy. The Ministry also decides whether medicinal products will be reimbursed under the standard health insurance scheme. It coordinates the efforts of health insurers, health care providers and patient organisations. In the regulatory system for medicinal products,

the VWS acts as a coordinating partner, bringing together relevant authorities and stakeholders.

4.2 Adaptive pathways: cooperation and alignment

In the interviews, we discussed the results of our literature search on early access tools and adaptive pathways (Sections 2 and 3). We applied a semi-structured interview approach with a topic list divided into two parts: a general part with questions regarding early access tools and the adaptive pathways pilot; and a part in which the questions were geared towards the interviewees' expertise. All interviews were audio recorded. The recordings were transcribed and the transcriptions were checked against the field notes of the second interviewer. We discussed any inconsistencies and, if necessary, went back to the original audio recording. The researchers invited respondents to react to the transcripts of the interviews (Krippendorf et al., 2013).

The data analysis phase involved an inductive content analysis of the interviews, starting with a close reading of the transcripts and developing a conceptual coding scheme, completing it with inductive codes. When coding, researchers paid special attention to similarities and differences in opinion and perception between experts. The results were then clustered in descriptive themes (Krippendorf et al., 2013).

4.2.1 *Adaptive pathways: an abstract concept with potential benefits*

Even though the EMA aims to include 'downstream' stakeholders, our interviews showed that parties not directly involved in the pilot have little or no information about the concept of adaptive pathways. This was especially the case with medical professionals and patient organisations. For those stakeholders, adaptive pathways was a highly theoretical concept. This sentiment was shared by other stakeholders, including the IGZ, the CCMO and LAREB. These organisations do not have the same sense of urgency with regard to adaptive pathways and do not have the same incentives to invest time and manpower as the CBG-MEB.

The relative unfamiliarity with adaptive pathways among stakeholders also nurtures the idea that adaptive pathways is a 'last resort' for manufacturers with products that may not meet the standard authorisation criteria. For some of the parties consulted, this impression appeared to be confirmed by the fact that some manufacturers submitted to the pilot products that did not meet the criteria for selection, were halfway through the normal authorisation process, or were at high risk of not gaining regular marketing authorisation.

Our interviews showed that all parties consulted shared the goal of expediting patient access to new medicinal products. However, parties that have a more direct link with patients, such as LAREB, NPCF and CCMO, voiced their concern about possible negative trade-offs between risks and benefits in early access programmes.

Most parties were well aware of the potential benefits of adaptive pathways. The main benefit would be patients getting access to promising and innovative treatments more quickly than under current procedures. In addition, adaptive pathways could offer a much desired instrument for

structural patient involvement in clinical study design marketing authorisation and reimbursement. The patient organisations consulted were confident that, by structurally involving patients and their organisations in early dialogues, endpoints regarding quality of life from a patient perspective would gain more prominence in the assessment of medicinal products. This would also benefit manufacturers, who would know sooner the key criteria for authorisation and reimbursement process. This, in turn, could lead to better clinical study designs, a decrease in the workload of regulators and, ultimately, better products. Additionally, adaptive pathways would strengthen the positions of payers in price negotiations with pharmaceutical manufacturers, because early dialogue would give more insight into the value of medicinal products in terms of health benefits and costs.

4.2.2 *Cooperation, authority and capacity*

The adaptive pathways pilot fostered greater understanding of the needs and responsibilities of organisations involved in the pilot, such as the CBG-MEB and ZIN. This has resulted in closer cooperation. The interviews indicated that, even though there is increasing willingness to cooperate throughout the Dutch medicines chain, closer collaboration between organisations is hampered by divergent and overlapping authority and responsibilities.

