EVERY DAY COUNTS

IMPROVING REGULATORY TIMELINES TO OPTIMISE PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

VINTURA

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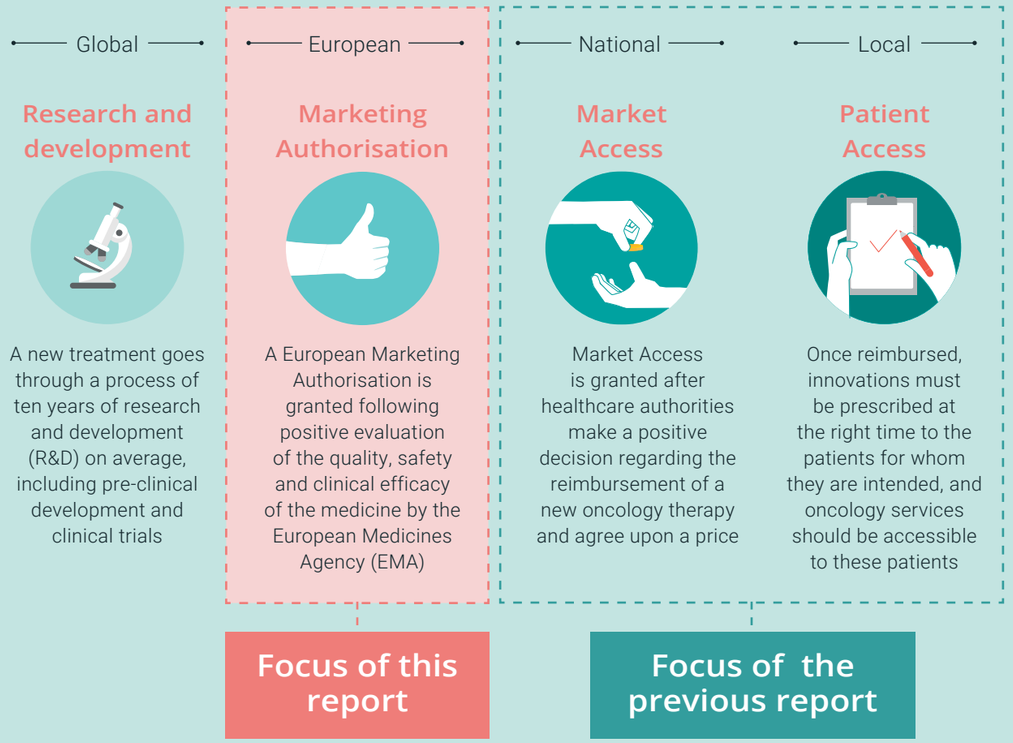
About this report

This report is a follow-up to the report "Every Day Counts - Improving Time to Patient Access to Innovative Oncology Therapies in Europe" (Vintura, 2020). Following a multi-stakeholder collaboration during 2019 and early 2020, the report established a collective understanding regarding the causes of delays in patient access to new cancer treatments across Europe. It focused on the stages following European Marketing Authorisation – Market Access and Patient Access (see Figure 1) – and included solutions and recommended next steps to reduce timelines for these stages. The report was commissioned by the Oncology Platform of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

This follow-up initiative concentrates on the final stage of Marketing Authorisation: the administrative process between the final opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision of the European Commission (EC). It aims to establish a clear and common understanding among European stakeholders of the steps involved in this part of the journey, and of potential opportunities to reduce timelines. This in turn will act as a basis for finding a common perspective on potential opportunities to accelerate the process. Understanding is fundamental, as all stakeholders are involved in the current system and cross-stakeholder collaboration is required to solve challenges, both today and in the future.

The final objective is to reduce time to patient access, without compromising careful and evidence-based decision making. Whilst this is important for all therapies, it is particularly applicable for therapies which provide significant added value in areas of high unmet need (such as oncology). Reducing time to patient access is the joint responsibility of all stakeholders involved, so this report serves as an invitation for further dialogue and joint action between stakeholders. Because for cancer patients, Every Day Counts.

Figure 1
The journey of any new treatment goes through four main stages: R&D, Marketing Authorisation, Market Access, and Patient Access



A message of thanks to all the stakeholders who contributed to this report

This publication is the result of a review of grey and academic literature. It is an assessment of the health- and socio-economic gains which can be achieved by reducing the time between the final CHMP opinion and the EC final marketing authorisation.

The findings were enriched and validated over 19 interviews and two sessions with a European Multi-Stakeholder Sounding Board. Participants in the interviews and the Sounding Board meetings represented perspectives from the EC, the European Medicines Agency (EMA) - including CHMP representatives, national regulatory authorities, national health technology assessment (HTA) bodies, professional healthcare associations, patient organisations, policy makers, payers, academic experts, and biopharmaceutical companies (see the List of Contributors for further details).

The project was initiated and financed by the EFPIA Oncology Platform (EOP). The EOP is a collaboration between 19 companies from the research-based pharmaceutical industry in Europe. It was launched in 2016 and aims to jointly improve cancer patient outcomes across the region.

We would like to express our gratitude to all the stakeholders who offered their time and shared their expertise and perspectives. These contributions enabled us to establish a comprehensive picture of the steps taking place between the final CHMP opinion and the granting of a marketing authorisation by the EC, and enabled the identification of impactful and feasible solutions to accelerate the process.

Every Day Counts - Improving Regulatory Timelines

The publication has explicit endorsement from the following organisations:

ALAN
Acute Leukaemia Advocates Network

Associação de Enfermagem Oncológica Portuguesa

Associação Melanoma Portugal

ACM Onlus
Associazione Contro il Melanoma

Bulgarian Association of Clinical Research

Bulgarian Pharmaceutical Union

Business School
Warsaw University of Technology

ccm
Connaître et Combattre les Myélodysplasies

Digestive Cancers Europe

EANM
European Association of Nuclear Medicine

European Cancer Patient Coalition

efpia
European Federation of Pharmaceutical Industries and Associations

Uehp
European Union of Private Hospitals

evita

Youth Cancer Europe

Textbox 1

EUROPE'S CANCER MISSION

Preventing cancer from becoming the leading cause of death in the EU

Today, Europe accounts for a tenth of the world's population, but a quarter of the world's cancer cases. In 2020, 2.7 million people in the European Union were diagnosed with the disease, and another 1.3 million people lost their lives to it. Unless we take decisive action, lives lost to cancer in the EU are set to increase by more than 24% by 2035, making it the leading cause of death in the EU (European Commission, 2021a).

Therefore, Europe's cancer mission for Horizon Europe supports Europe's Beating Cancer Plan. The goal of "Mission Cancer" is to improve the lives of more than 3 million people by 2030 through prevention, cure and for those affected by cancer including their families, to live longer and better (European Commission, 2021b).

Every Day Counts - Improving Regulatory Timelines

Textbox 2

FOR CANCER PATIENTS, EVERY DAY COUNTS

The case of metastatic colorectal cancer

In Europe, colorectal cancer is the second most common cancer, with more than 500,000 European citizens diagnosed every year. The number of cases is increasing, driven by an ageing population - the disease mainly affects the over 50s - as well as diet and lifestyle factors (Biller & Schrag, 2021; Field & Lipton, 2007).

Major advances in earlier diagnosis (especially through screening) and treatment options have significantly improved survival chances for patients.

Still, more than 20% of patients with colorectal cancer already have metastases at their initial diagnosis, and another 25% of patients develop metastases as their disease progresses over time (Jin & Hubbard, 2019; Kopetz, et al., 2009).

The 5-year survival rate for metastatic colorectal cancer patients is around 10%, underlying the urgency to provide patients in a timely manner the best possible treatment that can increase their chances of survival and quality of life. Delays in treatment access represent a missed opportunity for colorectal cancer patients and their families since the choice and sequencing of new therapies is critical to treatment outcomes. Patients' survival chances are maximised when the best available therapy is used immediately after diagnosis, rather than receiving another therapy first. When the best therapy is not yet available, chances of dying from the disease increase. For these patients, every day of waiting to access a new therapy counts.

- Zorana Maravic, CEO Digestive Cancers Europe

Executive summary

For cancer patients, Every Day Counts

The journey of new medicines from the laboratory to patients is a long and winding road. After years of clinical research and development, new medicines must receive marketing authorisation followed by reimbursement (market access) before they can be routinely given to patients.

This report focuses on the final part of the route to marketing authorisation. Before patients can access a new medicine, the European Commission (EC) must grant a marketing authorisation following a final scientific opinion by the Committee for Medicinal Products for Human Use (CHMP). The process officially takes 67 days, which includes a linguistic phase and a decision-making phase. In the last five years, the total process has taken a median of 60 days for oncology products, although the range extends from 33 to 198 days.

The experience of marketing authorisation being granted for COVID-19 vaccines within one day of the final CHMP opinion has shown clearly that the European community of stakeholders is able to work together to optimise this process greatly. The learning from COVID-19 is not that a one-day process for translating a positive CHMP opinion into an EC decision granting marketing authorisation should become the norm. It should be that there is an opportunity to reduce time to patient access, which is particularly important in oncology.

There is a need for reducing time to patient access. For cancer patients, every day counts; and the current timelines between CHMP opinion and EC decision come at a cost. An illustrative analysis of 11 recently authorised oncology treatments shows that the regulatory steps between CHMP opinion

and EC decision together accounted for 18,600 years of potential life lost, although the full extent of life years lost is far greater when considering all oncology indications. In addition, optimisation is necessary to increase efficiency and future-proof the system, which is currently overburdened as a result of challenges such as Brexit, COVID-19, and the rising number of new medicine assessments.

There is also momentum for change, as the EC is currently considering changes to pharmaceutical legislation as part of the EU pharmaceutical strategy; a process which only occurs once in a generation. Even if only small improvements are made, they could have a significant impact on patients.

A multi-stakeholder approach

This report was developed using the collective thinking of 35 organisations, covering health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, policy makers, academics, payers, and pharmaceutical companies. The aim is to ignite a constructive dialogue between different stakeholders on improving regulatory timelines, and ultimately provide patients across Europe with timely access to vital innovative cancer treatments.

Findings were generated through a review of grey and academic literature, and an assessment of the health- and socio-economic gains of reducing the time to access. Possible solutions were discussed through 19 interviews and two sessions with a European Multi-Stakeholder Sounding Board. This enabled different perspectives to be combined into the overall recommendations.

Three potential solutions

Several strategic options and concrete solutions were considered to improve the process between CHMP opinion and EC decision. When considering their impact and feasibility, the following potential solutions were prioritised, noting that these could be used in combination to reduce current timelines by more than half:

1.

Conduct the decision-making phase

In parallel to the linguistic phase

Acceleration: **12 days**

Life years saved: **3,300**

2.

Increase the use of digital tools

during the linguistic phase

Acceleration: **10 days**

Life years saved: **2,800**

3.

Shorten the written procedure in cases where Member States foresee no objections

Acceleration: **15 days**

Life years saved: **4,200**

In addition, improvements are needed to future-proof today's overburdened system and reduce the potential for future delays. Greater digitalisation and an increase in the number of human resources should be considered to reduce the workload pressure associated with today's process, and may further reduce timelines.

Lastly, important gains can be made by applying a holistic approach to the overall journey to patient access. Improving the transparency and predictability of the process between the final CHMP opinion and the EC decision would allow for better planning of the subsequent pricing and reimbursement (Market Access) process. Further optimisation could be achieved by starting national HTA processes immediately following a positive CHMP opinion as the final EC decision-making process continues. In the last 10 years EC decisions have always aligned with CHMP opinions. Starting the HTA process earlier would therefore be a pragmatic way to avoid more than 60 days of delay to patient access.

Combining these solutions can save thousands of years of life across the European Union, especially since these solutions are not limited to oncology therapies. Together, let's change this process and make use of the once-in-a-generation opportunity of the review of Pharmaceutical Legislation. Because for patients, Every Day Counts.

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Introduction

A spotlight on the regulatory process between the CHMP opinion and EC decision

Oncology medicines face significant delays in their journey from the laboratory to the patient. Each treatment requires around 10 years for research and development (R&D), plus two to three years of administrative processes (EFPIA, 2021a). After the initial R&D phase, there are three milestones which must be completed before patients can access a new cancer treatment (see Figure 2):

1. After an assessment process lasting a median of 408 days for oncology medicines (Uyl-de Groot CA, 2020), a centralised **European Marketing Authorisation** is granted by the European Commission (EC) following the scientific opinion of the European Medicines Agency (EMA). This authorisation confirms the quality, safety, and efficacy of a new therapy, and is necessary to authorise the use of a new therapy in all European Union (EU) Member States (MS), as well as the countries of the European Economic Area (EEA): Iceland, Liechtenstein, and Norway[1].

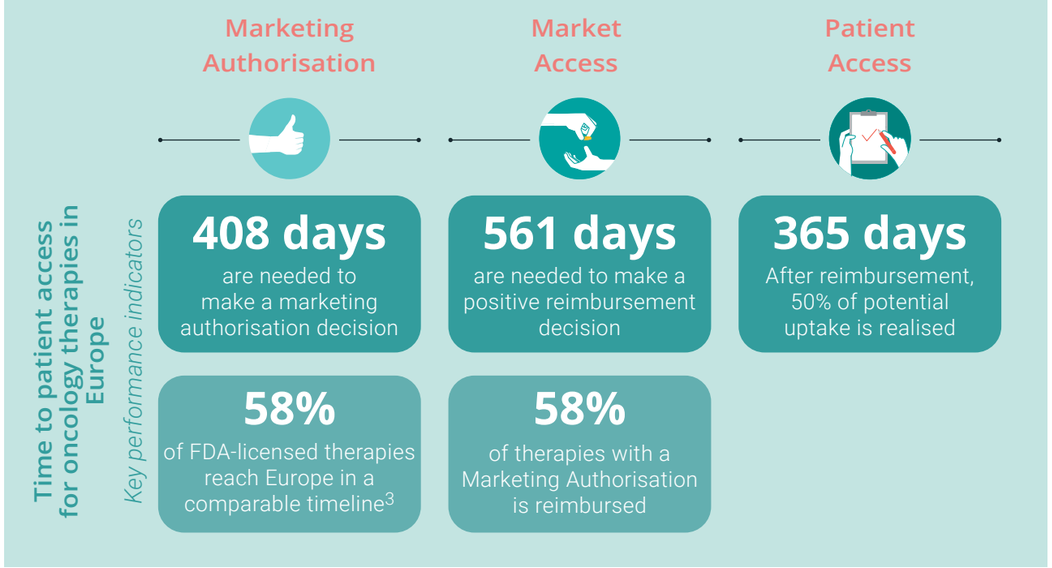
2. The next step is for national authorities to decide on **Market Access** for the therapy under an insurance or reimbursement scheme. This approval makes the intervention financially accessible to patients in each country. This process takes on average 561 days, and an average 58% of cancer therapies with a Marketing Authorisation are reimbursed (EFPIA, 2021b).

