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EFFICIENCY GAINS THROUGH INNOVATION IN MEDICINES DEVELOPMENT:

HOW CAN SCIENCE CONTRIBUTE?

ADVISORY REPORT

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EFFICIENCY GAINS THROUGH INNOVATION IN MEDICINES DEVELOPMENT

HOW CAN SCIENCE CONTRIBUTE?

Royal Netherlands Academy of Arts and Sciences
2021

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FOREWORD

Humankind has always sought out remedies to treat and prevent diseases. For many centuries, the discovery process into the therapeutic effects of substances extracted from natural sources was a matter of trial and error. For example, ancient Egyptians used bark from the willow tree to relieve pain. Many centuries later, salicin (the active agent within willow bark) formed the basis for the development of aspirin, the first blockbuster drug.[1] Since the 1800s, new systematic and scientific methods have been discovered for drug development, such as extracting substances from natural sources, developing synthetic compounds, discovering antimicrobial agents and developing vaccines and treatments to prevent and cure (previously lethal) diseases.

Over the last 250 years — particularly in the last century — drug development has seen spectacular progress. This has led to improved health, longer life expectancy and better quality of life. However, there is still an ever-pressing need to develop safe and effective high-quality medicines to meet as yet unmet medical needs, replace suboptimal ones and provide protection against new diseases (e.g. COVID-19 vaccines). This is the impetus for today's scientists to continuously innovate. Now that most of the so-called 'low-hanging fruit' has been picked, innovation in drug development is necessary for the sustainable development of the therapeutic agents of the future. Critical appraisal of the (academic) drug development environment is even more pressing because new, innovative approaches present both challenges (e.g. regarding cost-effectiveness and adaptations to the regulatory framework) and opportunities for personalised medicines, rare diseases and academic drug development.

1 Desborough, MJR and Keeling DM, The aspirin story – from willow to wonder drug, *Br J Haematol*, 177: 674-683, 2017 (https://doi.org/10.1111/bjh.14520)

I am proud that the members of the Royal Netherlands Academy of Arts and Sciences have taken the initiative to advise on such a socially relevant matter. The result of which is a considered analysis of the current challenges and opportunities in drug research and development, with a particular focus on what (Dutch) science can do for greater efficiency.

I hope and expect that this report will lead policymakers, funding agencies and academic institutions to support scientists in their attempts to seize the various important opportunities identified here. On the one hand, these concern important topics, methods and techniques that deserve attention in research and education. On the other hand, there are also opportunities for cultural changes in the academic environment. The drug development field can benefit from the current appreciation of team science, including acknowledgment of and rewards for the wide variety of tasks and roles in academic teams. Such developments offer great potential for attracting and retaining young talent and improving their career options.

Evidently, drug development is a global enterprise. International collaboration, however, starts at the national level. Historically, the Netherlands has been strong in medicines development. With its excellent and compact knowledge infrastructure, which includes universities, 'HBO' institutions (vocational training) and eight university medical centres (UMCs), the potential is there to foster a full-fledged national environment for drug development research and education. This will allow us to collaborate with and provide important impulses to the international scientific community.

Ineke Sluiter
President of the Royal Netherlands Academy of Arts and Sciences (KNAW).

SUMMARY

Safe, effective and accessible new medicines have huge benefits for individual patients and the greater society. Despite major scientific advances in past decades, the yearly number of newly approved medicines is stalling. The complete trajectory from initial target identification to a safe, effective and accessible new medicine remains long, expensive and obstacle ridden. This is becoming more pressing as innovative advanced therapy medicinal products, based on genes, tissues or cells, present new challenges and opportunities. This report inventories the opportunities in science to increase the efficiency of drug discovery research, development and access without a loss of quality or safety. Illustrated by showcases, this report identifies where science contributes to serve medical care and patient benefit, and where hurdles can be expected or observed. Clearly, advances in drug development are made in the international arena. While this report focusses on where specifically Dutch science and infrastructure can contribute, it aims to provide internationally relevant insights.

As described in chapter 2, scientific advances in science and (bio)technology over the past decades have revolutionised the initial steps of the medicine research and development trajectory by, for example, increasing the number of investigational compounds and biological targets and enabling faster screening methods, developing innovative data mining and a greater understanding of complex disease mechanisms. Optimal exploitation of these advances involves the ability to integrate, visualise and interpret the wealth of currently available data, which requires: i) close collaboration between researchers from various disciplines; ii) interdisciplinary training of researchers and; iii) long-term investments in technology platforms. In addition, we also draw attention to the fact that the predictive value of our current preclinical models is often too low to guarantee therapeutic efficacy and safety in human reality,

hampering smart decision-making on (continuing or discontinuing) development. Innovative models, such as human stem-cell models like organoids and organs-on-chips, have great potential to increase predictive value. However, the implementation of these and other innovative models requires regulatory consideration and adjustments regarding their use for predictive safety pharmacology and/or disease modelling. This underscores the importance of a timely dialogue with regulators.

After preclinical research and development, clinical studies are crucial and necessary to garner evidence on the safety, efficacy and effectiveness of a drug in humans, and are required for registration. New innovations come with new challenges, which are addressed in chapter 3, including: i) the high amount of wasted effort in science ; ii) limitations to the applicability of study outcomes in clinical practice; and iii) growing fragmentation of patient populations. Science can contribute here by standardising endpoints and defining the minimally clinically relevant difference. This requires: i) validation of surrogate endpoints ii) obtaining insight into the natural course of disease; iii) developing methods to measure outcomes as standardised as possible and developing mathematical models for data integration, iv) finding early markers for response and prognostic or predictive factors for treatment success; and v) actively seeking scientific advice from regulators prior to trial design and earlier interaction with Health Technology Assessment bodies and patient organisations to select the most important endpoints.
While randomised double blinded and placebo-controlled trials remain the standard to demonstrate that a drug is effective, searching for and validating alternative trial designs can help overcome challenges regarding feasibility (e.g. in case of rare diseases). Standardised, structured and stratified data collection in clinical practice should form the foundation for valuable real-world databases. Science can contribute here by developing methodology, such as integrative mathematical modelling, trial methodology and improving the usage (and acceptance) of real-world data and learning health-care systems.

As explained in chapter 4, after a new medicine receives approval, a long and difficult pathway to access may exist. The processes for clinical application assessment and reimbursement can take a long time and vary greatly between countries. This has also become increasingly complex for innovative (often expensive) therapies for rare diseases. Science could help shape the post-marketing landscape. In the area of regulatory science by: i) evaluating the use and value of post-marketing instruments and appropriate use; ii) validating these instruments against real-world outcomes; iii) identifying success and failure factors and; *in ultimo* iv) reshaping post-marketing instruments for improved evidence generation. We suggest that independent disease registries for pre-and post-approval of novel treatments should be encouraged and made readily available. In addition, the early establishment of international registries is called for in case of orphan diseases, ideally well before novel treatments are introduced. In the area of health technology assessment, science can contribute

by developing new pricing models. All with the aim to speed up access to novel medicines in combination with socially responsible pricing and appropriate use.

While focussing on the scientific opportunities mentioned in chapter 2, 3 and 4 may greatly contribute to progress in the development of new medicines, this alone will not be sufficient to enhance medicine R&D efficiency. Chapter 5 underscores that the medicines development ecosystem thrives through sustainable mutual partnerships between all parties involved (academia, research institutes, (academic) medical centres, clinicians, patient advocacy, pharmaceutical companies, regulatory agencies, government, etcetera.) throughout the trajectory. We underscore the importance of: i) a patient-centred approach; ii) modernisation of public-private partnerships iii) less bureaucracy and the earlier involvement of regulators and; iv) a complementary rather than a competitive international mindset. Furthermore, we reflect on the conditions within academia and the academic culture that will promote efficient medicines development, including: i) redefining the recognition and reward systems for academics; ii) providing professional support for technology transfer and regulatory affairs and; iii) stimulating career paths that transition smoothly between academia to industry. To maintain the strong and active role of academia in drug development, focussing on education and awareness is key. This involves: i) interdisciplinary education; ii) bridging the worlds of academia and industry at bio-science parks; iii) embedding technology transfer within the research and development process and making it accessible to researchers and in alignment with socially responsible licensing.

In conclusion, there are many wonderful examples of successful drug development initiatives that have sprouted from academia. But overall, the landscape remains scattered and development to final patient access is challenging. Smart use of public funding to reduce the costs of failure and the costs of capital, which currently account for 93% of the total drug development costs[2], can demonstrate that innovation and affordability can be mutually reinforcing. For greater efficiency, fostering the dialogue among (fundamental) scientists as well as between fundamental and (pre) clinical scientists, health-care professionals, the pharmaceutical industry, patient advocates and regulators is key to jointly realise a more efficient ecosystem based on collaboration, trust building and dialogue.