Cooperation is affected by the limited capacity of the various organisations to handle requests for assistance and by misalignment in expertise. According to ZIN, for example, staff limitations restrict their involvement in adaptive pathways procedures to about two products per year. The CCMO voiced similar concerns, and indicated that requests for assistance from the CBG-MEB usually relate to the technical rather than the ethical aspects of study reviews. The CCMO considers that requests for technical assistance from the CBG-MEB sometimes claim too much of their limited manpower. The CBG-MEB pointed out that offers to share manpower and expertise with other parties are usually turned down on account of incompatible interests.

To further improve cooperation, several of the parties consulted proposed a twofold solution. First, most organisations agreed that the complex process of adaptive pathways requires some form of central coordination. To ensure fluent transitions between phases of an adaptive licensing procedure, the Ministry of Health needs to take a more active role. Second, the parties in the medicines chain need to make more effort in cooperation. CBG-MEB stressed the importance of a shared goal. Commitment to a shared goal could foster a sense of unity and improve performance throughout the chain.

4.2.3 *Bridging the gap between marketing authorisation and reimbursement*

The interviews indicated that bridging the gap between these two domains is not easy. To a large extent, the gap is caused by tension between national and supranational levels of governance. Marketing authorisation of medicinal products is firmly embedded in EU legislation and the procedures of institutions such as the EMA, whereas reimbursement decisions are taken at national level by individual EU Member States.

The tension between national and supranational levels was considered to have other profound consequences. In some EU Member States, HTAs or payers have little or no legal leeway to conduct experiments, which affects the ability of HTAs to fully embrace the concept adaptive pathways. National Competent Authorities (NCAs) responsible for the authorisation of medicinal products do not have that problem because they have been part of a European system of marketing authorisation since the 1960s.

The interviews pointed to differences in working methods between NCAs and HTAs. HTAs have to base their advice on data that is publicly available, such as scientific studies and/or European Public Assessment Reports (EPARs). This means that HTAs cannot use the application dossiers used by NCAs. These files are confidential. Even though an EPAR is based on the application dossier, it is only published once it is complete. In the worst-case scenario, HTAs have to wait up to a year to gain access to this information. This time lag could slow the process of adaptive pathways. A possible solution offered by one of the experts interviewed is to stimulate manufacturers to make the application dossier publicly available after the marketing authorisation decision has been made, so that it can be used by HTAs.

Another problem that hampers the integration of marketing authorisation and reimbursement is that standard therapies used as comparators in HTA studies differ between Member States. Thus, there is no guarantee that the data collected in studies performed in one Member State will be accepted by the HTA of another Member State.

Not only governments and regulators, but also manufacturers are finding it difficult to bring together the domains of marketing authorisation and reimbursement. This distinction lies at the foundation of the organisational structure of most pharmaceutical companies. According to some of the parties consulted, many companies are at a loss as to how to deal with the adaptive pathways pilot. Some companies treat it as a 'normal' marketing authorisation procedure and send delegates from their regulatory affairs department. Others insist that HTAs could not be invited to the early dialogue phase of the pilot, despite the pilot's explicit aim to involve both NCAs and HTAs.

According to some of the parties consulted, the reluctance of manufacturers to involve HTAs in the early dialogue phase is at least partially based on the non-availability of data. Many clinical trials are conducted in the USA, a country that does not require the collection of data needed by HTAs to compare the effectiveness of a new medicinal product with standard therapies. The American regulator, the Food and Drug Administration (FDA), does not require the collection of this type of data in order to approve studies.

4.3 Adaptive pathways: potential opportunities and hurdles at different stages of the pilot

4.3.1 Product selection and adaptive pathways

Since the adaptive pathways approach could exponentially increase the workload of regulatory authorities, all the stakeholders consulted

stressed the need for a gatekeeper, a party that decides whether a product is eligible for an adaptive authorisation track. The increased involvement of public sector parties justifies a closer alignment between medicinal products developed and societal needs. This can be achieved, for example, by allowing only products that fulfil needs identified in the WHO Priority Medicines report to enter an adaptive pathways procedure or by sharpening the definition of 'unmet medical need'. This will create more opportunities to direct the process towards getting products onto the market that have a clear added value.