3. Finally, the treatment must achieve **Patient Access** by being prescribed for and used by the patients for whom it is intended. There

can be delays in this process, for example due to medical guidelines not being updated with the latest scientific advances. An analysis of 10 European countries found that one year after reimbursement, the average per capita use of innovative cancer medicines in Europe is only 50% of the average per capita use in the country in which the treatment is used most. Therefore, an important tranche of eligible patients are not being reached as fast as they could (Vintura, 2020).

As this is a multi-stakeholder process, there is a joint responsibility between European and national policy makers, authorities, pharmaceutical companies, payers, and professional and patient organisations to optimise timelines where possible to ensure timely access for patients.

Figure 2
Time to Patient Access for oncology therapies: key performance indicators for the European Union[2]
Source: Uyl-de Groot CA, 2020; EFPIA, 2021; Vintura, 2020



[1] Most innovative medicines follow this "centralised procedure". They are evaluated by EMA and receive a European Marketing Authorisation from the EC, which removes the need for pharmaceutical companies to seek marketing authorisation separately from each Member State. The centralised procedure is compulsory for cancer therapies. In addition, it is compulsory for any medicine containing an entirely new active substance, orphan medicinal products, and products for which the therapeutic indication is the treatment of AIDS, neurodegenerative disorders, diabetes, auto-immune diseases, other immune dysfunctions, and viral diseases. Unbranded (generic) versions of centrally approved medicines also follow the centralised procedure.
[2] These performance indicators are based on data for new molecular entities.
[3] Of the novel drugs licensed by FDA between 2015-2017, 58% were licensed by EU by the first quarter of 2018

This publication focuses on Marketing Authorisation (see Figure 3), and particularly the final step between the final opinion of the Committee for Medicinal Products for Human Use (CHMP) and the granting of a Marketing Authorisation by the European Commission (EC). The scope of this report only includes new molecular entities, as this is where the official duration of 67 days applies, and is where solutions will have the greatest impact.

The process in scope of this report starts at Day 210 and ends at Day 277:

Day 210

CHMP, the EMA's scientific assessment committee, finalises its recommendation (opinion) as to whether a marketing authorisation should be granted, including the final Summary of Product Characteristics (SmPC), the treatment label and specific conditions for use.

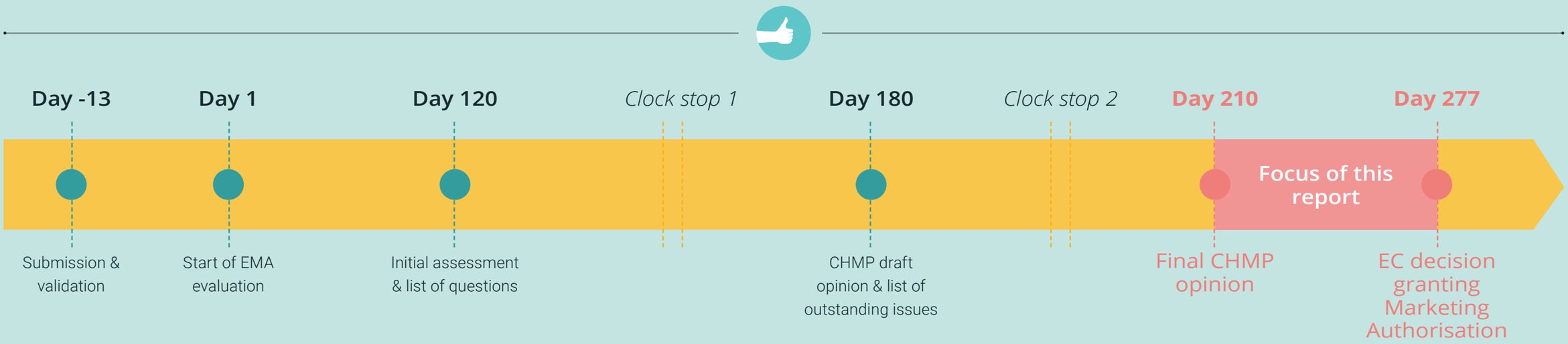
Day 277

The EC makes a final decision to grant or refuse the marketing authorisation.

Figure 3

This report focuses on the last part of the Marketing Authorisation stage: the administrative process between the final opinion of the CHMP and the final EC decision

Marketing Authorisation



With a maximum official duration of 67 days (and a range of 33-198 days in practice), this administrative process represents only a small part of a medicine's journey from the laboratory to patients, but nevertheless an important opportunity for improvement.

During the COVID-19 pandemic this process between final CHMP opinion and the EC decision was expedited to less than one day for COVID-19-related vaccines. This suggests it is possible to shorten timelines for other approvals significantly. Furthermore, this part of the process could be streamlined without affecting the quality and rigor of scientific review, which needs to be safeguarded. Last but not least, for cancer patients, Every Day Counts. Every effort should, therefore, be made to optimise time to patient access in oncology, including this small part of the long road to patient access.

Chapter 1 of this report provides a detailed description and explanation of the steps involved in the 67-day process. Chapter 2 describes how there is an opportunity to optimise the current process. Chapter 3 is an overview of strategic directions and recommendations for shortening the process. Lastly, Chapter 4 contains a call to action for improving time to patient access in oncology across Europe, which is presented on behalf of all co-signing stakeholder organisations involved in the development of this report.

The Current Process

A maximum of 67 calendar days to complete a linguistic phase and a decision-making phase

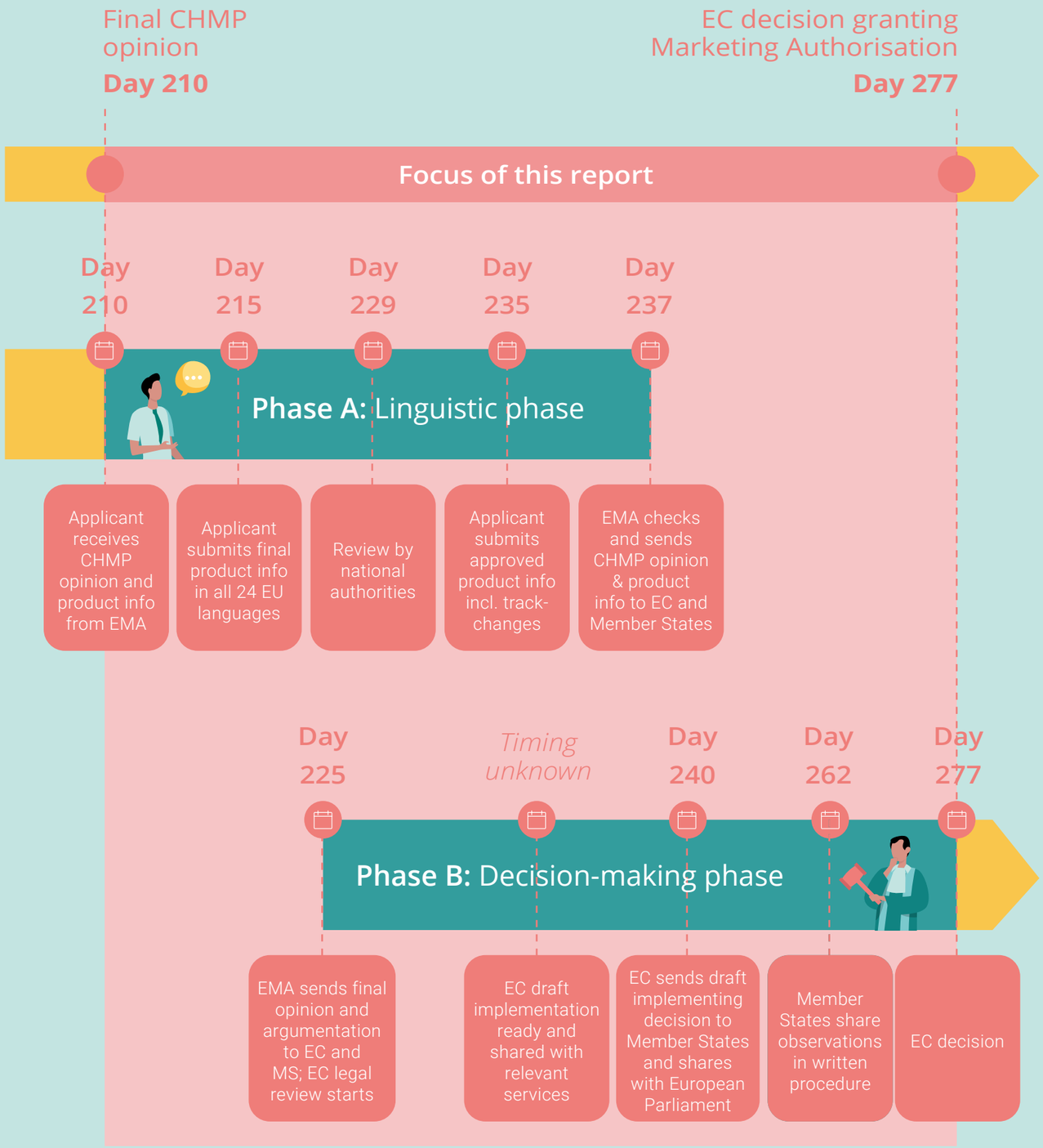
There are several steps to be taken in the 67 calendar days between the final CHMP opinion (Day 210) and the final EC decision granting marketing authorisation (Day 277). These steps can be divided into two phases: **the linguistic phase**, in which the product information is translated into all 24 official languages of the EU, and **the decision-making phase**, in which the EC prepares a decision to grant or refuse a centralised marketing authorisation (see Figure 4).[4]

[4] The process described in this chapter applies to new molecular entities. The same process applies to applications for an extension of the indication, when this is extension accompanied by a change in e.g. the dosage, form, or route of administration (an "extension of marketing authorisation"). Where the new indication does not involve one or more of these changes (a "Type-II variation"), the decision-making phase is shortened since consultation with the Standing Committee (Day 240 – Day 262) is not required (EMA, 2021a; European Commission, 2005).

Figure 4

Steps in the process between final CHMP opinion and EC decision

Source: European Commission, 2005; Vintura stakeholder interviews, 2021



The linguistic phase

The linguistic phase involves translating the product information (see Textbox 3) into all 24 official languages of the EU. This phase is designed to ensure high quality, consistent product information about centrally authorised products across every Member State (EMA, 2017). Its process is guided by very specific timelines set in calendar days (not working days). The linguistic phase starts with the final CHMP opinion (Day 210) and comprises four key steps.

Day 215

Following the adoption of the final CHMP opinion, manufacturers have five calendar days to send the final product information in all official EU languages (incl. Icelandic and Norwegian) to EMA (EMA, 2017).

Day 229

During a period of 14 calendar days, each translation is subject to Member States' linguistic review, coordinated by the Working Group on Quality Review of Documents (QRD) (EMA, 2017). The QRD comprises one representative from the EC and two experts per Member State selected by the national competent authorities: one for human and one for veterinary medicinal products (EMA, 2021b).

Day 235

Within six calendar days, the manufacturer sends final translations in Word format, incorporating Member States' comments in tracked changes (EMA, 2017).

Day 237

Two calendar days later, EMA will have checked the implementation of the final comments and transmits the final CHMP opinion and the product information to the EC and the Member States (EMA, 2017).

Every Day Counts - Improving Regulatory Timelines

Textbox 3

PRODUCT INFORMATION

The product information is provided as an annex to the EC decision and consists of a minimum of three annexes:

- **Annex I:** Summary of the product characteristics (SmPC)
- **Annex II:**
  - A. Manufacturer of the biological active substance and manufacturing authorisation holders responsible for batch release
  - B. Conditions or restrictions regarding supply and use
  - C. Other conditions and requirements of the marketing authorisation
  - D. Conditions or restrictions regarding the safe and effective use of the medicinal product
  - E. Specific obligation to complete post-authorisation measures for conditional marketing authorisation / marketing authorisation under exceptional circumstances *(where applicable)*.
- **Annex III:**
  - A. Labelling
  - B. Package leaflet

Where the draft decision is not in accordance with the opinion of the EMA, the Commission shall annex a detailed explanation of the reasons for the differences.

Source: EMA, 2017; EMA, 2021c

The decision-making phase

While the linguistic phase is governed by very clear steps and timelines, transparency and predictability of the decision-making phase to convert CHMP opinions into legal EC decisions can be improved. The various steps are less clearly described in publicly available documents, and reporting on actual timelines is less detailed. Actual timelines vary quite a bit (see Figure 6), and no tracking is available of a product's progress through each step during this phase.

Day 225

Within 15 days of its adoption, EMA sends the English version of the final CHMP opinion to the Directorate General for Health and Food Safety (DG SANTE), the Member States and the manufacturer, together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions (European Commission, 2004) (Vintura stakeholder interviews, 2021).

In the case of an orphan medicinal product, DG SANTE also needs to receive the orphan maintenance assessment report from the Committee for Orphan Medicinal Products (COMP), before a draft decision can be prepared. The COMP review takes place in parallel to the CHMP review, but it may be finalised later than the CHMP review if issues arise (EMA, 2021d).

Subsequently, to ensure conformity with the regulatory framework, the EC Pharmaceuticals Unit and/or Legal Department undertake legal scrutiny (Vintura Sounding Board, 2021).

Draft EC decisions are adopted via an empowerment procedure in which the Commission empowers DG SANTE to take management or administrative measures on its behalf. Therefore, DG SANTE prepares the initial draft of the Commission Decision (European Commission, 2005) (Vintura stakeholder interviews, 2021).

Since all the decisions of DG SANTE must reflect the position of the entire Commission as a collegiate body, DG SANTE consults the other services of the Commission on the draft decision during a five-day interservice consultation before it is sent to Member States. It is unclear when this starts and which services are involved in this step (European Commission, 2005; EMA, 2021e; Vintura stakeholder interviews, 2021).

[5] Or the Director General of Health within DG SANTE to whom marketing authorisation decisions are delegated (Vintura Sounding Board, 2021).

Day 240

Within 15 calendar days of receipt of a complete and compliant opinion from the EMA, DG SANTE shares the initial draft of the Commission Decision (European Commission, 2005; Vintura stakeholder interviews, 2021).

All EC decisions related to EC marketing authorisations for new applications, and applications for extension of indication, require consultation with, and voting by, the Member States. Therefore the draft decision and the format for consultation of Member State representatives is forwarded by the Commission to the competent national authorities designated by each Member State (in their own language), either electronically or as a hard copy (European Commission, 2005).