'Gaining efficiency through innovation' implies that scientists are seizing the various opportunities outlined in this report. This could be optimally stimulated by creating a coordinating expertise centre for medicines development tasked with supporting collaborations and steering and guiding decision-making to stimulate the development, validation and implementation of new methods or models for

2 Gupta. The costs of opportunity, 2019 (https://gupta-strategists.nl/studies/the-cost-of-opportunity)

evidence building, pricing, and public-private dialogues. This coordinating expertise centre could develop the necessary infrastructure to smoothen the development path for new therapies by concentrating expertise, creating facilities and making expertise readily available for all parties involved. Additionally, and in keeping with the FAST proposition recently adopted by the Dutch government, the expertise centre could also support the development of novel therapies to reach patients, thereby showcasing how novel collaborative approaches can benefit patients.

SAMENVATTING

Veilige, werkzame en toegankelijke nieuwe geneesmiddelen zijn van grote waarde voor individuele patiënten en de samenleving als geheel. Ondanks enorme wetenschappelijke vooruitgang in de afgelopen decennia stagneert het aantal nieuwe geneesmiddelen dat jaarlijks wordt goedgekeurd. Het volledige traject (vanaf de eerste doelwit-identificatie tot een veilig, werkzaam en toegankelijk nieuw geneesmiddel) is nog altijd kostbaar, vol hindernissen en vergt een lange adem. Dit is een actueel probleem nu er nieuwe uitdagingen en kansen ontstaan door innovatieve therapieën op basis van genen, cellen of weefsels (ATMP's).

In dit rapport worden de mogelijkheden geïnventariseerd die de wetenschap biedt om het onderzoek naar, de ontwikkeling van en de toegang tot nieuwe geneesmiddelen efficiënter te laten verlopen, zonder dat dit ten koste gaat van de kwaliteit en de veiligheid. Geïllustreerd met voorbeelden, wordt in dit rapport beschreven hoe de wetenschap bijdraagt aan de gezondheidszorg en patiëntenbelangen, en waar hindernissen te verwachten of te nemen zijn. Het spreekt vanzelf dat de ontwikkeling van geneesmiddelen een internationale aangelegenheid is. Hoewel in dit rapport de nadruk ligt op de wijze waarop de Nederlandse wetenschap en infrastructuur een bijdrage kunnen leveren, wordt tevens beoogd internationaal relevante inzichten te bieden.

In hoofdstuk 2 wordt uiteengezet dat de wetenschappelijke en (bio-) technologische ontwikkelingen van de afgelopen decennia de beginstadia van het geneesmiddelenontwikkelproces drastisch hebben veranderd. Bijvoorbeeld door de toename van het aantal te onderzoeken stoffen en biologische doelwitten, door snelle screeningmethoden en innovatieve datamining en door een beter begrip van complexe ziektemechanismen. Om optimaal van deze ontwikkelingen te kunnen

profiteren, moeten we in staat zijn het enorme aantal beschikbare gegevens te integreren, visualiseren en interpreteren. Hiervoor zijn verschillende zaken nodig: i) nauwe samenwerking tussen onderzoekers uit verschillende vakgebieden; ii) interdisciplinaire opleiding van onderzoekers; en iii) langetermijninvesteringen in technologieplatforms. Daarnaast signaleert de commissie dat de voorspellende waarde van onze huidige preklinische modellen voor de uiteindelijke therapeutische werkzaamheid en veiligheid in de klinische praktijk vaak te gering is. Dat maakt het lastig om goede beslissingen te nemen over het al dan niet voortzetten van een ontwikkelingstraject. Innovatieve modellen, waaronder humane stamcelmodellen zoals organoïden en *organs-on-a-chip*, hebben de potentie om de voorspellende waarde aanzienlijk te vergroten. Implementatie van deze en andere innovatieve modellen vereist echter dat nieuwe regelgeving wordt ontwikkeld en bestaande regelgeving wordt aangepast met betrekking tot het gebruik ervan voor farmacologische doeleinden en/of modellering van ziekten. Dit onderstreept het belang van tijdige dialoog met regelgevende autoriteiten.

Na preklinisch onderzoek en ontwikkeling (research & development, R&D) moeten er klinische studies worden uitgevoerd om te bewijzen dat een middel veilig, werkzaam en doeltreffend is bij de mens. Dit is tevens nodig voor registratie van het middel. Nieuwe innovaties gaan gepaard met nieuwe uitdagingen; deze komen aan bod in hoofdstuk 3. Het gaat hierbij om: i) verspilling van onderzoeks-tijd en energie; ii) beperkingen ten aanzien van de toepasbaarheid van onderzoeksresultaten in de klinische praktijk; en iii) toenemende fragmentatie van patiëntenpopulaties. De wetenschap kan aan oplossingen bijdragen door primaire uitkomstmaten (eindpunten) te standaardiseren en het minimale klinisch relevante verschil te definiëren. Dit vereist: i) het valideren van surrogaat eindpunten; ii) het verkrijgen van inzicht in het natuurlijk beloop van ziekten; iii) het ontwikkelen van methoden om resultaten zo gestandaardiseerd mogelijk te meten en het ontwikkelen van wiskundige modellen voor integratie van gegevens; iv) het vinden van vroegtijdige signalen voor respons en prognostische factoren voor een succesvolle behandeling; en v) het actief inwinnen van wetenschappelijk advies bij regelgevende instanties voorafgaand aan het opzetten van onderzoeken en vroegtijdig overleg met HTA[3]-instanties en patiëntenorganisaties om de belangrijkste eindpunten te selecteren. Gerandomiseerde dubbelblinde placebo-gecontroleerde studies blijven de norm om de werkzaamheid van een geneesmiddel aan te tonen, maar door alternatieve onderzoeksopzetten te onderzoeken en te valideren kan het hoofd worden geboden aan uitdagingen ten aanzien van haalbaarheid (bijvoorbeeld in het geval van zeldzame ziekten). Gestandaardiseerde, gestructureerde, gestratificeerde gegevensverzameling in de klinische praktijk moet de basis vormen van waardevolle,

3 HTA (Health Technology Assessment) behelst een systematische evaluatie van eigenschappen en (in-) directe effecten van medische technologie, met als doel om te komen tot geïnformeerde en gedegen besluitvorming

real-world-databases. De wetenschap heeft hier de taak methodologie te ontwikkelen, waaronder integratieve wiskundige modellering, trial-methodologie en verbetering van het gebruik (en de acceptatie) van real-world-data en lerende zorgsystemen.

In hoofdstuk 4 wordt uitgelegd dat na goedkeuring van een geneesmiddel het nog een lange en lastige weg kan zijn voordat de patiënt er toegang toe heeft. De processen waarbij de klinische toepassing en vergoeding worden beoordeeld, vergen vaak een lange adem en verschillen soms sterk tussen landen. Ook zijn ze steeds ingewikkelder geworden voor innovatieve (vaak dure) therapieën voor zeldzame ziekten. De wetenschap zou mede vorm kunnen geven aan het post-marketinglandschap. Op het gebied van regulatory science kan dit gebeuren door: i) het evalueren van het gebruik en de waarde van post-marketinginstrumenten en 'gepast gebruik'; ii) het valideren van deze instrumenten ten opzichte van real-world-resultaten; iii) het vaststellen van succes- en faalfactoren; en iv) het herzien van post-marketinginstrumenten voor verbeterde bewijsvorming. De commissie stelt voor dat onafhankelijke registers voorafgaand aan en volgend op goedkeuring van nieuwe behandelingen worden gestimuleerd en algemeen beschikbaar zijn. In geval van weesziekten moeten in een vroeg stadium internationale registers worden opgezet, bij voorkeur ruim voordat er nieuwe behandelingen worden geïntroduceerd. Op het gebied van HTA kan de wetenschap bijdragen door nieuwe modellen voor prijsstelling te ontwikkelen. Dit alles dient om nieuwe geneesmiddelen sneller toegankelijk te maken en daarnaast maatschappelijk verantwoorde prijsstelling en gepast gebruik te waarborgen.