The gatekeeper role is currently taken by the EMA, which selected all the products for the adaptive pathways pilot. According to the CBG-MEB, ZIN and the VWS, this should not remain the case. In their view, other parties should be involved, such as patient organisations, medical professionals and governments. This would not only create more public support for adaptive pathways; it would also give society a more direct influence on the entry of medicinal products into the market.

4.3.2 *Early dialogues and downstream stakeholders*

The first phase in the adaptive pathways process is 'early dialogue'. During these early dialogue sessions, the EMA, the manufacturer and the HTA discuss matters such as development and registration strategies, reimbursement plans and the collection and analysis of real-world data in a safe harbour environment.

Even though the EMA wants to incorporate other 'downstream' stakeholders in these discussions, this has not yet been achieved. Some of the stakeholders interviewed voiced their concern about this. One CBG-MEB expert pointed out that a lack of involvement by Medical Ethical Review Committees (MERCs) could lead to unpleasant surprises 'down the road'. By leaving these organisations out, there is a risk that manufacturers, NCAs and HTAs will come up with clinical study designs that will not pass a medical-ethical review, despite the fact that they might yield the information necessary for marketing authorisation and reimbursement. On the other hand, the CCMO has indicated that it does not have the capacity to attend all early dialogues, nor feels the need to be actively involved in this process. Patient organisations do believe they can provide valuable input in early dialogues, for example concerning appropriate endpoints for clinical study designs from the patients' perspective.

Since the early dialogue sessions also deal with the collection and analysis of real-world data, the Dutch pharmacovigilance centre, LAREB, and medical professionals are eager to be more involved as well. In the case of the medical professionals, their involvement would focus on identifying relevant clinical endpoints for study designs and the setting-up and maintaining of patient registries. For LAREB it is important to know beforehand which products are 'adaptive' and which not, in order to fine tune their surveillance systems.

Whether LAREB, other pharmacovigilance centres, medical professionals and patient organisations can fully participate in early dialogue discussions remains unclear. What kind of investment in terms of money, time and manpower is required is as yet unknown.

4.3.3 *Authorisation and reimbursement: an integrated approach?*

Adaptive pathways is based on the currently available fast tracking options. This has important repercussions. According to ZIN and the CBG-MEB, it means that existing problems with regard to the enforcement and control of these early access tools need to be addressed. Under the current legislation, a withdrawal of a Conditional Marketing Authorisation) is virtually impossible, even if the manufacturer fails to deliver the previously agreed additional data. Because of this, the CHMP is hesitant to grant conditional marketing authorisations. ZIN has doubts about the lenient nature of both conditional marketing authorisations and adaptive pathways, based on their own experience with conditional reimbursements. In their opinion, if the 'requirement' to collect additional data is not enforced, the data collection probably does not happen at all.

A potential solution to this problem is the intertwinement of Conditional Marketing Authorisation and conditional reimbursement. By linking the price paid for a certain product under a health insurance scheme with the obligation to collect data, it is possible to create stronger incentives for manufacturers to comply with this obligation. In this line of thought, the price of a product with Conditional Marketing Authorisation is set low. Manufacturers can get a higher price for their product once they have collected the agreed data.

Linking reimbursement and marketing authorisation could give Conditional Marketing Authorisations and adaptive pathways more 'teeth', but it could also lead to new problems: how to prevent society paying excessive prices for or taking excessive risks with a product that is not yet finished or proven to be effective. This dilemma prevents HTAs, payers and governmental parties, such as ZIN and VWS, from fully endorsing this kind of regulatory intertwinement. It would be impossible to explain to the public why unproven or uncertain medicinal products were allowed to be used or reimbursed. According to our respondents, this way of linking reimbursement and marketing authorisation also leads to specific ethical questions (see Section 4.3.5).