Day 262

Member States have 22 calendar days to forward their written observations on the draft decision to the Commission. Member States must inform the Commission during this period whether they approve the draft, reject it, or wish to abstain. Any Member State which, within the time limit, does not express its opposition or intention to abstain from voting is deemed to have agreed the draft. If a decision must be taken urgently, a shorter time limit may be set by the Commission. This time limit must not, other than in exceptional circumstances, be shorter than five calendar days.

The Commission is assisted during this process by the Standing Committee on Medicinal Products for Human Use (the "Standing Committee"), in which the Member States are represented. The Standing Committee is chaired by the EC representative. Within the Standing Committee, Member States representatives vote on the draft decision[6], and a decision is made by a qualified majority of 232 of 321 votes.

This opinion of the Standing Committee will normally be given by written procedure. However, there are four situations in which the draft decision will be discussed during the next Plenary Standing Committee meeting[7]:

- If no qualified majority is reached in the written procedure.
- During the written procedure, Member States may ask for a Standing Committee Meeting where the draft decision is discussed. This request must be accompanied by a clear description of the reasons for it.
- In urgent cases and where measures are to be applied immediately, a Standing Committee meeting is convened.
- In exceptional cases where the EC draft decision is not in accordance with the CHMP opinion, a Standing Committee meeting is convened.

[6] As described in Article 205(2) of the EC Treaty.
[7] This is a two-day meeting where Member State representatives meet in person and where an absolute majority is needed to arrive at a decision. Plenary Standing Committee meetings are called together as and when needed.

Lastly, based on the written comments forwarded by a Member State, the Commission may consider that important new scientific or technical questions have been raised which have not been addressed in the CHMP opinion. In this case, the EC will suspend the written procedure and refer the CHMP opinion back to the EMA with a request for further examination.

In parallel to the consultation of the Standing Committee, the European Parliament (EP) will be informed by DG SANTE of committee proceedings[8] on a regular basis. Updates are uploaded in the comitology register. The EP has a "droit de regard" period of seven days to check the EC has not exceeded its powers. If this is the case, the EP informs the Council (European Commission, 1999; European Commission, 2021c; Vintura stakeholder interviews, 2021).

277

Day 277

The Commission will take a final decision within 15 calendar days after the end of the Standing Committee phase. If the Standing Committee votes favourably on the draft decision, the Commission will proceed to the adoption of the decision. If the Standing Committee votes unfavourably, the Commission will not adopt the draft implementing act.[9]

[8] E.g. agendas, draft decisions, voting results, summary records, authorities/organisations, referral to Council.
[9] Where an implementing act is deemed to be necessary, the chair may either submit an amended version of the draft implementing act to the same committee within 2 months of delivery of the negative opinion, or submit the draft implementing act within 1 month of such delivery to the appeal committee for further deliberation. As of January 2023, the same procedure will apply to a situation in which the voting results are neither positive nor negative (the so-called no-opinion scenario).

WHY IS THE CURRENT PROCESS IMPORTANT?

Textbox 4

KEY PRINCIPLES UNDERPINNING THE CURRENT PROCESS

The current process between final CHMP opinion and EC decision is laid down in EU regulations and is based on three principles that are key to the governance of the European Union:

1. The decision-making mandate lies with the EC, not with EMA

In Europe, the technical review of medicines is split from the decision on marketing authorisation. EMA's independent and scientific CHMP is responsible for the assessment and provides a recommendation (opinion). However, EMA has no mandate to permit a marketing authorisation in the European Union. Only the European Commission has the mandate to grant the central marketing authorisation.

2. Member States have a vote in the EC decision to be able to prohibit use in their territory

Within the European Union, Member States are responsible for defining and delivering their national health services and medical care. According to Article 6 of the Treaty on the Functioning of the European Union, the EU can only intervene to support, coordinate, or complement the action of EU countries in the healthcare domain. Therefore, Member States need to be able to prohibit use of a new therapy in their territory. They currently have various ways in which they can intervene: (i) through their representative in the CHMP, (ii) by expressing a diverging opinion related to the CHMP opinion; (iii) by sharing their observations and vote in the written procedure, and (iv) by calling for a meeting of the Standing Committee.

3. All information should be available in all 24 official languages of the EU

The first ever act adopted by the Council was Regulation 1 from 1958 on the languages to be used in the European Union. It states that regulations and other documents of general application shall be drafted in all official languages of the European Union. In the case of the product information, the objective of translation is to ensure patient safety through correct product information for prescribers and patients, in their own language.

CAN THE ADMINISTRATIVE PROCEDURES THAT WERE DESIGNED TO DELIVER ON THESE PRINCIPLES BE OPTIMISED?

For a potential change in the current process to be feasible at all, it should not challenge these key principles governing EU collaboration. However, there might be an opportunity to optimise the administrative procedures that were designed to deliver on these principles.

For the first principle, process optimisation would require a fundamental legal change. Therefore, this has not been considered in this report.

For the second principle, the need for Member States to have oversight and the ability to scrutinise EC draft decisions should be respected. However, the question is whether the timeline for sharing observations during the written procedure should always be 22 days. Member States already have multiple moments to intervene prior to the written procedure. Furthermore, they can only prohibit use in their territory in exceptional cases and based on very specific reasons, due to rigorous pharmaceutical legislation. Consequently, Standing Committee meetings are only called for only in exceptional cases as a measure of last resort. This is reflected by the fact that over the last ten years, all CHMP opinions, EC draft decisions, Standing Committee votes and final EC decisions were aligned, as shown in Figure 5.

"Over the last ten years, all CHMP opinions, EC draft decisions, Standing Committee votes and final EC decisions were aligned"

Regarding the third principle, the question is whether translation into all 24 EU languages is required prior to EC decision-making, or whether translations can be made available after the formal decision. Because only the version in the authentic language (the language of the country where the marketing authorisation holder is based) is legally binding, and because there is still time between granting of the marketing authorisation and therapies being prescribed to patients. Furthermore, a precedent was created during COVID-19, where the linguistic phase and the decision-making phase were decoupled.

Figure 5

List of negative CHMP opinions, negative EC draft implementation decisions, negative Standing Committee votes and EC marketing authorisation refusals (2011-2020, all therapeutic areas, new molecular entities only)[10,11,12,13,14]

Source: EMA, 2021a; EMA, 2021e; EMA, 2021f; European Commission, 2021c

Year of CHMP opinion	Final CHMP opinions *(Day 210)*		Withdrawals	EC Draft Implementation Decisions *(Day 252)*		Standing Committee *(Day 274)*	Final EC Decision *(Day 277)*	
	Negative	Products that received a negative opinion	Prior to EC decision	Refusals[10]	Products that received a negative draft decision	No opinion or unfavourable	Refusals	Products that were refused authorisation
2011	2	Sumatriptan Galpharm, Movectro	0	2	Sumatriptan Galpharm, Movectro	0	2	Sumatriptan Galpharm, Movectro[11]
2012	8	Acrescent, Balaxur, Elelyso, Folotyn, Istodax, Kynamro, Qsiva, Fanaptum[12]	1	7	Acrescent, Balaxur, Elelyso, Folotyn, Istodax, Kynamro, Qsiva	0	7	Acrescent, Balaxur, Elelyso, Folotyn, Istodax, Kynamro, Qsiva
2013	3	Labazenit, Masican, Winfuran	0	3	Labazenit, Masican, Winfuran	0	3	Labazenit, Masican, Winfuran[11]
2014	3	Masiviera, Nerventra, Reasanz	3[13]	6[13]	Masiviera, Nerventra, Reasanz, Vynfinit, Neocepri, Folcepri[13]	0	6	Masiviera, Nerventra, Reasanz, Vynfinit, Neocepri, Folcepr[13]
2015	4	Solumarv, Heparesc, Lympreva, Dropcys	0	4	Solumarv, Heparesc, Lympreva, Dropcys	0	4	Solumarv, Heparesc, Lympreva, Dropcys
2016	0	-	0	0	-	0	0	-
2017	6	Adlumiz, Aplidin, Fanaptum IgG1 mab IL-1a, Masipro, Onzeald	0	6	Adlumiz, Aplidin, Fanaptum IgG1 mab IL-1a, Masipro, Onzeald	0	6	Adlumiz, Aplidin[14], Fanaptum IgG1 mab IL-1a, Masipro, Onzeald
2018	5	Alsitek, Dexxience, Eladynos, EnCyzix, Exondys	0	5	Alsitek, Dexxience, Eladynos, EnCyzix, Exondys	0	5	Alsitek, Dexxience, Eladynos, EnCyzix, Exondys
2019	4	Cabazitaxel Teva, Doxolipad, Hopveus, Vanflyta	0	4	Cabazitaxel Teva, Doxolipad, Hopveus, Vanflyta	0	4	Cabazitaxel Teva, Doxolipad, Hopveus, Vanflyta
2020	2	Gamifant, Turalio	0	2	Gamifant, Turalio	0	2	Gamifant, Turalio
Total	**37**		**4**	**39**		**0**	**39**	

[10] Centralised Procedure Refusals only.
[11] Withdrawn prior to EC decision, yet a formal decision was still made.
[12] Withdrawn prior to EC decision, no formal EC decision was made.
[13] Vynfinit, Neocepri, Folcepri (three therapies used together) received a positive CHMP opinion with conditional authorization, however the ongoing clinical trial was terminated which invalidated the conditional approval. The manufacturer withdrew this therapy before the CHMP decision was revised and the subsequent EC decision was negative.

[14] By its judgment of 28 October 2020 in case T-594/18, the General Court annulled the Commission Implementing Decision refusing marketing authorisation for Aplidin. As a result, the European Commission has returned the marketing authorisation application for Aplidin to the Agency. EMA is now taking the necessary steps to implement the judgment of the Court..

Every Day Counts - Improving Regulatory Timelines

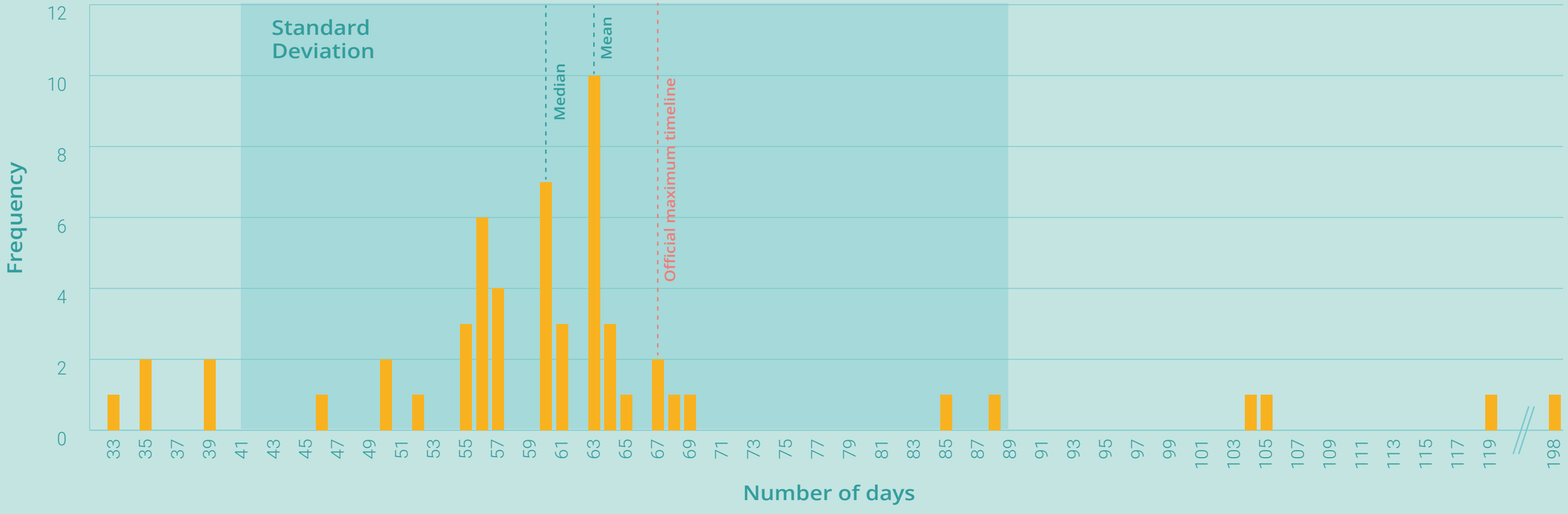
A median timeline of 60 days

In the last five years (2016 – 2020) the CHMP has developed 400 opinions for new molecular entities, of which 68 were opinions on innovative cancer treatments. 57 of these innovative cancer treatments received Marketing Authorisation, while seven applications were refused and four applications were withdrawn by the manufacturer.

On the whole, the EMA, EC and Member States were able to complete the regulatory process well within the official 67-day timeline. As shown in Figure 6, the time between the CHMP opinion and positive EC decision took 64 days on average. Timelines for the authorised oncology therapies ranged between 33 days and 198 days, with a median duration of 60 days (European Commission, 2021d).[15,16]

[15] Timelines were not available for one of the 57 therapies; this therapy is therefore excluded from Figure 6.
[16] Average timelines were shorter for therapies assessed within the framework of Exceptional Circumstances (n=2, mean=51 days) and Accelerated Assessment (n=4, mean=60 days, median=50 days). Average timelines were equal or longer for Orphan medicines (n=20, mean=67 days, median=63 days) and Conditional Marketing Authorisation (n=11, mean=70 days, median=63 days).

Figure 6
Overview of timelines between CHMP opinion and EC decision, for all oncology therapies evaluated by the CHMP between 2016 and 2020 (new molecular entities only).
Source: European Commission, 2021c



Every Day Counts - Improving Regulatory Timelines
The Current Process

Figure 7 provides an overview of the therapies for which timelines deviated the most. For the lower bound outliers, the official timeline of 67 days between a positive CHMP opinion and a final EC decision was reduced to 36 days on average.

For these therapies the main acceleration took place between the start of the Standing Committee consultation (Day 240) and the finalisation of the Standing Committee procedure (Day 262), which occurred 15 days faster than stated in the official process. As identified during a European Multi-Stakeholder Sounding Board, this may have been due to:

- The chair of the Standing Committee setting a time limit shorter than the maximum 22 calendar days, which is allowed in exceptional circumstances
- Fast voting by, and absence of further observations from the Member States

Additional acceleration took place between the final CHMP opinion (Day 210) and the start of the Standing Committee consultation (Day 240), meaning the Standing Committee consultation could be launched seven days earlier. This may have been due to:

- The absence of issues arising after the CHMP opinion, for example in relation to the COMP review, the completeness and compliance of the document, the legal review, intellectual property disputes or safety concerns
- Early availability of translations in all official EU languages
- The availability and responsiveness of the EMA Product Manager and the EC liaison officer

For the upper bound outliers, the official timeline of 67 days between a positive CHMP opinion and a final EC decision was extended to an average of 132 days (median: 112 days). The main delay occurred between the time of final CHMP opinion and the EC draft decision. This step took 107 days on average, which is more than 2.5 times the official duration of 42 days. This could have been due to:

- Issues arising after the CHMP opinion, for example in relation to the COMP review, the completeness and compliance of the document, the legal review, intellectual property disputes or safety concerns
- Limited availability or responsiveness of the EMA Product Manager and the EC liaison officer

For both the fastest and the slowest approvals, the adoption of the final EC decision after the end of the consultation of the Standing Committee took just six days. This represents a consistent acceleration of seven days compared to the maximum timeline.