Hoewel een focus op de in hoofdstuk 2, 3 en 4 genoemde wetenschappelijke kansen sterk zal bijdragen aan de ontwikkeling van nieuwe therapieën, is er meer nodig om de efficiëntie van onderzoek en ontwikkeling van geneesmiddelen te verbeteren. In hoofdstuk 5 wordt benadrukt dat het ecosysteem van geneesmiddelenontwikkeling, gedurende het hele traject, baat heeft bij duurzame wederzijdse partnerschappen tussen alle betrokken partijen (wetenschap, onderzoeksinstellingen, (academische) ziekenhuizen, clinici, patiëntbelangenbehartigers, farmaceutische bedrijven, regelgevende instanties, overheid, enzovoort). Het rapport onderstreept het belang van: i) een patiëntgerichte aanpak; ii) modernisering van publiek-private partnerschappen; iii) minder bureaucratie en het betrekken van regelgevers in een vroeg stadium; en iv) een internationale insteek die niet gericht is op elkaar beconcurreren, maar op elkaar aanvullen. Daarnaast reflecteert de commissie op de randvoorwaarden binnen de wetenschap en de wetenschappelijke cultuur die bevorderlijk zijn voor efficiënte ontwikkeling van geneesmiddelen. Het gaat hierbij om: i) herziening van de wijze van het erkennen en waarderen van wetenschappers; ii) professionele ondersteuning ten aanzien van technologieoverdracht en registratiezaken; en iii) stimulering van loopbanen waarbij men makkelijker kan schakelen tussen de wetenschap en het bedrijfsleven. Een blijvend sterke en actieve

rol van de wetenschap in de ontwikkeling van geneesmiddelen, vereist een focus op onderwijs en bewustwording, onder meer door: i) interdisciplinair onderwijs; ii) de wetenschappelijke wereld en het bedrijfsleven bijeen te brengen op (bio-) scienceparken; en iii) technologieoverdracht te integreren in het onderzoeks- en ontwikkelingsproces, en deze toegankelijk te maken voor onderzoekers en in lijn met de principes voor maatschappelijk verantwoord licentiëren.

Ten slotte, er zijn veel prachtige voorbeelden van geslaagde initiatieven voor therapieontwikkeling voortgekomen uit de wetenschappelijke wereld, maar over het geheel genomen is het landschap gefragmenteerd en is het een flinke uitdaging om eenmaal ontwikkelde geneesmiddelen toegankelijk te maken voor patiënten. Door slim gebruik te maken van overheidsfinanciering om de faalkosten en de kapitaalkosten te verminderen (op dit moment verantwoordelijk voor 93% van de totale kosten voor geneesmiddelenontwikkeling[4]) kunnen innovatie en betaalbaarheid elkaar versterken. Om efficiëntie te bevorderen blijft het essentieel om de dialoog te stimuleren tussen (fundamentele) wetenschappers onderling en tussen fundamentele en (pre-)klinische wetenschappers, de gezondheidszorg, de farmaceutische industrie, patiëntbelangenbehartigers en toezichthouders. Gezamenlijk zullen zij op deze manier een efficiënter ecosysteem realiseren dat is gebaseerd op samenwerking, vertrouwen en dialoog.

'*Meer efficiëntie door innovatie*' impliceert dat wetenschappers de verschillende kansen aangrijpen die in dit rapport worden genoemd. Dit kan optimaal worden gestimuleerd door een coördinerend expertisecentrum voor geneesmiddelenontwikkeling op te zetten, dat ten doel heeft samenwerking te ondersteunen, richting te geven en besluitvorming te begeleiden teneinde de ontwikkeling, validatie en implementatie van nieuwe methoden/modellen voor bewijsvorming, prijsstelling en publiek-private dialoog te stimuleren. Dit coördinerende expertisecentrum kan de infrastructuur ontwikkelen die nodig is om het ontwikkelingstraject voor nieuwe therapieën soepeler te laten verlopen door expertise te bundelen, faciliteiten te creëren en expertise eenvoudig toegankelijk te maken voor alle betrokken partijen. Daarnaast, en in lijn met het FAST-voorstel dat onlangs positief is ontvangen door de Nederlandse regering, kan het expertisecentrum ondersteuning bieden bij het naar de patiënt brengen van nieuw ontwikkelde therapieën, en zo aantonen dat nieuwe samenwerkingsvormen de patiënt ten goede komen.

4 Gupta. The costs of opportunity, 2019 (https://gupta-strategists.nl/studies/the-cost-of-opportunity)

1. INTRODUCTION

1.1 Background

The complete trajectory, from initial target identification to a safe, effective and accessible new medicine, is long, expensive and full of obstacles. It takes many steps to determine the quality, efficacy and safety of a medicine, to understand its pharmacology and to bring it *from bench to bedside* (see figure 1). Traditionally, the process begins with target identification, followed by screening and selection of new molecules affecting the identified target, preclinical testing of selected candidates, clinical testing during phase I, II, and III trials, national and international market approval from regulatory authorities, health technology assessment and patient usage during which phase IV research with pharmacovigilance continues. In total, this process may take three to fifteen years.

Over past decades, the financial investment in medicine research and development (R&D) has rapidly increased. The estimated R&D costs per new molecular entity are between $80 million and $2.5 billion US (Gupta, 2019; Uyl-de Groot & Löwenberg 2018; Gronde et al., 2017). However, even while costs are skyrocketing, the number of newly approved medicines remains relatively low (Munos 2009). In Europe, the number of new active substances approved for marketing authorisation varies yearly; between 27 (in 2016) and 39 (in 2020). Since the 1950s, there has been a steady decline in the number of newly approved drugs per billion USD spent on R&D (Scannell et al., 2012). Consequently, there are still many unmet and pressing needs (see box 1.1). Effective, safe and accessible new medicines are hugely beneficial for individual patients (e.g. when they increase longevity and/or quality of life) and

society (e.g. when they reduces medical expenditures and/or costs of sick leave) (Lichtenberg 2013; Lichtenberg 2005). Therefore it is key to identify opportunities that could boost medicine research and development efficiency, without loss of quality or safety.

BOX 1.1 THE PRESSING NEED FOR NEW ANTIMICROBIAL AGENTS

Bacteria and other microorganisms are increasingly resistant to antimicrobial agents, meaning that they can withstand exposure to a medicine that would normally kill them or stop their growth. This is a major global concern. Without effective antimicrobial drugs, common diseases become untreatable and key medical procedures become riskier (e.g. operations and treatments that suppress the immune system like chemotherapy). According to estimates, drug-resistant diseases cause around 700,000 deaths per year and various public-health bodies, scientists and governments have warned that this number is likely to rise sharply in the coming years if no action is taken (IACG report, 2019; O'Neill, 2016).

While the need for new antimicrobial agents is pressing, the discovery of new antimicrobials has stalled since the 1980s due to scientific and economic challenges. As microbes have evolved more mechanisms to escape the antimicrobial arsenal and the 'low-hanging fruit' of easily isolated natural antibiotic products has been picked, the scientific challenge has increased. Meanwhile, public and private parties have a limited economic incentive to invest in microbial research, as it is less commercially lucrative than other areas of disease (Plackett, 2020). This is partly because the newest antibiotics are typically included in national guidelines as a 'last resort' medicine.

In an attempt to slow the growing antimicrobial resistance, scientist are using innovative approaches for the discovery and development of novel classes of antimicrobials (see also Box 2.1), the repurposing of existing drugs and the identification of new innovative antimicrobial therapies. However, as with all drug development, once a new compound is identified it takes many more steps and much more time and money before the new agent can be used safely and effectively in people.

The development of new innovative treatments like advanced therapy medicinal products (ATMPs) that are based on genes, tissues or cells, offers ground-breaking clinical potential. ATMPs are very different to conventional medicines, often requiring complex manufacturing processes, orphan indications and tailored production (de Meij et al., 2019). This not only present new challenges (for instance, regarding cost-effectiveness and adaptations to the regulatory framework), but it also offers new opportunities for (academic) drug development. Many innovative therapies largely depend on scientific advances, the majority of which originate in academia (Bryans et al., 2019), such as small interfering RNA therapeutics (Hu et al., 2020) and CAR-T immunotherapy. The path from initial scientific discovery to therapeutic translation often involves multiple discoveries which coalesce to form

advance. While most academic activities advance the development of medicines indirectly, several academic (spin off) activities have directly result in new medicines (see, for example, boxes 1.2 and 3.1). The struggles and successes of these projects are outlined in this report to illustrate the major implications of innovation for drug development as well as the challenges faced by researchers, clinicians, industry, regulators and patients.