According to ZIN, another possible solution to the 'early access/reimbursement' dilemma is the introduction of a 'milestone' system. Payer and manufacturer can negotiate a price for a certain product in the 'adaptive' phase in advance. This price should reflect the uncertainty about the efficacy of the product. Only if the manufacturer has met certain previously agreed milestones can negotiations for a higher reimbursement rate or a different kind of marketing authorisation be reopened. Additionally, this would give both the HTA and the payer the option to set maximum prices for products in the 'adaptive' phase.

The Dutch Association for Medical Oncology (NVMO) argues that medical professionals should be involved at an earlier stage of the assessment process. By combining the appraisal of the medical necessity of a medicinal product by medical professionals with the assessment of the potential budget impact, price negotiations could start at a much earlier stage of the authorisation and reimbursement processes.

The CBG-MEB, ZIN and VWS point out that a closer link between the procedures of reimbursement and marketing authorisation also requires 'exit strategies': ways to withdraw reimbursement or marketing authorisation for products that fail to meet the agreed endpoints. Conditional authorisations (both marketing and reimbursement) can function properly only when rescinding the authorisation is an option. This is easier said than done. In previous years, attempts to withdraw reimbursement for medicinal products has led to societal turmoil. Withdrawing either reimbursement or marketing authorisation requires political support (for regulators) and consensus about who is ultimately responsible. The CBG-MEB points out that it also requires the support of medical professionals. They are of vital importance when it comes to stopping the use of ineffective or unproven products. The NVMO endorses this view and is more than willing to take up this role. The NPCF stressed the importance of patient organisations in the management of the often extremely high expectations of new medicinal products.

4.3.4 *Real-world data*

The collection of 'real-world data' is one of the cornerstones of adaptive pathways. It is expected that data on the actual use of a medicinal product in a clinical setting can be used to either expand the indication/target population of a medicinal product, or to confirm an acceptable benefit-risk ratio based on the (surrogate) endpoints agreed during the adaptive pathways process. ZIN has some doubts about the feasibility of this aspect of adaptive pathways. It has had disappointing experiences with the collection of additional data by manufacturers after a conditional reimbursement decision. Collecting high-quality additional data through the monitoring of 'real-world use' requires that both regulators and manufacturers think carefully about the questions they want to answer with this data. The data needs of NCAs and HTAs are usually very different. The data needed for marketing authorisation (i.e. on safety and efficacy) is not necessarily useful for cost-effectiveness studies (i.e. use in a clinical setting).

There are some important legal issues concerning real-world data as well. Once reimbursement for a particular medicinal product is added as a benefit to standard health insurance, it becomes a right. This means that patients cannot be forced to take part in studies that collect real-world data when they use the product.

Both the CBG-MEB and ZIN are hopeful that the current effort to set up high-quality patient registries will solve some of the problems mentioned above. Still, some of the parties consulted have concerns about the high hopes that are currently surrounding patient registries. The CCMO, for example, points out that if studies based on these registries also involve the collection of blood or other body materials from patients, they have to be reviewed by a Medical Ethics Review Committee or the CCMO itself.

While the CBG-MEB expressed its confidence in the ability of medical professionals to set up and maintain high-quality patient registries, the medical professionals themselves seem to have doubts about the usefulness of registries for pharmaco-therapeutic or pharmaco-economic assessments. The NVMO warns that the evidence gathered through patient registries is seen as 'second best' evidence by most of the

medical professional community. Moreover, it is worried that the maintenance of the registries will be put on the shoulders of already overburdened medical professionals without proper funding. This could affect the quality of these registries and subsequently also the studies and assessments based on them.

4.3.5 *Ethical aspects of the use of 'uncertain' products*

By aiming to provide patients with access to medicinal products that are still under development, the adaptive pathways approach raises some important ethical questions. These questions concern not only how much should be paid for an 'unfinished' product, but more importantly also how much risk regulators, patients and medical professionals should be willing to take and how much risk society should be willing to accept. The CCMO, LAREB and the NPCF stress the need to provide patients with independent and comprehensive information about the products they will be using and the aim of their enrolment in a patient registry or other monitoring programmes. This is all the more important because, during the use of products undergoing adaptive authorisation, serious adverse events, however unlikely, cannot be ruled out. Therefore, informed consent is key.