Every Day Counts - Improving Regulatory Timelines

Figure 7
Overview of timelines for fastest and slowest approvals, for oncology therapies with timelines outside of the standard deviation.
Source: European Commission, 2021d

	Therapy	TOTAL Days between CHMP final opinion & final EC Decision (Formal timeline: 67 days)	Days between CHMP final opinion & EC sending draft implementing decision to MS (Formal timeline: 30 days)	Days between EC sending draft implementing decision to MS & MS finalizing SC procedure (Formal timeline: 22 days)	Days between MS finalizing SC procedure & final EC Decision (Formal timeline: 15 days)
Fastest approvals	A	33	20	9	4
	B	35	22	9	4
	C	35	22	9	4
	D	39	26	0	13
	E	39	26	9	4
	Average	36	23	7	6
Slowest approvals	F	104	86	9	9
	G	105	78	21	6
	H	119	93*	21	5
	I	196	172	21	5
	Average	132	107	18	6

** In these cases, the documentation sent by the EMA to the EC included a reassessment of the Committee for Orphan Medicinal Products with respect to the orphan designation of the medicine.*

A one-day timeline during COVID-19

It is possible to accelerate the formal process if it is required. The median timeline of 60 days shows that accelerations are also applied in practice.

This capability of the EMA and Member States to expedite the process was also clearly demonstrated during the COVID-19 pandemic. For every approved COVID-19 vaccine, the process between final CHMP opinion and the EC decision to grant a conditional marketing authorisation took just one day (European Commission, 2021d).[17] This major acceleration was realised in both the linguistic phase and the decision-making phase.

The linguistic phase for COVID-19 vaccines

Product information was prepared prior to the final CHMP opinion and published in English within one day of the positive CHMP opinion (EMA, 2021i). The English version was used as the basis for further decision-making. Translation into the other official EU languages took place after the granting of conditional marketing authorisation (Vintura stakeholder interviews, 2021).

The decision-making phase for COVID-19 vaccines

Being an observer, the EC could follow the EMA pandemic task force during the scientific assessment (rolling review) of COVID-19 vaccines and was kept informed during the EMA evaluation process (EMA, 2021j). This allowed for early identification of potential issues related to the legal review and the Standing Committee procedure, and facilitated the acceleration of the EC decision-making phase upon receipt of the final CHMP opinion (EMA, 2021k).

While these measures were reasonable during the COVID-19 crisis, stakeholders believe that adopting this approach to all marketing authorisation decisions will not be feasible or realistic. However, as in the COVID-19 crisis, where time to access to innovative COVID-19 vaccines was critical, oncology patients have no time to lose. Lessons from COVID-19 should be drawn to accelerate marketing authorisation timelines for innovative oncology medicines.

[17] Regarding the process prior to CHMP opinion, the conditional marketing authorisation procedure was used as the fast-track authorisation during public health emergencies, to speed up approval and save lives. This process was combined with a rolling review of data during the development of a promising vaccine, to further expedite the evaluation (EMA, 2021j).

The regulatory process for COVID-19 vaccines has clearly shown that the European community of stakeholders is able to work together to optimise this process greatly. The learning from COVID-19 is not that a one-day process should become the norm. It is that there is an opportunity to reduce time to patient access, and that that opportunity exists in oncology.

The Case for Change

A need and a once-in-a-generation opportunity to optimise the current process to improve time to patient access

The COVID-19 pandemic demonstrated that for major public health emergencies, the community of European stakeholders can work together to considerably expedite the regulatory approval process. This effort was made possible for COVID-19 vaccines due to a strong sense of urgency to ensure fast patient access to vaccines. Triggered by the high and acute impact of the disease and the clarity of the solution, this caused a strong willingness to re-evaluate existing processes and increase collaboration between scientific, regulatory, legal, and political stakeholders.

For cancer patients, expediting marketing authorisation – even the short process between a final CHMP opinion and the EC decision – would have an important impact on the life expectancy of cancer patients.

Although there is awareness of cancer's impact on patients and society, its true urgency is often overlooked. This is, in part, due to the slower – yet steady – growth of the number of cancer patients, which may lower the sense of urgency. However, the increase in the size of the healthcare workforce which will be required in the future, and the economic dependency this will create, mean timely access to innovation in oncology should become important, to reflect the true impact of cancer on patients and society; as outlined in Europe's Beating Cancer Plan (European Commission, 2021a).

The aim of this report is to increase this sense of urgency, by re-emphasizing the impact and importance of timely access to innovative oncology therapies, and in particular by providing more clarity on the current situation and potential solutions (see Figure 8).

Figure 8
The sense of urgency to ensure fast patient access depends on the perceived impact of the disease and the clarity of the solution to deploy.

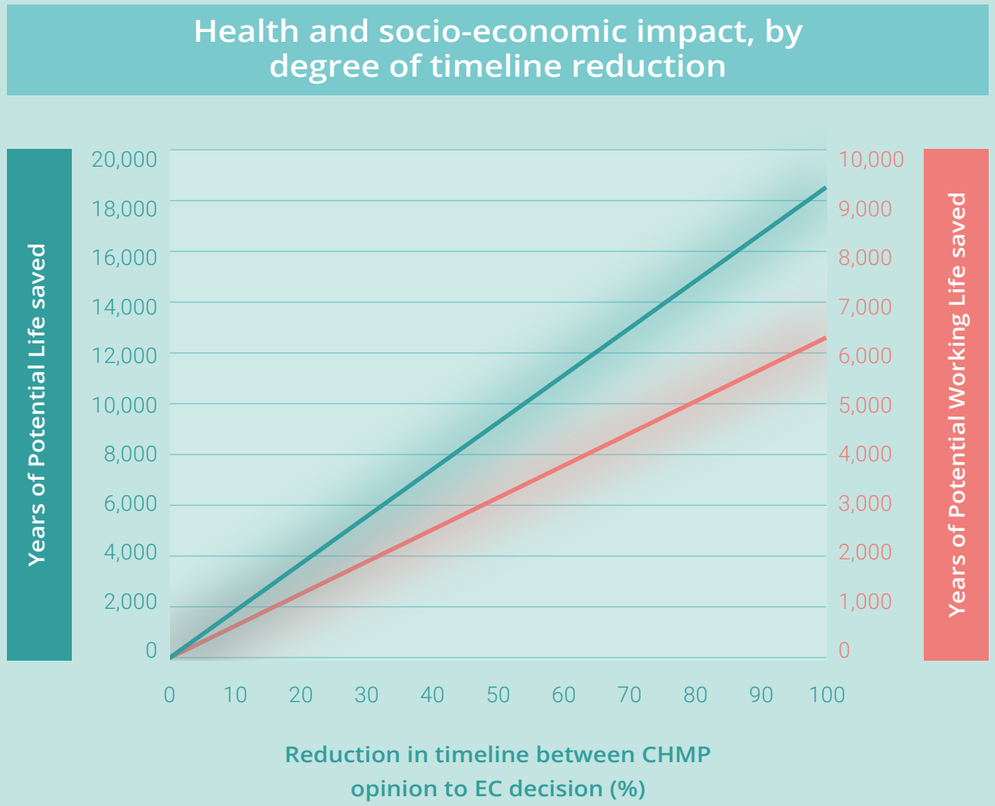
During the marketing authorisation process, time to patient access can seem like an abstract objective. But the current timelines come at a cost. An indicative analysis of the impact of current timelines on patients across the European Union (see Figure 9) reveals that for the 11 oncology indications studied, the current time between a positive CHMP opinion and EC granting a marketing authorisation represents a loss of 18,600 years of potential life (YPL). This corresponds to a productivity loss with an economic value of €120 million.

If the timeline between CHMP opinion and EC decision could be conducted at least as quickly as the fastest oncology assessment achieved during the period 2016-2020 (33 days), there is a potential saving of 13,300 YPL and 4,800 Years of Potential Working Life (YPWL) gained in these indications. The economic value of these YPWL gained corresponds to a potential saving of €87 million in productivity gains.

The methodology for this impact assessment is outlined in Textbox 5 (with further detail in Annex B).

For 11 oncology indications studied, the current time between a positive CHMP opinion and EC granting a marketing authorisation represents 18,600 years of potential life (YPL) being lost.

Figure 9
The years of potential life (YPL) saved and years of potential working life (YPWL) saved depending on the degree of reduction of the timeline between CHMP opinion and EC decision
Source: IHE analysis (see Textbox 5 and Annex B for further details)



Textbox 5

IMPACT ASSESSMENT METHOLODGY

The impact assessment is based on 11 oncology treatments / indications

The purpose of the impact assessment is to understand and quantify the gains of reducing time to patient access. This involves calculating both health and socio-economic effects:

- The Years of Potential Life (YPL) lost or gained; an estimate of the average years a person would have lived if they had not died prematurely.
- The Years of Potential Working Life (YPWL) lost or gained, and the economic value associated with these YPWL.

The analysis was made for 11 oncology treatments (in specific indications). The indications were selected by considering oncology therapies which received a European marketing authorisation between 1 January 2015 and 31 December 2020, which target major cancer types, and demonstrated a statistically significant gain in overall survival (which is needed to calculate the socio-economic impact in a uniform manner).

The YPL lost were calculated by multiplying the annual number of eligible patients, the median gain in overall survival per patient (in years), and the time between the final CHMP opinion and the EC decision granting marketing authorisation (in years).

The YPWL lost were then determined using a subset of YPL lost, covering only patients of working age. Subsequently, the economic value of these YPWL lost (defined as the cost of productivity loss arising from premature death of people in working age, due to the disease) were assessed. This was calculated by multiplying sex-specific mean annual earnings and sex-specific employment rates, per country. Per country, the annual number of eligible patients was re-calculated for the age group 15–64 years (working age), and separately for men and women. Epidemiological input parameters were assumed to be the same as the ones for the whole age range.

The YPWL lost for the age group 15–64 years were multiplied with the economic value of one YPWL lost. To aggregate the results, for the YPL lost, the YPWL lost and the economic value of the YPWL lost, data was summed across all indications and countries.

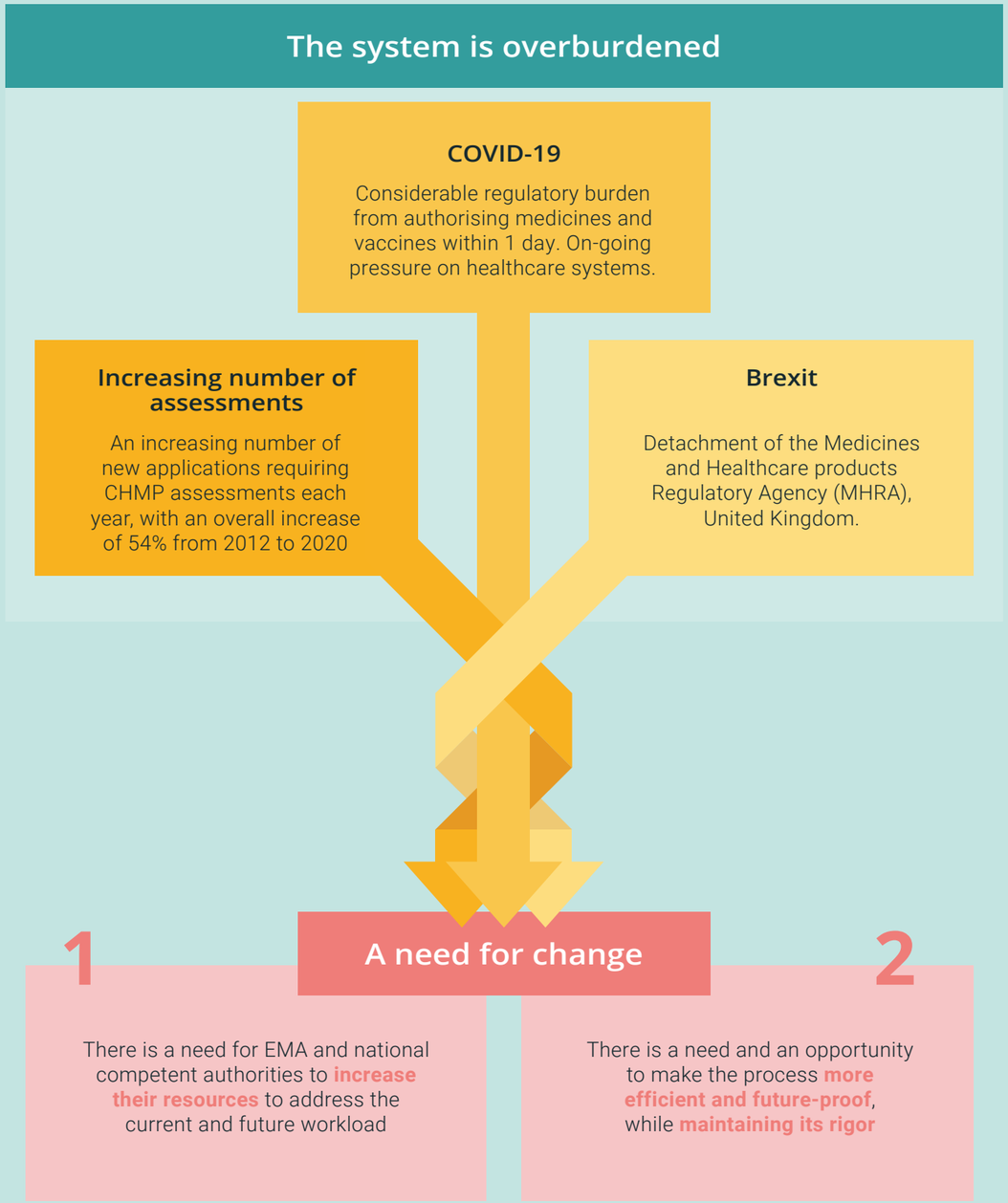
The potential impact could be far greater across all oncology indications

This impact analysis underestimates the actual impact of shortening timelines on patients' lives. The actual impact is far greater, since the methodology does not capture:

- The median timeline across oncology therapies: for this analysis, actual timelines for the indications in scope were used, and these are relatively short (median of 42 days instead of 60 days for oncology therapies in general)
- All new oncology therapies: the analysis considered only 11 out of the 59 oncology therapies which received initial EC marketing authorisation between 1 January 2015 and 31 December 2020
- The benefits of improved quality of life: the analysis captures the years of potential life only
- The cost of productivity loss due to morbidity (e.g. sickness absence, disability) and the cost of productivity loss by informal caregivers: the analysis captures formal productivity loss due to premature death
- Opportunities for accelerating timelines along the complete journey from the laboratory to the patient: the analysis captures the impact of accelerating timelines between the final CHMP opinion and EC decision only

More details on the methodology can be found in Annex B.