BOX 1.2 THE FIRST GLOBALLY LICENSED HUMAN GENE THERAPY

Lipoproteinelipase-deficiency (LPLD) is a rare genetic disease with a risk of potentially life-threatening pancreatitis. In 1986, Hayden and Kastelein identified the gene mutations that cause LPLD. Finding the genetic defect was the first step in a long scientific journey toward the innovative therapy to repair it: LPL-gene delivery via a viral vector. Building on previous scientific advances and in collaboration with scientists around the world, the proof of concept was established and the preclinical evidence on safety and efficacy was collected (Kastelein et al., 2013). To translate these discoveries into clinical application in patients, Kastelein co-founded Amsterdam Molecular Therapeutics (AMT) at the Academic Medical Centre in Amsterdam. In December 2009, four years after the drug was first used in humans in a clinical trial, the application for regulatory approval was submitted. However, the assessment process proved long and arduous due to: a lack of previous regulatory experience with this product class; the long product development time, during which science and specific regulatory requirements evolved; and the fact that LPLD is a very rare disease with a fluctuating clinical outcome (Melchiorri et al., 2013). In 2012, after a long period of regulatory uncertainty, Glybera® (alipogene tiparvovec) became the first globally licensed human gene therapy for LPLD patients. By the time both the European Medicines Agency (EMA)'s Committee for Advanced Therapies (CAT) and the EMA's Committee for Medicinal Products for Human Use (CHMP) advised the approval of the drug in Europe, AMT had gone bankrupt and its assets had been acquired by another company named uniQure. When the therapy finally went to market in 2015, it became infamous for its incredibly high price of a $1 million US for a single dose. The 'valued-based-pricing' drove up the price to an (at the time) unaffordable limit. A mere two-and-a half years later, the therapy was taken off the market when uniQure allowed its European marketing license to expire; not because it was not effective or unsafe, but because it was not profitable. Although worldwide, only thirty-one people have ever been treated with the therapy (most of whom for free in clinical trials), the scientific journey toward the first licensed gene therapy in the world opened doors for the new advanced therapies to come.

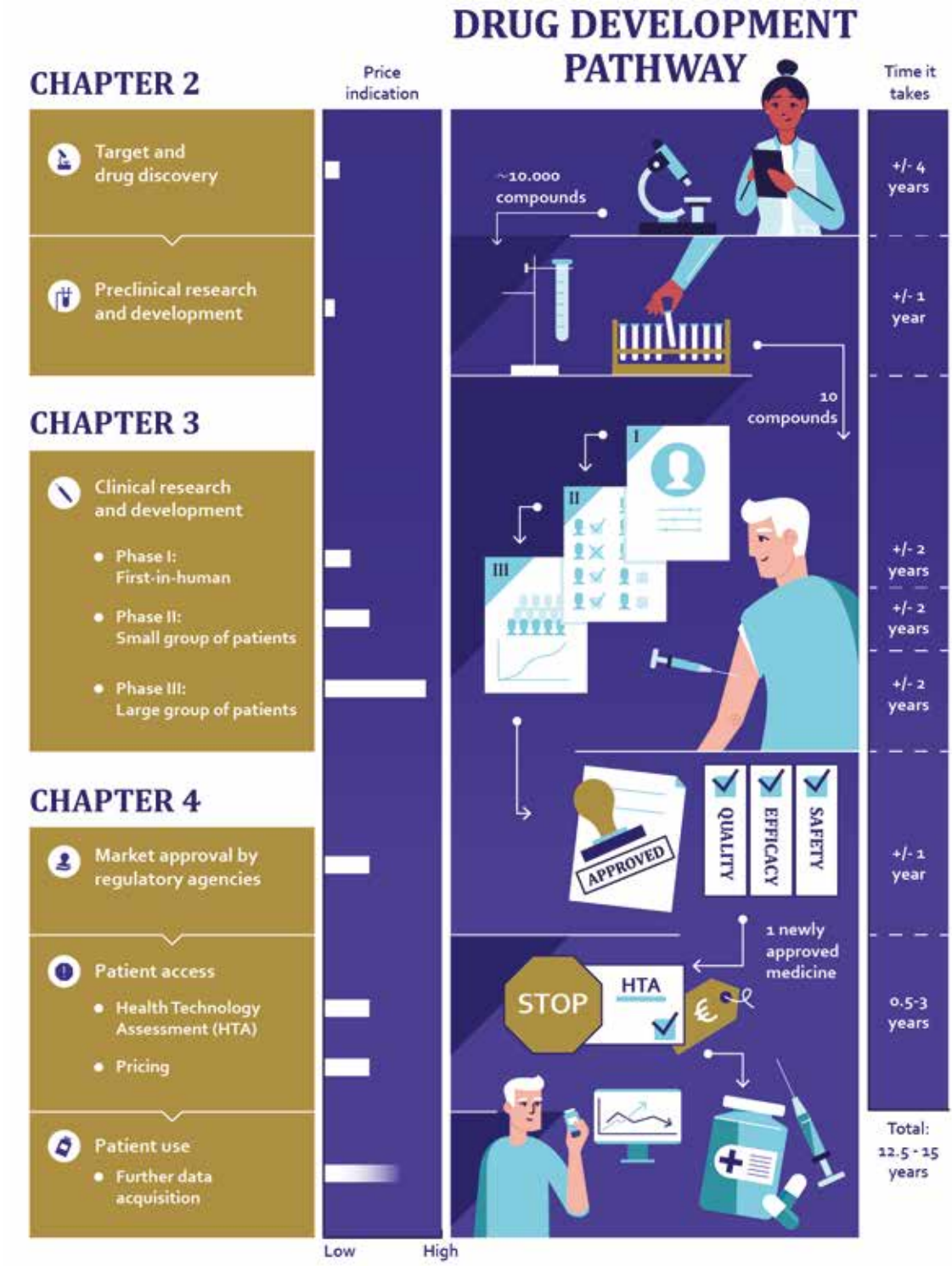

DRUG DEVELOPMENT PATHWAY
CHAPTER 2
Target and drug discovery
Preclinical research and development
CHAPTER 3
Clinical research and development
Phase I: First-in-human
Phase II: Small group of patients
Phase III: Large group of patients
CHAPTER 4
Market approval by regulatory agencies
Patient access
Health Technology Assessment (HTA)
Pricing
Patient use
Further data acquisition
Price indication
Low
High
~10.000 compounds
10 compounds
I
II
III
APPROVED
QUALITY
EFFICACY
SAFETY
1 newly approved medicine
STOP
HTA
Time it takes
+/- 4 years
+/- 1 year
+/- 2 years
+/- 2 years
+/- 2 years
+/- 1 year
0.5-3 years
Total: 12.5 - 15 years

Figure 1

1.2 Task

In February 2020, the board of the Royal Netherlands Academy of Arts and Sciences established the *Committee on the Development of New Medicines* (annex 1). The committee was tasked with inventorying the scientific techniques and methods that could contribute to more efficient development of new medicines and to issue recommendations for the further development of these techniques and methods. The committee was also asked to indicate the steps required to realise the techniques and methods indicated to gain efficiency in medicines development.

1.3 Scope of the report

Although much has been written in recent years on how to improve the process of medicines development (FAST, 2020; License to Heal, 2019; RVS, 2017), we still lack a comprehensive overview that describes the core scientific issues in the development trajectory for therapeutic medicines. Therefore, this report specifically focusses on the areas where science contributes to enhancing medicine R&D and making it more efficient without compromising the level of quality and adequate safety, efficacy and effectiveness. Illustrated by showcases, this report identifies where science is contributing to medical care and patient benefit and where hurdles can be expected or observed. While this report focusses on where specifically Dutch science and infrastructure can contribute, it also aims to provide internationally relevant insights as, clearly, advances in drug development are made in the international arena.

1.4 Outline of the report

The structure of the report follows the order of the traditional trajectory of the R&D process for medicines (see figure 1): from discovery and preclinical R&D (chapter 2), via clinical development (chapter 3) to patient access (chapter 4). It should be noted, however, that modern drug development is no longer a linear pipeline with closed segments from target discovery to patient access, but rather a collection of interconnected processes with iterative feedback loops. Critical go/no-go decisions must be made on a continuous basis: from discovery all the way to market approval. At each step, investments in time and money (and patient involvement during clinical development) simultaneously increase the value of the lead drug in terms of intellectual property and potential economic value. That is why it is essential, throughout the process, to have the best possible predictors of success or failure. This allows for the halting of useless development at an early stage and the avoidance of fruitless investments once success appears unlikely. But most importantly, it prevents patients from being unnecessarily exposed to agents that lack effect or present a risk. The sooner an ineffective or unsafe agent can be identified in the

process, the more money and time can be saved and subsequently invested for developing other candidates. Therefore, smart decision-making is key to efficient drug development. In chapters 2-4, we identify the scientific opportunities that may contribute to such smart decision-making in order to gain efficiency while retaining high quality and adequate safety.