Both LAREB and the NPCF underline the idea that, especially in the case of adaptive pathways, post-marketing monitoring should be in the hands of independent (non-manufacturer) agencies. This would not only increase public trust; it would also acknowledge the fact that adaptive licensing represents a greater risk to society.

5 Conclusions

The main objective of adaptive pathways is to accelerate patients' access to new medicines. In order to achieve a shorter time-to-patient, adaptive pathways aims to integrate the process of marketing authorisation and reimbursement. It explicitly refrains from instituting new legislation, but instead aims to optimise the use of existing early access tools on a case-by-case basis. Based on the interviews, we can reach the following conclusions.

5.1 Potential benefits of adaptive pathways

5.1.1 *Closer cooperation between relevant stakeholders*

Even though adaptive pathways itself is not yet a clear concept, the adaptive pathways pilot has had some beneficial side-effects. It has increased the readiness to communicate and cooperate more closely among all parties in the Dutch medicines chain. The 'safe harbour' environment of adaptive pathways fosters an increasing willingness to share information, data and expertise. This, in turn, is supported by a legislative and administrative system in the Netherlands that provides room for experimentation.

5.1.2 *Structural patient involvement*

From a patient's point of view, the current effort to provide earlier access to promising therapies for seriously ill or dying patients through adaptive pathways is an encouraging development. Not only does the adaptive pathways programme aim to shorten the time-to-patient; it also offers a much desired instrument for structural patient involvement in clinical study design, marketing authorisation and reimbursement. By structurally involving patients in early dialogues, endpoints regarding quality of life from a patients' perspective will gain more prominence in the assessment of medicinal products. Involving patient organisations in the authorisation and reimbursement processes could also lead to more effective management of the often extremely high expectations of new medicinal products.

5.2 Potential hurdles in the adaptive pathway process

5.2.1 *Differences in governance levels and data needs*

From a system perspective, one of the main barriers to shortening time-to-patient is the time gap between marketing authorisation and reimbursement. Even though adaptive pathways aims to address this issue by involving HTAs in the marketing authorisation process, the question remains whether this barrier can be overcome completely.

Full integration will take more time and effort. The reasons behind this are manifold. However, based on the interviews, we can identify two major hurdles in the adaptive pathways process:

- *Difference in governance levels.* The marketing authorisation of medicinal products is firmly rooted in EU legislation and institutional procedures, whereas HTAs are bound to national medical standards and practices.

- *Divergent data needs.* NCAs and HTAs have different views on relevant endpoints (patient-centered vs. clinical setting) and comparators (placebo vs. active substance) used in the clinical trials needed for assessment. It will be difficult to collect all the data needed by HTAs and NCAs in one set of trials, given that the comparator studies will have to take into account various nationally defined comparators. Yet, not only do HTAs and NCAs need to cooperate more closely; the regulatory affairs and reimbursement departments of pharmaceutical companies need to do so as well.

5.2.2 *Managed entry, use and exit for medicinal products*

Adaptive pathways also entails gatekeeping: what kinds of product merit early access? Shortening the time-to-patient of promising medicinal products also implies taking more risk. This justifies restraint. All the parties consulted pointed out that adaptive pathways should focus on products that either meet a major unmet medical need or have a clear added value in terms of clinical efficacy or health benefit.

Once products have entered an adaptive regime, other questions become important: how much should be paid for an 'unfinished' product and how much risk is society willing to accept. The importance of providing patients with independent and comprehensive information about products, registries and monitoring programmes was stressed regularly. High-quality monitoring programmes and patient registries will help the collection of additional data on clinical efficacy and safety. Yet the quality of patient registries depends on funding and the trustworthiness of monitoring programmes on the objectivity of the monitoring agency.