Figure 10
The need for change



There is a clear case to expedite the process between the final CHMP opinion and the EC decision. In addition to accelerating timelines, re-evaluating the current process could also ensure it is efficient and future-proof. Fast-track rolling reviews for COVID-19 vaccines and medicines have caused serious pressures on the EMA and regulatory organisations.

This pressure added to the challenges of Brexit, which required the EMA to move from London to Amsterdam and the detachment from the UK regulator, MHRA (EMA, 2021l). Moreover, the system was already overburdened due to the increasing number of new applications requiring CHMP assessments every year: from 2012 to 2020 the number of applications increased by 54% (EMA, 2021f). Fundamental change is therefore needed to sustain the system through its current challenges and prepare it for the future (Ventura stakeholder interviews, 2021).

While current pressures provide a need for change (see Figure 10), there is also an opportunity to reflect the actual importance of timely oncology access, within the marketing authorisation timelines. As part of the implementation of the European Pharmaceutical Strategy[18], the European Commission is evaluating the general pharmaceutical legislation and plans to make amendments by the end of 2022 (European Commission, 2021e). This general pharmaceutical legislation includes Regulation (EC) No 726/2004, which lays down the Community procedures for the authorisation and supervision of medicinal products. Revision of this legislation rarely occurs; and therefore this review offers a once-in-a-generation opportunity to shape changes which would optimise the regulatory process for the future, helping European patients suffering from cancer and other serious conditions.

We currently have a once-in-a-generation opportunity to shape changes which optimise the regulatory process for the future and for European cancer patients.

18 The Pharmaceutical Strategy for Europe and Europe's Beating Cancer Plan will ensure that patients across Europe can access high-quality treatment and new therapies when they need them and ensure the availability and affordability of essential medicines for cancer patients across the EU (European Commission, 2020).

Recommended Solutions

An overview of strategic options and the most impactful and feasible solutions

To make the most of the current opportunity, regulators and stakeholders should seek out solutions which are both impactful and feasible. This chapter provides an overview of strategic options and potential solutions identified based on a review of grey and academic literature, stakeholder interviews and two sessions with a European Multi-Stakeholder Sounding Board. The impact assessment described in the previous chapter[19] was used to assess the health- and socio-economic impact of each potential solution. This is based on an estimate of the number of days saved by each solution. The impact and feasibility of each potential solution was assessed with the members of the European Multi-Stakeholder Sounding Board, based on a review of pros and cons per solution. This resulted in a set of recommended solutions based on impact and feasibility.

[19] *See Annex B for further details.*

As outlined in Figure 11, four overall strategic options were considered to shorten regulatory timelines and ensure improved time to patient access.

- Increase the speed of the current steps
- Remove one or more steps
- Conduct steps in parallel
- Rearrange the order of the steps

Within the four strategic directions, five concrete solutions have been identified (also shown in Figure 11). Based on their impact and feasibility, the following solutions are recommended as a basis for further discussion and are listed in order of priority:

1. Conduct the decision-making phase in parallel to the linguistic phase
2. Accelerate the linguistic phase through greater digitalisation
3. Provide an opportunity to shorten the written procedure in cases where Member States foresee no objections

Closer involvement of the EC during the EMA evaluation process (which was the solution applied for COVID-19 vaccines) is not recommended. The reason for this decision is a belief that the current independence of the CHMP should be maintained, and that authorisation decisions under the centralised procedure should be taken based on the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. This emergency option should be reserved only for urgent health issues or true breakthrough therapies.

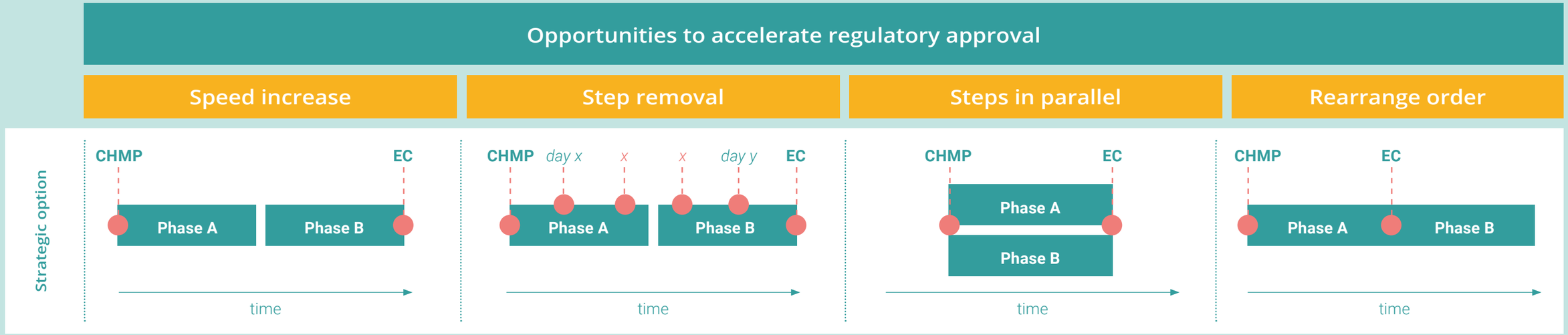
Another solution applied during the pandemic was to conduct the decision-making phase before the linguistic phase. This solution is also not recommended since it is more feasible to conduct the phases in parallel and the impact would be almost as high.[20]

All the recommended solutions could apply to new assessments across indications and are not limited to oncology therapies. Using them in this way would expand their beneficial impact on patients significantly. However, should it be decided to pilot one or more solutions, therapies addressing a high unmet need, for example in oncology, could be prioritised.

[20] *Provisions should be put in place to ensure manufacturers commit to delivering the approved translations into all 24 EU languages immediately after the EC decision, to address a potential fear by Member States of translations becoming available in priority markets first. Furthermore, in situations where the product is to be prescribed immediately after Marketing Authorisation, patients still would need to wait for the documentation to become available in all official languages.*

Every Day Counts - Improving Regulatory Timelines

Figure 11
Four strategic options and five potential solutions to optimise the regulatory process and improve the time to patient access.



Description

The timeline for individual steps and phases are shortened

Within a phase, specific steps are removed to reduce timelines

Regulatory steps take place in parallel to reduce overall timelines

The process is reorganized to allow for prioritisation of the EC decision

Recommended solutions

2 **Accelerate the linguistic phase through digitalisation** e.g. by working in a shared document, using databases with previous translations, deploying user-friendly electronic review formats

Impact:	**10 days**
Feasibility:	**Low-Medium**

3 **Provide an opportunity to shorten the written procedure** in cases where Member States foresee no objections (2-step approach with a light/ conditional and hard objection)

Impact:	**15 days**
Feasibility:	**Low-Medium**

1 **Conduct the decision-making phase in parallel to the linguistic phase,** as the legally-binding CHMP and EC decisions are only in one language

Impact:	**12 days**
Feasibility:	**Medium-High**

Deprioritised solutions

5 Accelerate through closer EC involvement within the CHMP process

Impact:	**7 days**
Feasibility:	**Low**

4 Conduct the decision-making phase before the linguistic phase, based on the English version of the documents

Impact:	**15 days**
Feasibility:	**Low**

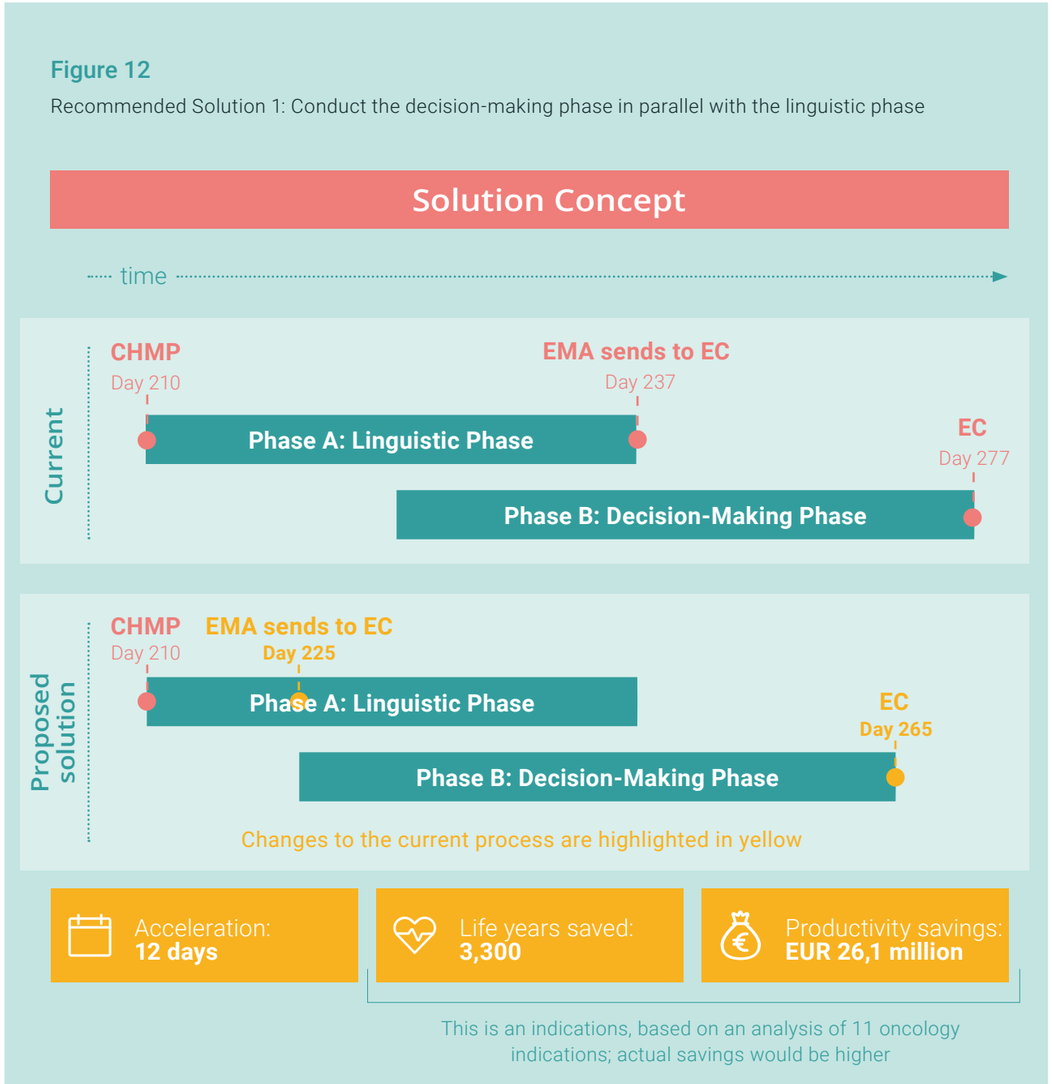
Recommended Solutions

Solution 1

Conduct the decision-making phase in parallel to the linguistic phase

Figure 12

Recommended Solution 1: Conduct the decision-making phase in parallel with the linguistic phase



In the current process, product information must be translated into every official language of the EU before the Standing Committee consultation can be launched. This leads from the principle that all documents of general application must be drafted in all official languages of the European Union (European Commission, 2004).

However, there are arguments to decouple the linguistic phase from the launch of the Standing Committee consultation phase. Firstly, the only legally binding version of EC decisions is the version in the authentic language: usually this is the official language of the country where the marketing authorisation holder is based.

Secondly, the objective of translation is not to enable decision making, but rather to ensure correct product information and patient safety after marketing authorisation. This means full translation into all EU-24 languages is not a pre-requisite for launching the consultation with Member States, but rather for prescription and use (Patient Access). The only prerequisite for EC decision-making is the availability of the documentation in one of the working languages of the EC (English, German, French) and for the draft decision to be available in the authentic language.

Finally, for COVID-19 vaccines, the linguistic phase was conducted after the EC decision, emphasising that conducting all translations could become an optional step before the Standing Committee consultation, rather than an obligatory requirement. This leads to the recommended solution of optimising the regulatory phase by conducting the decision-making phase in parallel to the linguistic phase (see Figure 12).

In this scenario, after the final CHMP opinion has been delivered, the EMA would still have 15 days to share the English version of the final CHMP opinion and the assessment report with the EC (Day 225). The EC would subsequently share a draft decision with Member States within three days of receipt of these documents, thereby launching the Standing Committee consultation on Day 228 instead of Day 240.

This solution has a tangible positive impact of 12 days. It may be supported by a change in the basic pharmaceutical legislation. Currently Article 10.1 of Regulation (EC) No 726/2004 prescribes that the Commission will prepare a draft of the decision to be taken within 15 days. This maximum timeline could be reduced to reflect the solution.