Chapter 5 describes the conditions that enable efficiency gains by science. While scientific advances and technological innovations may greatly contribute to progress in the development of new medicines, this alone will not be sufficient to enhance medicine R&D efficiency. During the COVID-19 pandemic — with its major social, economic and health consequences — we have seen that 'the system' can be both efficient and inefficient when rapid progress is crucial. While vaccine development classically requires several years, several COVID-19 vaccines have been developed, tested, approved and applied within a single year. Indeed, vaccine development greatly benefitted from converging advances in biomedical, computing and engineering sciences, but the exceptionally rapid development has also been attributed to the fact that several other hurdles (related to approval, finances, data sharing, international collaboration and public private partnerships) could be successfully overcome. However, further systematic clinical evaluation is still lagging. For example, randomised comparisons between vaccination strategies, such as different time intervals between the first and the second dose, have yet to be performed.

In section 5.1, we underscore the importance of sustainable mutual partnerships among all parties involved (patients, academia, research institutes, (academic) medical centres, clinicians, pharmaceutical companies, regulatory agencies, government, etc.), throughout the entire trajectory of development. Although issues with respect to a defined drug development ecosystem are crucially important, these mainly fall outside the scope of this report since there already many excellent policy reports on these issues (FAST, 2020; License to Heal, 2019; RVS, 2017). Instead, we take 'a look in the mirror' and address (in section 5.2) the conditions *within* academia and the academic culture that will benefit efficient medicines development. We end the report by listing recommendations in chapter 6 on how the scientific opportunities addressed in previous chapters could be implemented by forming a coordinating expertise centre for medicines development.

1.5 Approach of the committee

For this report, the committee researched the literature and consulted a wide range of experts (see annex 2). In addition to core committee meetings, three online expert-meetings were organised for an in-depth understanding of the scientific opportunities present during the different phases of medicines development. During

these expert meetings, six to eight invited external experts gave talks, followed by round-table discussions. The expert meeting on 'Truly predictive models' was the basis for chapter 2 (see annex 3). Insights from the expert meeting on 'Clinical trials in the era of personalised medicines' provided the basis for chapter 3 (see annex 4). The discussions during the expert meeting on 'patient access' shaped chapter 4 (see annex 5). Members of the Medical, Biomedical and Health Sciences domain were invited to provide input on the draft report during a consultation meeting. The committee gratefully acknowledges the valuable input given by all of the experts during these meetings. The report was finalised after review of the draft by external reviewers, the Academy's Council for Medical Sciences and the Academy's Council for Natural Science and Engineering, the KNAW board and various stakeholders.

2. DISCOVERY AND PRECLINICAL RESEARCH AND DEVELOPMENT

2.1 Innovation in target and drug discovery; opportunities and bottlenecks

Drug development traditionally entails finding a small molecule or biological that interacts with a target in order to alter pathophysiological processes and thereby the course of disease. This requires a deep understanding of the causal role of a chosen target in human disease and of the consequences of modulating that target with a drug. Moreover, adequately estimating the potential of candidate drugs to modulate off-targets, often responsible for side effects, is crucial in developing a safe and effective therapeutic agent. In the traditional view, the drug development process starts with target discovery and target validation, followed by lead compound identification and optimisation. However, the traditional view of the drug development pathway which holds that it is a linear pipeline with a series of discrete steps is obsolete. Modern drug development entails a collection of interrelated processes with iterative feedback loops, meaning that the processes of target discovery, lead finding and understanding biology go hand-in-hand. This is evident, for example, in the chemical biology field (where approaches intrinsically rooted in chemistry are used to study fundamental biological processes), which is in close continuum with the field of medicinal chemistry (concerned with the design and synthesis of biologically active molecules).

Over the past decades, major developments in science and (bio)technology have revolutionised the initial steps in the medicine R&D trajectory by increasing both the number of investigational compounds as well as the number of biological

targets. Currently, next to the development of new drugs on the basis of the 'single target-single drug' concept, systems therapeutics, where the focus is on targeting biological networks rather than single transduction pathways, is also explored (Danhof et al., 2018). While it has led to important drugs in the past and largely shaped the traditional drug development trajectory, the 'one drug for one target for one disease' approach oversimplifies disease mechanisms and emphasises the control of isolated symptoms rather than modifying the disease mechanism. In fact, '*a disease is rarely a straightforward consequence of an abnormality in a single gene, but rather reflects the interplay of multiple molecular processes'* (Menche et al., 2015). Systems therapeutics aims to understand the larger picture, and it defines disease mechanisms as networks best targeted by multiple, additive- or synergistic drugs. The research into how drugs can have multiple interactions within a biological network can form the basis for new ground-breaking systems therapeutic interventions which can be: i) personalised, with respect to both the selection of the drug (or the combination of drugs) as well as the dose, ii) disease modifying (instead of modifying isolated symptoms) and iii) complex, based on a rational combinations of multiple drugs (Danhof, 2016). This field, which builds on major progress in genetics, cell- and molecular biology and computational modelling, strongly depends on academic research because claiming ownership on the usage of combinations of drugs is difficult and because it often involves drugs from different product owners. Further development of this field will require the earlier involvement of regulators to promote the conditions enabling the registration of combinational treatments, which may offer new challenges, such as those related to adverse effects and their accumulation.

2.1.1 The power of numbers: innovation provides a wealth of methods, biobanks and databases

Advances in chemical and structural biology as well as computational modelling benefit model-based compound development that uses a rational approach. Furthermore, our knowledge of potential molecular targets for intervention greatly benefits from genomic sequencing techniques, where major progress has been made in terms of speed, throughput and cost (Goodwin et al., 2016). One human genome can now be entirely sequenced within a single day. Lead discovery greatly benefits from advances in combinatorial chemistry, i.e. the technologies based on synthesising numerous drug-like molecules rapidly at small scale in small reaction cells. This enables the generation of large chemical libraries that can be tested for their potential.

High-throughput screening (HTS) allows testing of these compounds for interaction with biological targets thanks to advances in robotics, miniaturised assay development and large-scale data analysis. Since its advent in the early 1990's, HTS has greatly contributed to lead discovery. However, while current HTS readout technologies cover most conventional drug targets (e.g. enzymes,

nuclear hormone receptors, G-protein coupled receptors and some ion channels), it remains challenging to approach other promising drug target classes (e.g. most ion channels, transporters, transmembrane receptors, protein-protein, protein-DNA and protein-RNA interactions) (Mayer & Fuerst, 2008). Therefore, further development of readout technologies and adequate chemical libraries for these new and more difficult target classes will open new avenues for drug development.

A celebrated example of a joint approach that is driving precompetitive drug discovery and target validation is The European Lead factory, which was established in 2013 (Besnard et al., 2015). In this (originally Dutch) initiative, eight members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) decided to make their heavily safe-guarded compound libraries freely available for the European research community and each other. Over 300,000 lead-like compounds were collected. In addition, nearly 200,000 novel compounds were synthesised by the Public Chemistry Consortium, based on design proposals from European academic groups and small- and medium-sized enterprises. To date, the compound library of the European Lead Factory contains over 500,000 unique compounds that can be used for screening.

Thus major scientific advances in recent decades have yielded an enormous amount of valuable data. However, many of these technologies have not yet lived up to initial expectations on how they would enhance medicine R&D efficiency by adequately filling the pipeline. After the quantitative increase, scientists are now shifting their focus on the 'qualitative increase'.

Technology platforms and comprehensive open-access software tools can be helpful to integrate, visualise and interpret the wealth of available data. An example of a (non-exhaustive) list of such tools developed to help scientists is the catalogue on the website of the Innovative Medicines Initiative (IMI). Other examples include the Open Targets Validation Platform (target validation.org, developed to aid drug target identification and prioritisation (Carvalho-Silva et al., 2019) and CellminerCBG (which combines an enormous amount of pharmacological, genomic and molecular data obtained from experiments in patient-derived cancer cell-lines (Luna et al., 2020). Although such tools and datamining techniques enable optimal usage of the numerous biological and chemical databases available, it remains increasingly challenging for researchers to select appropriate resources from hundreds of databases and various software tools. This highlights the growing importance for chemistry and biology researchers to closely collaborate with bioinformaticians, cheminformaticians and computer scientists, as well as the need for interdisciplinary training. Though critical for success, technology platforms are very difficult to maintain in a sustainable way with project-based (short-term) funding. Therefore, long-term investments to organise and maintain such platforms are necessary. In addition, professional knowledge from technology transfer experts should be

available in academia to ensure adequate patenting and protection of scientist's discoveries.