In addition to procedures for the managed entry and monitoring of medicinal products, adaptive pathways requires instruments for their managed exit: ways to withdraw reimbursement or marketing authorisation from products that fail to meet the agreed endpoints. This, however, is a complex issue, which requires effort at the legislative level in order to repair the deficiencies in existing early access tools such as Conditional Marketing Authorisation, as well as societal and political effort.

In short, managed entry, use and exit requires a social basis, which can be created by involving parties such as patient organisations, medical professionals, pharmacovigilance agencies and payers at an early stage. The early dialogue settings of the adaptive pathways process provide an accessible platform for this, on the condition that these organisations have the manpower to support such an involvement.

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Appendix 1. Main characteristics of stakeholders consulted

Medicines Evaluation Board (CBG-MEB)

Primary aim of the organisation	To assess and guard the efficacy, safety and quality of both human and veterinary medicinal products. To evaluate a medicinal product on the basis of criteria stated in the Medicines Act and determine the conditions for its approval on the Dutch market
Capacity	288 employees
Position vis-à-vis national government	Autonomous administrative body associated with the Government of the Netherlands
Geographical location	Utrecht
European involvement	Strong (EMA)
Involvement in the AP pilot	Core business
Modes of leverage concerning AP	Key position in the process, expertise, ability to block

National Health Care Institute (ZIN)

Primary aim of the organisation	To advise the Minister of Health, Welfare and Sport on the content and composition of the insured package
Capacity	?
Position vis-à-vis national government	Autonomous administrative body associated with the Government of the Netherlands
Geographical location	Diemen
European involvement	Average (EUnetHTA/IMI/etc.)
Involvement in the AP pilot	Significant
Modes of leverage concerning AP	Key position in the process, expertise, ability to block

Dutch Health Care Inspectorate (IGZ)

Primary aim of the organisation	To enforce legal obligations on manufacturers, distributors and importers of medicinal products (intended for human use)
Capacity	?
Position vis-à-vis national government	Part of the Ministry of Health, Welfare and Sport
Geographical location	Utrecht
European involvement	Low
Involvement in the AP pilot	None
Modes of leverage concerning AP	Key position in the process, expertise, ability to block

Netherlands Pharmacovigilance Centre (LAREB)

Primary aim of the organisation	To collect and analyse reports of adverse reactions of pharmaceuticals and vaccines in order to guard the safety of medicines and vaccines in the Netherlands
Capacity	40 employees
Position vis-à-vis national government	Independent foundation, publicly financed
Geographical location	Den Bosch
European involvement	Low
Involvement in the AP pilot	None
Modes of leverage concerning AP	Expertise, reputation power

Central Committee on Research Involving Human Subjects (CCMO)

Primary aim of the organisation	To protect subjects taking part in medical research by reviewing the research on the basis of the statutory provisions laid down for them and taking into account the interests of medical progress
Capacity	16 employees
Position vis-à-vis national government	Autonomous administrative body associated with the Government of the Netherlands
Geographical location	The Hague
European involvement	None
Involvement in the AP pilot	None
Modes of leverage concerning AP	Key position in the process, expertise, ability to block

Dutch Patients and Consumer Federation (NPCF)

Primary aim of the organisation	To strengthen the position of patients both in the consultation room and in the health care system as a whole. NPCG represents over 160 patient and health care consumer organisations
Capacity	75 employees
Position vis-à-vis national government	Independent foundation
Geographical location	Utrecht
European involvement	?
Involvement in the AP pilot	None
Modes of leverage concerning AP	Expertise, reputation power

Dutch Association of Medical Oncology (NVMO)

Primary aim of the organisation	To uphold the quality of medical oncology and to provide the best possible access to oncological care.
Capacity	?
Position vis-à-vis national government	Independent foundation
Geographical location	Den Bosch
European involvement	Average (ESMO)
Involvement in the AP pilot	None
Modes of leverage concerning AP	Expertise, reputation power

RIVM

Committed to *health and sustainability*