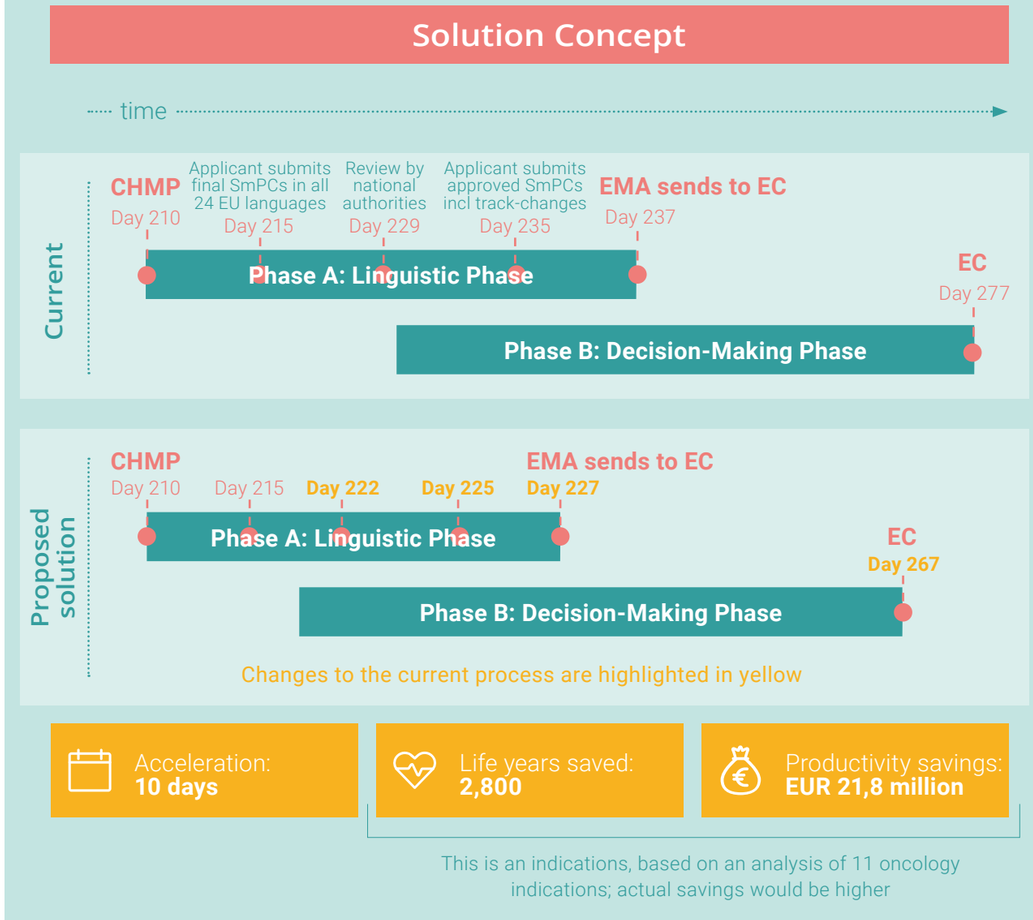
This solution does require that the legal scrutiny, the drafting of the decision and the interservice consultation all take place during the first 18 days after adoption of the final CHMP opinion. In cases where the authentic language is not one of the working languages of the EC, there would be a need to have a translation of the authentic language in place before launching the Standing Committee consultation (Vintura stakeholder interviews, 2021). Another potential challenge may be that the solution requires Member State representatives to work in an EC working language during the decision-making phase, or with (draft) translations if they are not fluent in English. Finally, the use of a single language may be politically sensitive, as Member States may perceive it as a threat to their sovereignty. However, since the linguistic phase is not removed but simply conducted in parallel, this objection is expected to be minimal.

Solution 2

Accelerate the linguistic phase through greater digitalisation

Figure 13

Recommended solution 2: Accelerate the linguistic phase through greater digitalisation



The second recommended solution is to increase the speed of the regulatory process through greater digitalisation (see Figure 13). This would involve greater use of digital tools within the current linguistic phase, i.e. working in one shared document, using information from previous translations optimally, deploying artificial intelligence to facilitate translation, and using electronic formats which allow Member States to review texts faster.

Since this solution only requires the use of advances in digital technology and maintains the current steps, it could be implemented without changes to the current legislative texts.

The solution should be aligned with ongoing digitalisation initiatives such as the EC project on electronic product information (EMA, 2020). This structured template would allow for improved electronic handling of the product information texts, which could also accelerate the speed to review.

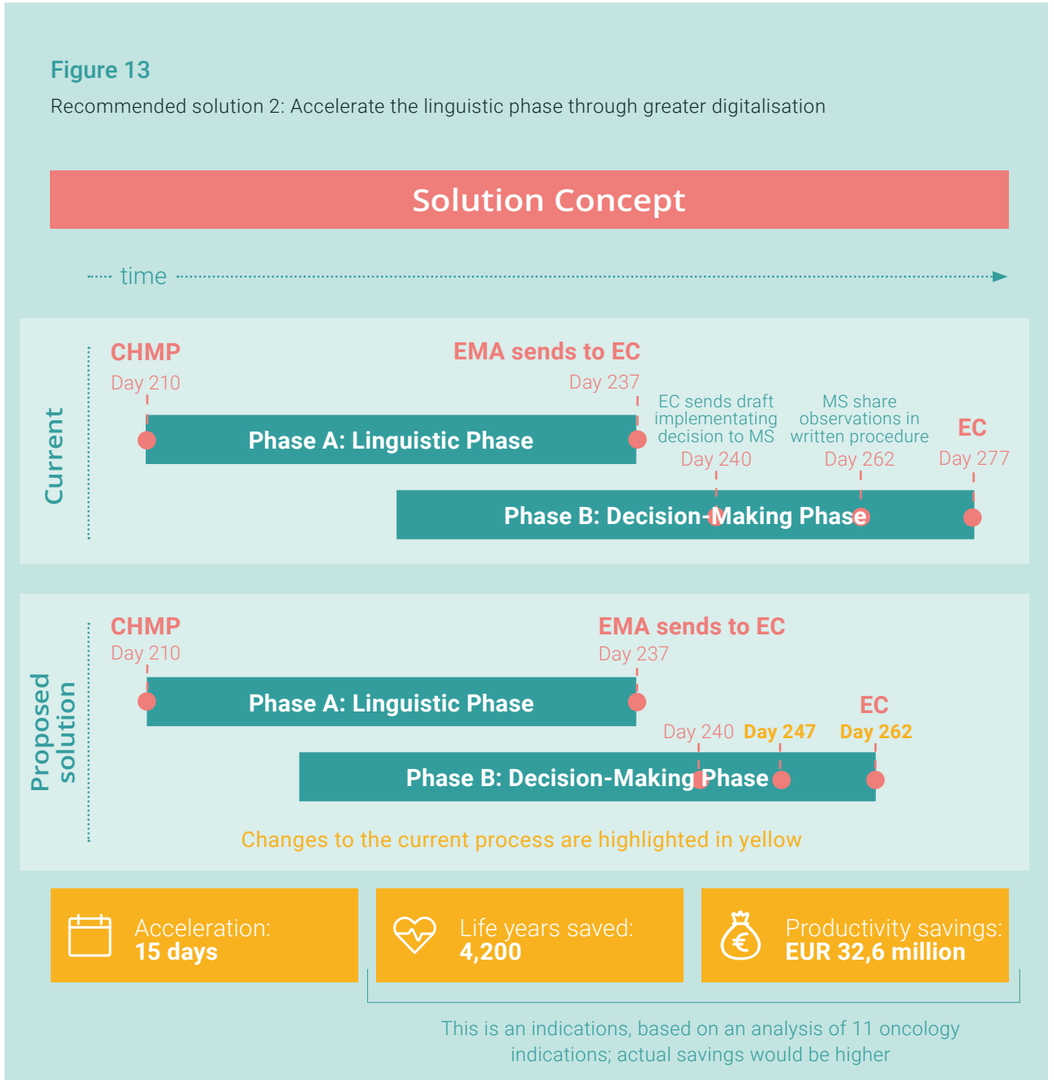
The solution is expected to reduce current timelines by ten days. This involves shortening the time to finalise national authority reviews by seven days (by Day 222 instead of Day 229) and shortening the time for the applicant to submit approved SmPCs (from six to three days). The result is that the linguistic phase is completed by Day 227 instead of Day 237. The risks, costs and time associated with complex IT projects pose the biggest challenge to implementing this solution.

Solution 3

Shorten the written procedure in case where Member States foresee no objections

Figure 13

Recommended solution 2: Accelerate the linguistic phase through greater digitalisation



The third recommended solution involves splitting the current 22-day Standing Committee procedure into two steps. Firstly, Member States have the opportunity to provide a "light objection" or a "conditional objection" within a period of seven days. If this occurs, in the second step Member States would have a further 15 days to decide on whether to provide a "formal objection". As a result, Member States would still have a total of 22 calendar days to forward written observations to the EC. However, if no light objections are provided, the second step is skipped and the EC proceed to granting Marketing Authorisation after a Standing Committee procedure of seven days (see Figure 14).

There is opportunity to accelerate this Standing Committee procedure, as over the last 10 years, CHMP opinions, EC draft implementation decisions, Standing Committee approvals and final Marketing Authorisation decisions have all been aligned (see Figure 5). Furthermore, contentious assessment cases are usually identifiable at an early stage, as discussion is raised during the CHMP process. This allows Member States to be prepared for making a light or conditional objection within seven days.

Potential challenges could be related to a risk of adding further complexity to the process. Removing a step in this process could also be politically sensitive, and may result in an overuse of light or conditional objections in order to gain time and ensure Member States have sufficient opportunity to provide their inputs.

The solution may expedite the process between final CHMP opinion and EC decision with 15 days in those cases where no light objections are raised within the first seven days. It may be supported by a change in the basic pharmaceutical legislation. Currently Article 10.3b of Regulation (EC) No 726/2004 prescribes that "Member States shall have 22 days to forward their written observations on the draft decision to the Commission. However, if a decision has to be taken urgently, a shorter time limit may be set by the Chairman according to the degree of urgency involved. This time limit shall not, other than in exceptional circumstances, be shorter than five days". This article and the rules of procedure for the Standing Committee could be reformulated in support of the solution.

A Holistic Approach

Final considerations to maximise the impact of solutions

Combine solutions

The three solutions outlined above are independent of each other and could therefore be combined to increase the total impact. The most impactful and feasible solution would be to conduct the decision-making phase in parallel to the linguistic phase, thereby saving 12 days. The impact could be augmented by combining this solution with a two-step approach for the Standing Committee consultation.

Make the system future-proof

Although greater digitalisation will not in itself further shorten timelines when the recommended solutions are combined, it will help to relieve pressure on a currently overburdened system. This is necessary to ensure the system is future proofed for the increasing number and complexity of the scientific reviews of tomorrow. Similarly, an increase in the number of human resources at the level of Member States, the EMA and the EC could relieve today's overburdened system and ensure that for any given assessment, the timeline is not significantly extended (such as with the slowest approvals in Figures 6 and 7). It is even arguable that increasing resources substantially could provide another means to expedite the process.

This could be part of a broader optimisation project which re-evaluates each step in the process between final CHMP opinion and EC decision. This project would identify opportunities for reducing the workload and using regulatory resources within EMA, Member States and pharmaceutical companies as efficiently as possible. This could potentially lead to further acceleration of the process, through shortening steps such as the five days taken up by the interservice consultation (since there is no knowledge of objections from other services that were raised in recent years), or the 15 days allowed for the EC to take a final decision upon the voting in the Standing Committee – a step which in practice usually takes half this time.

Apply a comprehensive perspective

Important gains can be made by applying a comprehensive perspective to the overall journey to patient access. The stages of Marketing Authorisation and Market Access should not be envisaged as fully sequential steps. In fact, there are important overlaps and critical touchpoints.

The first critical touchpoint is the final CHMP opinion. In parallel to changing the steps of the regulatory process, overall patient access timelines could be accelerated by beginning national HTA processes as soon as a positive CHMP opinion is announced at Day 210. This would essentially remove the impact of the time between final CHMP opinion and EC decision on overall patient access timelines. This is a feasible solution given the fact that for the last 10 years EC decisions have always aligned with final CHMP opinions (see Figure 5 for further details). However, it requires joint action and close collaboration from all relevant stakeholders:

- Member States may need to make changes in current national rules and regulations. This is the case, for example, in Romania where marketing authorisation is required before national submission can occur.
- National regulatory bodies need to provide information from the centralised marketing authorisation process to the national HTA

body before it is formally made available.
- Manufacturers need to be able and willing to submit their reimbursement dossiers to national HTA bodies level prior to EC decision. This may be challenging, depending on the timeline of evidence generation and the availability of pricing information.
- National HTA bodies need to be able and willing to start the HTA process based on the preliminary information. This may be challenging considering the limited resources available (Vintura, 2020)

Parallel procedures implemented in, for example, the Netherlands and Denmark (EFPIA, 2020); CBG-MEB, 2021) demonstrate it is possible to start the national HTA process as soon as the CHMP opinion is published. They even indicate that early alignment and collaboration have positive trickle-down effects in accelerating the rest of the national reimbursement process (Vintura stakeholder interviews, 2021). This solution would have the largest overall impact (minus 60+ days) and is one of the first recommendations outlined in the previous Every Day Counts report to improve timelines for the next milestones of the journey from laboratory to patients: Market Access and Patient Access (Vintura, 2020).

The second critical touchpoint is the date of the EC decision granting a European marketing authorisation. This is a key reference point in the overall planning for bringing a new therapy to patients. Allowing manufacturers to better understand this process and better anticipate the date of this milestone will increase the transparency and predictability of the process, and will have a positive impact on timelines for the rest of the journey towards patient access.

These solutions will be especially impactful when applied as part of the new EU HTA regulation. As part of this regulation, Joint Clinical Assessments (JCA) are planned to start for new molecular entities in oncology as of 2024 (European Commission, 2021g).[21]

[21] Countries like Germany are even more ambitious by ensuring Patient Access from the moment a dossier for the early benefit assessment is submitted: patients do not have to wait until the HTA is finalised. Plans for applying a similar system, targeting the most innovative therapies, have recently been announced in France and the United Kingdom as well (CSIS, 2021; NICE, 2021).

"The COVID-19 pandemic and the experience with vaccine development have clearly shown us that when we come together, when we pool our efforts and resources, it is possible to make unprecedented progress. It requires the unique convening power of the EU, fixing goals, setting clear deadlines, committing the necessary funding, and connecting the main actors through effective partnerships. Applying this approach to cancer can deliver effective results. By working as a team and combining efforts at national and EU level, we can overcome individual weaknesses, reduce fragmentation, and deliver a more effective and more equal response to cancer."

– Europe's Beating Cancer Plan

The Call to Action

A call for further dialogue among stakeholders

The current timeline between CHMP opinion and EC decision comes at a cost. When considering 11 recently authorised oncology therapy-indications, 18,600 years of potential life were lost during this process. Therefore, every effort should be made to optimise the time to patient access.

This report represents a call to action to use today's once-in-a-generation opportunity to contribute to key elements of the Pharmaceutical Strategy for Europe, to Europe's "Mission Cancer", thereby reducing time to patient access to (oncology) therapies across Europe.

The report offers three potential solutions to be used as a basis for further discussion and alignment on ways to optimise patient access:

- Conduct the decision-making phase in parallel to the linguistic phase, thereby allowing Marketing Authorisation to be granted 12 days sooner[16]
- Increase the use of digital tools during the linguistic phase, which could shorten this phase by 10 days
- Provide an opportunity to shorten the written procedure in cases where Member States foresee no objections, thereby shortening the decision-making phase by 15 days

In addition, there are proposals to future-proof today's overburdened system and apply a more holistic approach to the overall journey to patient access.

Combining these solutions has the potential to save thousands of years of potential life across the European Union, especially since their applicability is not limited to oncology therapies. They would apply to all other products that receive a European marketing authorisation by means of the centralised procedure. This includes any medicinal product for human use containing an entirely new active substance, orphan medicinal products, and products for which the therapeutic indication is the treatment of AIDS, neurodegenerative disorders, diabetes, auto-immune diseases, other immune dysfunctions, and viral diseases.