2.1.2 New techniques and methods to bolster creative thinking

Advances in technology (e.g. 'omics' approaches, 3D modelling, artificial intelligence, data-mining and synthetic biology) have led to new screening methods to find lead candidates more rapidly, reliably and cheaply. For example, artificial intelligence (AI) tools (e.g. machine learning and deep learning tools) have been developed to predict the 3D structure of proteins based on their amino acid sequence (Tunyasuvunakool et al., 2021), leading to an open access protein structure database (https://alphafold.ebi.ac.uk/) with great potential for drug development. AI tools have also been developed to identify potential biologically active molecules from collections containing millions of candidates and predict their properties. The success of such predictive approaches is illustrated by the recent discovery of new antibiotic compounds using AI (see box 2.1).

BOX 2.1 HALICIN

Researchers trained a deep neural network (i.e. an AI algorithm inspired by the brain's architecture) on a set of 2,335 molecules with known antibacterial activity to predict which molecules have antibacterial properties, based purely on their structure and without any assumptions about how drugs work. When the programme subsequently screened multiple online chemical libraries (a pool of more than 100 million molecules), it identified several new antibacterial compounds that were structurally different from known antibiotics. From the Drug Repurposing Hub, a database with 6,000 molecules, it identified a molecule that was under investigation for the treatment of diabetes, as a potent antibiotic. The drug, subsequently named halicin (after HAL, the intelligent computer in the film *2001: A Space Odyssey),* has a structure and mechanism of action that is different from conventional antibiotics, but animal testing revealed that it is effective against a wide range of bacteria, including strains considered untreatable (Stokes et al., 2020). Halicin is the first antibiotic to be identified from scratch by AI.

The Halicin example illustrates the great potential of machine learning for repurposing, i.e. finding new applications for existing drugs, discontinued or shelved compounds and candidates under development. In the past, repurposing often emerged from serendipitous findings or it was based on known off-target effects (the most well-known example is sildenafil citrate (Viagra®), a common hypertension drug repurposed as a therapy for erectile dysfunction). Nowadays, advances in chemoinformatics, bioinformatics, network biology and systems biology have enabled organised, systematic, data-driven drug repurposing approaches that involve computational modelling. The relevance of repurposing has gained momentum in recent years because it can lead to lower overall development costs and shorter

development timelines since the new indication is based on prior knowledge (Pushpakom et al., 2019). While working with such de-risked compounds enables some of the initial phases of drug development to be bypassed, drug *re*discovery still requires the proof of concept that an existing drug can be successful for a new indication. This type of research should be encouraged for obvious reasons, and it requires effort to overcome challenges regarding patentability and market exclusivity and the regulatory hurdles related to building the evidence base for the synergistic action of medicines and problems with data and compound accessibility (Talevi & Bellera, 2020).

To return to Halicin; this showcase indicates that new technologies can help us think 'outside the box' during the process of lead discovery and to make better predictions about chemical properties based on patterns that are new to human experts. This has enormous potential considering that, in a standard drug discovery project, 10-100 small molecules are made; while it is estimated that the massive number of 10^{33}-10^{60} drug-like molecules could exist. Due to its sheer size, it is impossible to explore this chemical space using conventional chemical techniques, hence there is a need to accelerate this process using new technology. Deep-learning approaches can be used to investigate and characterise the unknown 'chemical space' and identify new candidate drug molecules (that have not been previously imagined or made, see Liu et al, 2021).

While our report describes AI's potential benefits during the process of lead discovery, it should be noted that AI applications are gaining importance in every phase of the R&D trajectory and that its potentials (and restrictions) are not limited solely to the preclinical phase. Currently, three bottlenecks hamper the large-scale implementation of AI. The first bottleneck is the limited synthetic accessibility of novel compounds designed by deep-learning algorithms. While steps have been taken to allow machine learning to determine synthetic routes (Segler et al., 2018), the data required to train these models remain inaccessible and at the discretion of Elsevier and the American Chemical Society. The second difficulty is scientific in nature and involves the interpretability of deep-learning models (Baskin, 2020). Without being able to interpret and understand algorithmic decisions and recommendations, these models end up operating as a black box. This makes it difficult to use these algorithms to direct scientists in the medicinal chemistry process and to rationalise why certain predictions are wrong. The third bottleneck is linked to this because algorithmic accuracy depends on the types of data being analysed. When data are similar to the information used to train the algorithm, they typically perform well. But when data look very different, the predictions may be less accurate. While various techniques aim to address this challenge, they can only provide a rough estimation.

The inability to understand and prevent erroneous predictions forms a bottleneck in applying these methods. A problem that is aggravated when multiple modelling techniques are combined, e.g. artificial-intelligence based design, bioactivity prediction and computational pharmacokinetic modelling. Hence it is urgent to gain a better idea of the prediction errors and the potential occurrence of compounding errors in AI models (Burggraaf et al., 2020.). In this area, medicinal chemistry and drug discovery can learn from informatics and computer science (where methods have been developed to overcome these problems, e.g. by models that estimate the uncertainty of their own predictions). Strengthening collaboration between these fields may provide even better innovative bioinformatic and cheminformatic approaches that form powerful tools to generate the right hypothesis. As is often said in the field: *'AI will never replace medicinal chemists, but medicinal chemists using AI may eventually replace the ones that do not.'*

2.1.3 Drug formulation and delivery

Equally important to identifying a lead candidate is the subsequent testing needed to confirm its 'drug-like properties'. Not every chemical can be used to produce a good drug that is 'deliverable' to the patient at the disease site in the correct dose. Patients often prefer intranasal, oral or dermal routes over intramuscular or venous injection; however, in all cases reformulation may be required to ensure the drug can bind to its target in the body. Important considerations include ensuring adequate bioactivity, selecting physical-chemical structures that can be feasibly synthesised and that can cross cell membranes and account for individual differences in metabolism. In other words, the compound should be 'developable' in an appropriate form with acceptable pharmacokinetics. This requires research into the mechanisms underlying the pharmacokinetics (including deep understanding of, for example, membrane passage, transporter function and metabolic enzyme activity). In this respect, the method of drug delivery is also important. In certain instances, administering drugs locally rather than systemically can decrease toxicity while maximising efficacy. This can be as simple as dermal application of antibacterial cream at local infection sites and as advanced as nanoparticles targeting tumour cells. In recent years, major advances in bioengineering have produced new delivery systems that allow drugs to be targeted to specific body parts and for the controlled release of therapeutic agents. Therefore, research on drug formulation and drug delivery systems, including the science focussing on routes of delivery, delivery vehicles, cargo, and targeting strategies, is key to innovative medicines development.

2.2 How science can contribute to improving the predictive value of preclinical models

2.2.1 Why do we need preclinical models?

After *in vitro* testing, promising substances are moved into preclinical studies where the activity, bio-distribution, pharmacokinetics, toxicity and safety (e.g. its effects on vital organs and whether it impacts the reproductive system) are tested in animal models.

Why are all these steps necessary? Strict regulatory standards for drug testing exist to protect patients against ineffective or unsafe drugs. We have learned harsh lessons from mistakes in the past, such as the thalidomide disaster; one of largest man-made medical disasters in history (see box 2.2).

BOX 2.2 THALIDOMIDE DISASTER

The tranquiliser thalidomide (known as Softenon in Europe) was introduced in 1957 by the German company Chemie-Grünenthal. The sedative was soon found to be effective against morning sickness in early pregnancy. It was advertised as being entirely safe and used by pregnant women in 46 different countries. However, by 1961 it had become clear that thalidomide use in pregnant women caused severe birth defects in over 10,000 children and an unknown number of miscarriages (Vargesson, 2009). The drug was taken off the market in 1962. Nowadays, under strict and carefully controlled guidelines, thalidomide and various thalidomide analogues are being used as standard of care drugs in the treatment of diseases like leprosy, multiple myeloma, HIV, Hereditary Haemorrhagic Telangiectasia and Crohn's disease.

The thalidomide disaster demonstrated, for the first time, differences between species in the response to drugs. Mice, traditionally used to screen for drug action, turn out to be less sensitive to thalidomide than other species such as non-human primates and chicken. This insight resulted in modification of the regulatory standards, which now require that each drug candidate must undergo *in vitro* testing and preclinical trials in two different animal species before being admitted to human clinical trials. Yet, even when this raises no safety concerns and confirms that the drug is effective at reducing signs of the disease, the costly and time-consuming phase of animal testing cannot guarantee clinical success. The predictability of animal models for some human diseases is very limited. Even if the full spectrum of animal tests is encouraging, the drug might fail to be effective in humans due to physiological differences between species and limitations in test availability and feasibility (or the other way around: see box 2.3 for an example that demonstrates how preclinical experiments might not predict true risk in human clinical practice).