All stakeholders are part of the current regulatory and approvals system, and none can single-handedly solve today's challenges. The description of the process and the proposed solutions, therefore, serve as a basis for further dialogue among stakeholders (the EC, the EMA, European and national policy makers, authorities, pharmaceutical companies, payers, and professional and patient organisations). Although the proposed recommendations are possible within the current legislative framework, changes in the basic pharmaceutical legislation could facilitate the policy changes required. Therefore, it is useful to discuss the recommendations, within the context of the ongoing re-evaluation of general pharmaceutical legislation and future changes to national HTA and reimbursement processes, such as new EU HTA regulation with a focus on JCA (European Commission, 2021g).

The 67-day process in scope of this initiative represents only a small piece of the entire journey of a medicine from the lab to patient. However, when stakeholders can address this piece as part of a joint and comprehensive effort to align and accelerate Marketing Authorisation, Market Access and Patient Access, important gains in terms of life years, quality of life and productivity can be made across the EU.

Together, let's address this challenge and make use of this opportunity. Because for cancer patients, Every Day Counts.

[16] *If this is not possible, the linguistic phase should at least be conducted in parallel, which would save 12 days.*

List of Abbreviations

CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
DG SANTE	Directorate-General for Health and Food Safety
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EOP	EFPIA Oncology Platform
EP	European Parliament
EU	European Union
FDA	U.S. Food and Drug Administration
HTA	Health Technology Assessment
IHE	Swedish Institute for Health Economics
JCA	Joint Clinical Assessments
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MS	Members States
OS	Overall Survival
QRD	Working Group on Quality Review of Documents
R&D	Research & Development
SC	Standing Committee
SmPC	Summary of Product Characteristics
YPL	Years of Potential Life
YPWL	Years of Potential Working Life

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The following organisations contributed to this report by providing inputs, discussing report set-up and findings during the European multi-stakeholder Sounding Board meeting, and/or reviewing the final report.

Disclaimer: this publication is the result of a multi-stakeholder collaboration but does not necessarily reflect the views of individual organisations or people involved.

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References

Biller, L., & Schrag, D. (2021). Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. JAMA, 325(7), 669-685. Retrieved November 2021, from https://pubmed.ncbi.nlm.nih.gov/33591350/

CBG-MEB. (2021). Pilot 'Parallelle Procedures CBG-ZIN'. Retrieved from https://www.cbg-meb.nl/onderwerpen/hv-pilot-parallelle-procedures-cbg-zin

CSIS. (2021). Healthcare Innovation 2030. Strategic Council for the Healthcare Industries (CSIS). Retrieved August 2021, from https://www.elysee.fr/admin/upload/default/0001/10/878189f8b95f7905f5b4ecf540701a425e615cdf.pdf

EFPIA. (2020). The root cause of unavailability and delay to innovative medicines: reducing the time before patients have access to innovative medicines. Retrieved October 2021, from https://www.efpia.eu/media/554527/root-causes-unavailability-delay-cra-final-300620.pdf

EFPIA. (2021a). Phases of the Research and Development Process. Retrieved November 2021, from https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-rd/rd-process/

EFPIA. (2021b). EFPIA Patients W.A.I.T. Indicator 2020 Survey. Retrieved October 2021, from https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf

EMA. (2017). The linguistic review process of product information in the centralised procedure – human. Retrieved October 2021, from https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/linguistic-review-process-product-information-centralised-procedure-human_en.pdf

EMA. (2020). Key principles for the use of electronic product information for EU medicines. Retrieved October 2021, from https://www.ema.europa.eu/en/news/key-principles-use-electronic-product-information-eu-medicines

EMA. (2021a). Type-II variations: questions and answers. Retrieved Oct 2021, from EMA: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers

EMA. (2021b). Working Group on Quality Review of Documents. Retrieved October 2021, from Committees: https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/working-group-quality-review-documents

EMA. (2021c). QRD Product Information: Annotated Template. Retrieved October 2021, from https://www.ema.europa.eu/en/documents/template-form/qrd-product-information-annotated-template-english-version-102-rev1-highlighted_en.pdf

EMA. (2021d). Applying for marketing authorisation: orphan medicines. Retrieved November 2021, from Human Regulatory: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/orphan-medicines/applying-marketing-authorisation-orphan-medicines

EMA. (2021e). Authorisation procedures - The centralised procedure. Retrieved from Medicinal products: https://ec.europa.eu/health/authorisation-procedures-centralised_en

EMA. (2021f). Annual reports and work programmes. Retrieved from About us: https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes

EMA. (2021g). Dataset - Draft Measures. Retrieved from Comitology Register: https://ec.europa.eu/transparency/comitology-register/screen/datasets?lang=en

EMA. (2021h). Datasets - Voting Sheets. Retrieved from Comitology Register: https://ec.europa.eu/transparency/comitology-register/screen/datasets?lang=en

EMA. (2021i). Transparency: exceptional measures for COVID-19 medicines S. Retrieved from Human Regulatory: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines

EMA. (2021j). COVID-19 vaccines: development, evaluation, approval and monitoring Share. Retrieved October 2021, from Human Regulatory: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring

EMA. (2021k). EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and. Retrieved October 2021, from https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf

EMA. (2021l). Brexit: the United Kingdom's withdrawal from the European Union. Retrieved October 2021, from https://www.ema.europa.eu/en/about-us/brexit-united-kingdoms-withdrawal-european-union

European Commission. (1999). Council Decision 1999/468/EC laying down the procedures for the exercise of implementing powers conferred on the Commission. Official Journal of the European Communities. Retrieved October 2021, from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999D0468&from=EN

European Commission. (2001). Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Retrieved October 2021, from https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32001L0083

European Commission. (2004). Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official Journal of the EUropean Union. Retrieved October 2021, from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN

European Commission. (2005). VOLUME 2A - Procedures for marketing authorisation. CHAPTER 6 - Decision making procedure for the adoption of Commission decisions. Enterprise and Industry Directorate-General. Retrieved October 2021, from https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/a/vol2a_chap6_2005-11_en.pdf

European Commission. (2011a). Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers. Retrieved October 2021, from https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32011R0182

European Commission. (2011b). Rules of procedure for the Standing Committee on medicinal products for human use. Retrieved October 2021, from https://ec.europa.eu/health/sites/default/files/files/pharm_stand_comm/2011_09_13_human.pdf

European Commission. (2020). Pharmaceutical Strategy for Europe. Retrieved October https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf, 2021

European Commission. (2021a). Communication from the Commission to the European Parliament and the

Council - Europe's Beating Cancer Plan. Retrieved October 2021, from https://ec.europa.eu/health/sites/default/files/non_communicable_diseases/docs/eu_cancer-plan_en.pdf

European Commission. (2021b). EU Mission: Cancer. Retrieved from Missions in Horizon Europe: https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/missions-horizon-europe/cancer_en

European Commission. (2021c). Volume 2A - Procedures for marketing authorisation. Retrieved from Medicinal Products: https://ec.europa.eu/health/documents/eudralex/vol-2_en

European Commission. (2021d). Public Health - Union Register of medicinal products. Retrieved from https://ec.europa.eu/health/documents/community-register/html/

European Commission. (2021e). About this intiative. Retrieved from Revision of the EU general pharmaceuticals legislation: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en

European Commission. (2021f). Report from the Commission to the European Parliament and the Council on the working of committees during 2020. Retrieved October 2021, from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52021DC0544&from=EN

European Commission. (2021g). Topic 1. Recent developments and next steps regarding EU cooperation on HTA. DG SANTE. Retrieved November 2021, from https://ec.europa.eu/health/sites/default/files/technology_assessment/docs/ev_20210707_co01_en.pdf

Field, K., & Lipton, L. (2007). Metastatic colorectal cancer-past, progress and future. World J Gastroenterol, 13(28), 3806-3815. Retrieved November 2021, from https://pubmed.ncbi.nlm.nih.gov/17657834/

Hofmarcher, T., Brådvik, G., Svedman, C., Lindgren, P., Jönsson, B., & Wilking, N. (2019). Comparator Report on Cancer in Europe 2019. Retrieved October 2021, from https://ihe.se/en/publicering/comparator-report-on-cancer-in-europe-2019/

Jin, Z., & Hubbard, J. (2019). Optimizing biologic sequencing in metastatic colorectal cancer: first line and beyond. Curr Oncol, 26(Suppl 1), S33-S42. Retrieved November 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6878937/

Joppi R., B. V. (2020). Food and Drug Administration vs European Medicines Agency: Review times and clinical evidence on novel drugs at the time of approval. British Journal of clinical pharmacology . doi:doi:10.1111/bcp.14130

Kopetz, S., Chang, G., Overman, M., Eng, C., Sargent, D., Larson, D., . . . McWilliams, R. (2009). Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol, 27(33), 3677-3683. Retrieved November 2021, from https://pubmed.ncbi.nlm.nih.gov/19470929/

NICE. (2021, August). NICE changes to provide faster, fairer access to new drugs and devices. Retrieved from National Institute for Health and Care Excellence: https://indepth.nice.org.uk/methods-review/index.html

Uyl-de Groot CA, H. R. (2020). Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe. Cancers. doi:https://doi.org/10.3390/cancers12082313

Vintura. (2020). Every day counts – Improving time to patient access to innovative oncology therapies in Europe. Retrieved October 2021, from https://www.vintura.com/wp-content/uploads/2020/08/White-paper-every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe_from-EFPIA_and_Vintura.pdf

Annexes

A. Overview of governing legislation

Basic pharmaceutical legislation

Basic legislation governing EC implementation powers

B. Impact assessment methodology

Indication and drug selection process

Health and socio-economic impact calculations

A Overview of governing legislation

European Union (EU) law is divided into two main categories: primary and secondary legislation. **Primary legislation** refers to EU Treaties. These binding agreements between EU Member States set out the basic principles for all EU collaboration: objectives, rules for EU institutions, how decisions are made and the relationship between the EU and its members. **Secondary legislations** are derived from the principles and objectives set out in the treaties. Examples of these are:

- **Regulations**: a binding legislative act which must be applied in its entirety across the EU
- **Directives**: a legislative act setting out a goal which all EU countries must achieve by devising their own laws on how to reach it
- **Decisions**: a binding legislative act that is applicable to a specific country, institution, or company.

The process between CHMP opinion and final EC decision is governed by two basic pharmaceutical acts and two documents related to the basic legislation governing EC implementation powers:

Type of legislation		Title
Basic pharmaceutical legislation	1	**Directive 2001/83/EC** of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (European Commission, 2001)
	2	**Regulation (EC) No 726/2004** laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (European Commission, 2004)
Basic legislation governing EC implementation powers	3	**Regulation (EU) No 182/2011**[23] laying down the rules and principles concerning Member States' control of the Commission's implementing powers (European Commission, 2011a)
	4	**Standing Committee rules of procedure**, defined by the Standing Committee in accordance with Regulation (EU) No 182/2011 (European Commission, 2011b)

[23] *Regulation (EU) No 182/2011 replaced Council Decision 1999/468/EC.*

Basic pharmaceutical legislation

1

Directive 2001/83/EC sets out the goal to improve the functioning of the EU internal market and the free movement of medicinal products by harmonizing national marketing authorisation requirements.

2

Regulation (EC) No 726/2004 establishes the centralised marketing authorisation procedure. This is made compulsory for: orphan medicinal products; any medicinal product for human use containing an entirely new active substance; and products for which the therapeutic indication is the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune diseases and other immune dysfunctions, and viral diseases.

The regulation reiterates how within the EU, the technical assessment is separated from the decision-making, and that Member States should have a final say:

*"In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the **objective scientific criteria** of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations."*

*"However, **Member States should be able exceptionally to prohibit the use in their territory** of medicinal products for human use which infringe objectively defined concepts of public policy and public morality."*

It also reiterates the importance of speed:

*"Only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards, should marketing authorisation be granted by the Community, and this should be done by means of a **rapid procedure ensuring close cooperation between the Commission and Member States**."*

Articles 9 and 10 of the Regulation describe the timelines for the decision-making phase.

Basic legislation governing EC implementation powers

The two basic pharmaceutical acts build upon the foundation of documents governing the EC implementation powers:

3

Regulation (EU) No 182/2011[24] describes the 'comitology procedure' to be used for the adoption of implementing acts by the Commission. Comitology refers to a set of procedures, including meetings of representative committees, that give EU countries a say in implementing acts in cases where EU law mandates the European Commission to adopt implementing decisions.

As such, it also applies to the EC's draft implementation decision to grant or refuse a marketing authorisation, which is dealt with by the Standing Committee on medicinal products for human use. This Standing Committee (Committee Code C02500) is one out of 322 Committees included in the European Commission Comitology Register that were active in 2020 (European Commission, 2021f). The Regulation dictates the procedure for adoption of the Standing Committee opinions relating to Commission decisions[25]:

*"The Commission shall be assisted by a **committee composed of representatives of the Member States**. The committee shall be chaired by a representative of the Commission. The chair shall not take part in the committee vote."*

The Standing Committee provides the opportunity to share observations and opinions using the written procedure. The Regulation mandates that the chair decides on the timelines:

*"In duly justified cases, t**he chair may obtain the committee's opinion by written procedure. The chair shall send the committee members the draft implementing act and shall lay down a time limit for delivery of an opinion according to the urgency of the matter**. Any committee member who does not oppose the draft implementing act or who does not explicitly abstain from voting thereon before the expiry of that time limit **shall be regarded as having tacitly agreed** to the draft implementing act."*

The Regulation establishes the right of scrutiny ("droit de regard") for the European Parliament and the Council:

*"Where a basic act is adopted under the ordinary legislative procedure, either the **European Parliament or the Council may at any time indicate to the Commission that, in its view, a draft implementing act exceeds the implementing powers** provided for in the basic act."*

[24] *Regulation (EU) No 182/2011 replaced Council Decision 1999/468/EC.*
[25] *The 'Examination Procedure' as described in Article 5.*

4

The Standing Committee rules of procedure were adopted by the Standing Committee in 2011 and describe the timelines of this process:

"When the committee's opinion is required for the adoption of a Commission decision [...], the opinion is to be given by written procedure, in accordance with the following rules:

- *Member States shall have **22 calendar days to forward their written observations** on the draft decision to the Commission. However, if a decision has to be taken urgently, **a shorter time limit may be set by the chair** according to the degree of urgency involved. This time limit **shall not, otherwise than in exceptional circumstances, be shorter than five calendar days**.*
- *Where, in the opinion of the Commission, written comments put forward by a Member State raise **important new questions of a scientific or technical nature** which have not been dealt with in the opinion delivered by the European Medicines Agency, the chair shall suspend the procedure and the Commission shall r**efer the matter to the Agency** for further examination. The chair shall inform the members of the Committee thereof."*

These rules of procedure can be amended by the Standing Committee members based on a simple majority vote. The committee's discussions are confidential and there is no transparency regarding which participants represent Member States within the Standing Committee.