BOX 2.3 FILGOTINIB

The story of filgotinib shows how rules created to protect the safety of patients might potentially defeat their purpose. Filgotinib (brand name *Jyseleca*) is an orally administered preferential JAK1 inhibitor, developed by Galapagos and Gilead to treat rheumatoid arthritis (and other immune-inflammatory diseases).

In preclinical efficacy studies in a rodent arthritis model, the drug was shown to reduce disease progression. In addition, the toxicological profile of filgotinib was evaluated in non-clinical studies in accordance with relevant guidelines. Five phase II trials confirmed its efficacy in humans. Subsequent large clinical trials showed that the drug was effective at improving signs and symptoms of rheumatoid arthritis vs. placebo or adalimumab in patients with moderate or severe rheumatoid arthritis, as well as patients resistant to other therapies. While the benefit-risk profile was assessed positive by EMA's Committee for Medicinal Products for Human Use (CHMP), in August 2020 the FDA issued a Complete Response Letter (CRL) indicating that, at this time, they considered the available data insufficient for approval of filgotinib for rheumatoid arthritis. Specifically, as a consequence of preclinical effects in animal studies that showed that high doses of filgotinib affected spermatogenesis, the production of sperm cells and fertility in male animals(with evidence of reversibility), the FDA requested to see the completed MANTA and MANTA RAy human studies designed to assess whether filgotinib has an impact on semen parameters.

Many rheumatoid arthritis patients in the US not responding well to existing therapies could benefit from filgotinib, since around 70% of the patients with rheumatoid arthritis are women.

The FDA also expressed concerns regarding the overall benefit-risk profile of the 200mg dose. In Europe and Japan, however, marketing approval was received in September 2020 for both 100 and 200 mg filgotinib, based on a benefit-risk profile that was considered positive by both agencies, demonstrating the limited uniformity between regulatory bodies. This example ultimately shows how evaluations by different regulatory agencies can lead to different decision, and how these can impact patients. Other examples involving treatments for rheumatoid arthritis patients have occurred in the past.

While we focus on minimising the chance of making a 'type I error' of approving drugs that are ineffective or unsafe (e.g. thalidomide), we increase the likelihood of making the opposite 'type II error' of *not* approving drugs that are effective and safe for a specific patient group. Type II errors deny patients and doctors access to effective treatment options and stall the drug development process.

For regulatory authorities, the challenging task is to carefully evaluate the potential benefit-risk ratio based on available knowledge. The better our understanding of a drug's mechanisms of action and the higher the predictive value of our models, the more type I and type II errors can be prevented. Unfortunately, the predictive

value of our current models is too low to guarantee therapeutic efficacy and safety in human reality. This '*absence of non-clinical models with good predictive properties is considered the greatest hurdle for efficient drug development within the foreseeable future*' (EMA, guideline on the clinical evaluation of anti-cancer medicinal products, 2020).

2.2.2 Different preclinical models for different questions

The development and validation of high-quality predictive preclinical models remains a great scientific challenge as a model remains a model, and it might not capture all aspects of clinical reality. Therefore, various types of models are required to answer a range of questions.

Although policymakers have high ambitions regarding the minimisation of animal research, for the time being, animal models are still indispensable when we lack integrative replacement models to study complex bodily functions (e.g. organ-organ interactions and systemic responses), and to study effects of whole-body treatments like radiation. In addition, they remain necessary for *in vivo* imaging of organs and tissues and monitoring the bio=distribution of drugs and chemicals. Given that organs do not function in isolation but rather in interaction with other body systems and the environment, only a living organism as a whole can provide answers to certain biomedical questions that currently cannot be addressed in other model systems (Genzel et al., 2020; KNAW, 2019). It is important to note that regulators may also insist on specific sets of animal experiments before new molecular entities (NMEs) are approved for clinical trials.

Established animal models have the advantage that detailed descriptions of their development, physiology and species-specific databases (genetic, histological) are available. This is often crucial for obtaining insight into pathophysiology and disease mechanisms. However, for certain genetic and lifestyle conditions, there are no good animal models available. Most importantly, experience has shown that many targets that seem promising in early animal and *in vitro* studies fail to translate to the clinic. New innovations offer methods that could make preclinical testing more predictive. For example, human stem cells are just one out of the several options that could be used. Human stem-cell models might predict whether a drug really affects healthy or diseased human cells, albeit under very simplified conditions (see box 2.4 for an example).

BOX 2.4 ORGANOIDS INFORMING THE CLINIC

During the COVID-19 epidemic the antimalarial drug chloroquine was tested in (expensive) clinical trials because *in vitro* studies had shown that the drug abolished replication of the SARS-CoV2 virus in VERO E6 cell lines (Liu et al., 2020). Immortalised VERO cell lines, derived from African Green monkey kidney, are commonly used in research and extensively used in virology. However, in clinical testing, chloroquine turned out to be ineffective in patients (Pathak et al., 2020). The reason was that, in VERO cells, SARS-CoV2 virus particles enter through chloroquine-sensitive endocytosis, but they enter the primary epithelial cells in patients through membrane fusion, which is a chloroquine-insensitive process. Here, preclinical testing in a human organoid system (e.g. adult human intestinal organoids (Lamers et al., 2020)) rather than a single cell line could have predicted the clinical failure and prevented the conduction of the clinical studies.

We can now produce many of the approximately 200 types of body cells from stem cells. Human pluripotent stem cells can be used to form all the cells of the body. Adult stem cells, derived from biopsies from certain organs, can form what we call 'organoids, the 'epithelial' component of the organ (e.g. the cells lining the intestine or lung) grown as spheroids in suspension culture. Currently, many of these cell types can be created from any individual (as organoids from adult tissue or as induced pluripotent cells if derived by 'reprogramming' normal cells of the body). These can be used in laboratory assays directly or as more realistic models of the human body in three-dimensional 'suspension cultures' or in organs-on-chip where the physical environment resembles that of the body and sensors can be integrated for online monitoring (Low et al., 2021). In contrast with organoids, organs-on-chip can contain microfluidic channels through which liquid can flow, for example, to mimic blood or lymphatic vessels in tissues. Early organs-on-chip contained cells collected from human biopsies (e.g. liver), fluid collected from lung (lung epithelium for lung-on-chip) and blood vessel cells like those from umbilical veins (known as HUVECs). More recently, human stem cells have been used since they are immortal, do not run out and they have minimal batch-to-batch variability while capturing donor and disease differences. We can use them as a source of cells for organ-on-chip models essentially indefinitely without needing new donor tissue.

Human stem-cell models may contribute to precision medicine since they can be derived from different ethnic groups and sexes, even from specific families and individuals. These models can form informative tools for selecting *the right drug for the right patient* (see box 2.5 for an example).

BOX 2.5 A FUNCTIONAL READOUT IN HUMAN ORGANOIDS TO SELECT THE *RIGHT* DRUG FOR THE *RIGHT* PATIENT

Cystic Fibrosis is a severe, progressive, genetic disease caused by a mutation in the *CFTR* gene. Over 1900 genetic subtypes of cystic fibrosis exist, which all relate to a defect (e.g. a decrease, misfolding or dysfunction) of the CFTR protein. This affects multiple systems, including the lungs and the gastrointestinal tract, where the accumulation of mucus causes bacterial infections, inflammation and malnutrition. The median life expectancy of patients is approximately forty years.

Most current therapies for cystic fibrosis focus on reducing symptoms, while more recently, drugs that restore the function of mutant CFTR proteins have been developed. However, those CFTR-modulating drugs (that focus on the most prevalent genotypes) are very costly and are not equally effective in different individuals. Currently, the indication of these drug relates to the genotype, while drug responses largely depend on how the *function* of the protein is affected. However, as long as the genotype is on the drug label, the drug will also be prescribed to patients who will not be responsive in clinical practice. Changing this will require that regulatory authorities consider allocating drugs based on the *function* of the protein rather than on genetics. This would mean that it is important to use functional tests in the preclinical stage.

A relatively simple functional assay in human intestinal organoids has been developed, based on the principle that forskolin induces rapid swelling of organoids derived from healthy controls but not in organoids of subjects who have cystic fibrosis (Dekkers et al., 2013). This offers a functional read-out that facilitates drug screening and development and personalised medicine use for cystic fibrosis patients. For example, the assay allows screening of large compound libraries in patients who have rare mutations. It also allows testing combinations of compounds (in different combinations and/or doses). This is impossible to test in patients and will likely not be done by the pharmaceutical industry (since it most frequently involves different product owners).