B Impact assessment methodology

The purpose of the impact assessment is to understand and quantify what could be gained from reducing the time to patient access. This includes both health effects (the Years of Potential Life, YPL, lost/gained) and the socio-economic effects (the economic value of formal productivity associated with the YPL lost/gained). Firstly, a selection process was used which identified 11 suitable treatment-indications to study. Then, the health and socio-economic impact was calculated.

Indication and drug selection process

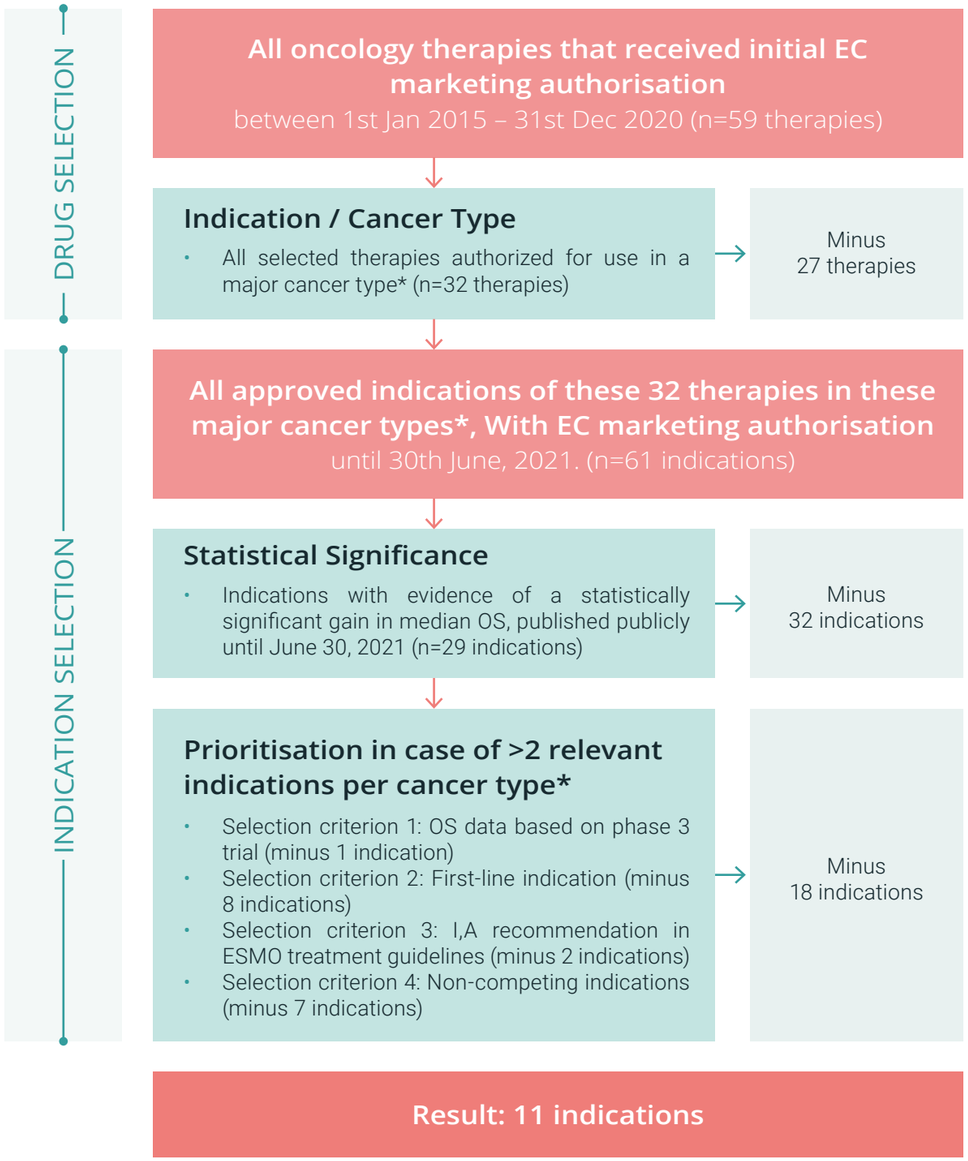
The scope of the assessment was to include a set of 10-12 oncology treatment-indications, considering only therapies which:

- received an initial EC marketing authorisation between 1st Jan 2015 and 31st Dec 2020
- target the major cancer types (including both solid tumours and haematology)
- demonstrated a statistically significant gain in overall survival (OS), which is needed to calculate the socio-economic impact in a uniform manner.

An overview of these inclusion criteria is provided in Figure 15. The final list of treatment-indications is shown in Figure 16.

Figure 15

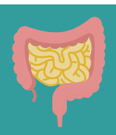
Selection process for the choice of drugs and indications to be used in the impact assessment



** At least 1 authorised indication related to the following cancer types: lung cancer, breast cancer, prostate cancer, colorectal cancer, bladder cancer, haematology (leukaemia AML+CLL).*

Figure 16

Final list of 11 treatments and indications, covering 6 cancer types

Cancer type	Therapy	Indication	CHMP opinion date	EC Authorisation date
 Lung	**Pembrolizumab**	As monotherapy, for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in tumours expressing PD-L1 with a ≥50% tumour proportion score with no EGFR or ALK positive mutations	**2016-12-15**	**2017-01-27**
	Osimertinib	As monotherapy, for the first-line treatment of locally advanced or metastatic NSCLC with EGFR mutations	**2018-04-26**	**2018-06-07**
 Breast	**Atezolizumab**	In combination with nab-paclitaxel, for the first-line treatment of unresectable locally advanced or metastatic triple-negative breast cancer in tumours with a PD-L1 expression ≥ 1%	**2019-06-27**	**2019-08-26**
	Ribociclib	In combination with an aromatase inhibitor, for the first-line treatment of pre- or perimenopausal women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer	**2018-11-15**	**2018-12-17**
 Prostate	**Apalutamide**	As monotherapy, for the first-line treatment of non-metastatic castration-resistant prostate cancer at high risk of developing metastatic disease	**2018-11-15**	**2019-01-14**
 Colorectal	**Encorafenib**	In combination with cetuximab, for the second-line treatment of metastatic colorectal cancer with a BRAF V600E mutation	**2020-04-30**	**2020-06-02**
	Trifluridine / tipiracil	As monotherapy, for the third-line treatment of metastatic colorectal cancer	**2016-02-25**	**2016-04-25**
 Bladder	**Avelumab**	As monotherapy, for the first-line maintenance treatment of locally advanced or metastatic urothelial carcinoma (UC) in progression-free patients following platinum-based chemotherapy.	**2020-12-10**	**2021-01-21**
	Pembrolizumab	As monotherapy, for the second-line treatment of locally advanced or metastatic UC in patients with prior platinum-bassed chemotherapy	**2017-07-20**	**2017-08-24**
 Haematology	**Midostaurin**	In combination with daunorubicin and cytarabine, for the first-line treatment of acute myeloid leukaemia (AML) with a FLT3 mutation	**2017-07-20**	**2017-09-18**
	Venetoclax	In combination with a hypomethylating agent, for the first-line treatment of AML in patients who are ineligible for intensive chemotherapy	**2021-04-22**	**2021-05-19**

Health and socio-economic impact calculations

For each of the 11 treatment-indications (listed in Figure 16), the YPL lost were calculated, using all EU-27 countries, plus Iceland and Norway as the scope.[26]

The following publicly available data was used as an input for the calculations:

- EU marketing authorisation data and label (EMA)
- Incidence by broad cancer type (ECIS/ GLOBOCAN)
- Epidemiological data per sub-classification defined in the approved label – European average (EPAR, targeted literature search)
- Median OS (publicly available information from clinical trials until 30th June 2021)
- Whether a change in timeline between CHMP and EC affects the national reimbursement timeline (literature search)
- Incidence in the age group 15 – 64 years (working age), male vs female (ECIS/ GLOBOCAN)
- Sex-specific mean annual earnings (Eurostat)
- Sex-specific employment rates (Eurostat)

The calculation and its inputs are described in Figure 17.

The YPL lost were calculated by multiplying the annual number of eligible patients, the median gain in overall survival per patient (in years), and the time between the final CHMP opinion and the EC decision granting marketing authorisation (in years).

The YPWL lost were then determined using a subset of YPL lost, covering only patients of working age. Subsequently, the economic value of these YPWL lost were defined.

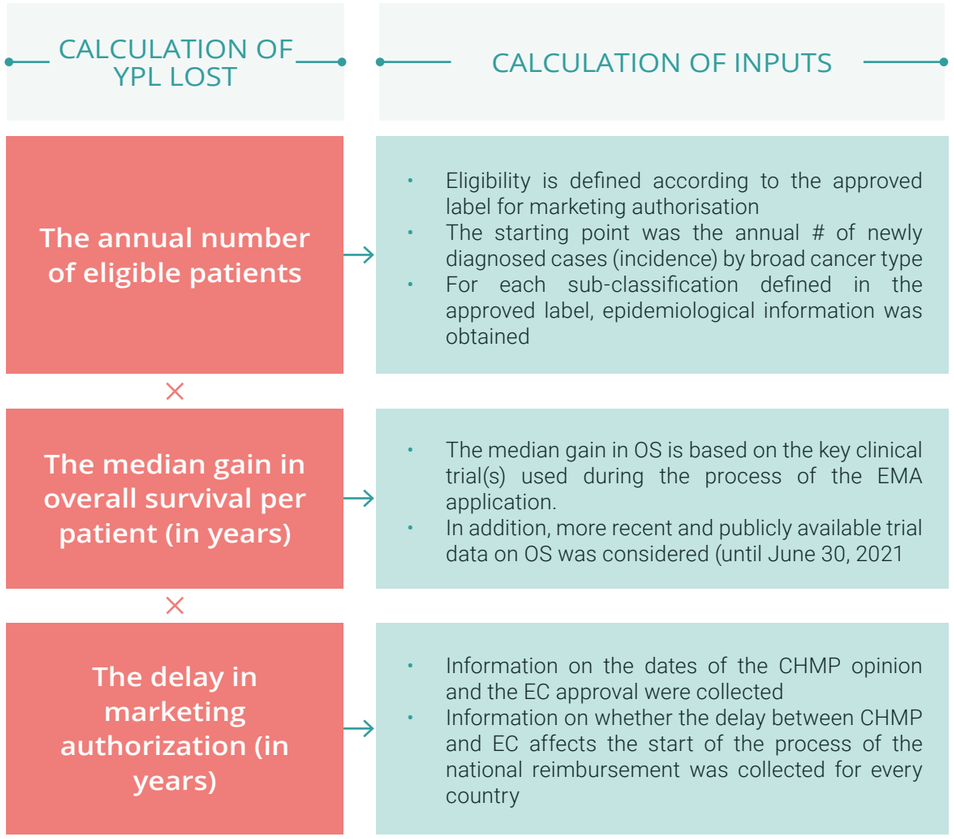
The economic value of one YPWL lost was assessed. The economic value was defined as the cost of productivity loss arising from premature death of people in working age due to the disease. This is based on the current value of the future earnings that a person who dies would have been expected to receive. This is according to the Human Capital Method; a conservative method in which the cost of productivity loss due to morbidity, e.g. sickness absence, disability, and the cost of productivity loss by informal caregivers is not included (Hofmarcher, et al., 2019).

This economic value was calculated by multiplying sex-specific mean annual earnings and sex-specific employment rates by country. By country, the annual number of eligible patients was re-calculated for the age group 15–64 years (working age), and separately for men and women. Epidemiological input parameters were assumed to be the same as the ones for the whole age range. The YPWL lost for the age group 15–64 years were multiplied by the economic value of one YPWL lost.

[26] Once granted by the European Commission, the centralised marketing authorisation is valid in all European Union (EU) Member States, plus Iceland, Norway, and Liechtenstein. Liechtenstein was excluded due to absence of data.

Figure 17

Calculation of Years of Potential Life lost



To aggregate the results for YPL lost, YPWL lost and the economic value of the YPWL lost, data was added across all indications and countries.

This resulted in the analysis of the impact of current timelines[27] on patients across the European Union: for the 11 oncology indications studied, the current time between a positive CHMP opinion and the EC decision granting a marketing authorisation means that 18,600 years of potential life (YPL) are lost. This corresponds to a productivity loss with an economic value of €120 million.

This impact analysis underestimates the actual impact of shortening timelines on patients' lives. The actual impact is far greater, since the methodology does not capture:

- The median timeline across oncology therapies: for this analysis, actual timelines for the indications in scope were used, and these are relatively short (median of 42 days instead of 60 days for oncology therapies in general)
- All new oncology therapies: the analysis considered only 11 out of the 59 oncology therapies which received initial EC marketing authorisation between 1 January 2015 and 31 December 2020
- The benefits of improved quality of life: the analysis captures the years of potential life only
- The cost of productivity loss due to morbidity (e.g. sickness absence, disability) and the cost of productivity loss by informal caregivers: the analysis captures formal productivity loss due to premature death
- Opportunities for accelerating timelines along the complete journey from the laboratory to the patient: the analysis captures the impact of accelerating timelines between the final CHMP opinion and EC decision only

To calculate the potential impact for each recommended solution, in terms of life years gained and in terms of the economic value of the associated productivity gains, the speed increase was considered as a percentage relating to the actual timelines for this set of 11 indications.

[27] Defined as actual timelines for this set of 11 indications. For this set of indications timelines were relatively short (mean: 45 days; median: 42 days), which provides for a conservative estimation of the 'cost' of current timelines.

The publication is endorsed by the following organisations:

- Acute Leukemia Advocates Network (ALAN)
- Associação de Enfermagem Oncológica Portuguesa (AEOP), Portugal
- Associação Melanoma Portugal, Portugal
- Associazione Contro il Melanoma (ACM), Italy
- Bulgarian Association of Clinical Research (BACR), Bulgaria
- Bulgarian Pharmaceutical Union (BPhU), Bulgaria
- Business School, Warsaw University of Technology (WUTBS), Poland
- Connaître et Combattre les Myélodysplasies (CCM), France
- Digestive Cancers Europe (DICE)
- European Association of Nuclear Medicine (EANM)
- European Cancer Patient Coalition (ECPC)
- European Federation of Pharmaceutical Industry Associations (EFPIA)
- European Union of Private Hospitals (UEHP)
- EVITA - Hereditary Cancer, Portugal
- Youth Cancer Europe (YCE)