Using patient-based organoid models, it may be possible to predict the clinical outcome in specific patients, thus facilitating the development of personalised or precision medicine. In addition, such models may facilitate the selection of those patients who are at risk and will benefit most from the treatment. In conclusion, both animal-based and cell-based models have their place in biomedical research, depending on the question that is being asked. Continuous improvement of our models is required to improve their predictive value for therapeutic efficacy and safety in human reality.

2.3 Stimulating timely dialogue with regulators

The Netherlands is at the forefront in the development of these and other innovative models. To further encourage a productive climate where new models with a higher predictive value are implemented, the focus should lie not only on the development of new models but also on the validation and qualification required to allow the actual use of these new assays and/or models to gather evidence on efficacy and safety. Scientists are very well-equipped to initiate this dialogue, see box 2.6 for an example.

BOX 2.6 DRUG-INDUCED QT PROLONGATION

Certain drugs or drug-drug interactions can cause an electrical disturbance of the heart, where the heart needs more time than normal to 'recharge' between two beats. This so-called 'drug-induced QTc prolongation', visible on an electrocardiogram (ECG), is one of the most notorious adverse drug reactions as it may lead to cardiac arrhythmias and sudden cardiac death.

Therefore, assessing the risk of QT prolongation is an important aspect of drug safety testing. For this reason, two regulatory documents were implemented in 2005: the ICH S7B document (describing two nonclinical assays) and the ICH E14 guideline (describing the protocol for clinical QT assessment). However, integration of the clinical and nonclinical data was often lacking. Nonclinical data may steer strategies for clinical studies and it has additional value for assessing the risk of QT prolongation in case of limited clinical evaluations. For example, during the development of anticancer drugs for which the administration of the drug in healthy volunteers is unacceptable, or in a situation where a placebo-controlled comparison is not possible. Even so, regulatory authorities require appropriate assessment of the risk of QT prolongation.

Scientists contributed significantly to the dialogue with the ICH in order to meaningfully merge clinical and nonclinical data to enable a more comprehensive, but flexible, clinical risk assessment strategy for QTc monitoring, as described in the updated ICH E14 Questions and Answers (see ICH 'E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential—Questions and Answers'). Modifications were possible thanks to the careful investigation of alternatives for the design, conduct, analysis and interpretation of QT studies, which benefits both the quality of the data and the timeliness of the drug development process.

Implementing these models requires regulatory considerations and adjustments regarding their usage for predictive safety pharmacology and/or disease modelling. Because, as long as the traditional animal-based assays remain the standard, these new models will only be used in addition to what is currently required. Therefore, scientists should proactively disseminate the possibilities of newly developed assays for toxicity and efficacy assessment and to explain how the outcome variables may

be interpreted and compared to existing models. The question as to how to qualify these models needs to be addressed through dialogue with regulators. This may necessitate reference compound lists with known effects in humans, to be agreed upon with the regulatory authorities that validate or qualify the *in vitro* assay by giving the expected outcome (de Korte et al., 2020). In addition, it requires the standardisation of assays, which stand to benefit from open technology platforms that allow for rapid exchanges between research groups and pharma or biotech.

Scientific insights into the mechanisms underlying diseases could also be a starting point to address (and possibly reconsider) the indication of specific drugs (see box 2.5 for an example in cystic fibrosis). For these changes to be implemented in the medicines development pathway, fostering the dialogue between fundamental and clinical scientists, pharma, patient advocates and (importantly) regulators remains key (see also chapter 5). This could be achieved by bundling forces in a coordinating expertise centre for medicines development that is tasked with stimulating collaborations and guiding decision-making in order to boost the development, validation and implementation of new methods and models to test preclinical efficacy and safety and to stimulate the development of regulatory science as an academic discipline.

3. CLINICAL RESEARCH AND DEVELOPMENT

3.1 The challenges

Internationally and within regulatory agencies, (academic) clinical trial activity is considered one of the most sensitive indicators for progress in medicines research. In the Netherlands, drug-development related trial activity has been relatively stable over the past four years, albeit relatively low compared to other European countries like Belgium, Denmark and France (CCMO, 2020; https://clinicaltrials.gov). Fuelling this activity, which may entail structuring our UMCs into the collaborative clinical organisations required to conduct large phase III trials, could drive the activity in medicines research in its totality.

3.1.1 Wasted efforts in science

Once preclinical studies have indicated that a candidate therapy is safe and feasible for humans, phase I clinical trials are conducted. Phase I, or 'first-in-human' studies, form the bridge from preclinical and clinical research. The aim of this early-stage clinical drug research is to obtain as much information as possible on the action of the drug in a human being, including the safety (pharmacovigilance), tolerability, pharmacokinetics and pharmacodynamics. Each new compound presents unique challenges. Therefore, for phase I to be as informative as possible often requires innovative methods. And academia greatly contributes to these innovations (e.g. in the Centre for Human Drug Research in Leiden, the Netherlands). The transition success rate between phase I and phase II is roughly 60% (Thomas et al., 2016).

Once the safety of a drug — acceptable percentages of unintended effects — in humans has been confirmed and information on how it acts in humans has been collected, phase II clinical trials are conducted to demonstrate the potential intended effects in a typically small group of patients (single arm study). The candidate drug therapy might indeed work in a small group of patients. However, phase II trials have a transition success rate of approximately 30% (Thomas et al., 2016).Even if a candidate drug therapy enters a large phase III study, there may be no significant difference in the intended effects (as compared to a randomised control group that did not receive the drug, but a placebo or the standard of care) due to a dilution of the treatment effect. Roughly half of the candidate drugs entering late-stage clinical development fail during or after late-stage clinical development (Hwang et al., 2016). While modern drug development is often no longer a linear pipeline with closed segments and strictly sequential phases, referring to the transition success rates in the traditional phase I, II or III settings helps illustrate the inefficiency of the process. Indeed, only around 10% of candidate drug therapies that enter clinical phases end up being approved by regulatory agencies; an incredible amount of effort (from researchers and participants), money and time is lost. What can be done to avoid this wasted effort in science?

3.1.2 Clinical applicability

Clearly, clinical phase I, II and III studies are crucial and necessary for evidence on the safety and efficacy or effectiveness of a medicine in humans, and they are required for registration. Randomised and placebo-controlled trials still leave room for uncertainty about the benefits of the treatment when applied in daily practice. The long-term effects of a medicine are typically not available from trials at the point of marketing authorisation, and more subjective (but certainly patient relevant) outcomes such as health-related quality of life, may not always have been taken into account. To assess the burden of disease and its treatment from a patient perspective, patient reported outcome measures (PROMs) can be powerful tools to help guide clinical decision-making. Quality research on the development and validation of generic as well as disease-specific patient-reported outcome instruments may further encourage the integration of PROMs into clinical trials.

Strict inclusion criteria typically hamper extrapolation of the study results and expected effects of the drug when applied to the average patients encountered and treated in daily practise. In addition, average (marginal) or group-related effects complicate decision-making on how much an individual patient will benefit from a specific treatment. Treatments will not be equally effective in all patients, particularly if the disease is heterogeneous. In addition, randomised trials may focus on finding statistically different effects in intermediate outcomes that may not translate into clinically relevant effect differences. In other words: a ‘statistically significant’ difference is not necessarily a ‘clinically meaningful’ difference (see section 3.2.1).

3.1.3 Fragmentation of patient populations

Innovations in medicine often present a new set of challenges. Advanced insight into the mechanisms that underlie a disease and its progression and the effects of genes, environment and lifestyle result in increased disease subtyping and classification. In cancer, for instance, there is growing evidence that similar genetic mutations may be driving different types of cancers. Consequently, a drug focused on a specific genetic change may have similar (intended and unintended) effects in different cancers. This has led to the so-called tumour agnostic treatment of cancer, which implies the use of drugs that are active against specific molecular alterations that can be identified by genomic characterisation of the tumour. However, as genomic tools stratify disease, 'common' diseases segregate into many rarer ones.

A consequence of the increased disease subtyping is that modern drug development by necessity tends to focus on rare diseases. While this results in more targeted and patient-oriented approaches, it also results in smaller patient groups for which a specific treatment is being developed, thereby limiting its applicability to wider patient groups. This not only has consequences for profitability, it also challenges traditional clinical study designs. As each subgroup requires a separate trial, many more trials are needed in totality. Furthermore, more time is required to recruit the necessary number of trial subjects as the subgroup is smaller than the total patient population. Therefore, providing evidence on effectiveness has become increasingly challenging with the arrival of orphan and agnostic indications, complex diseases and personalised medicines.

3.2 Clinical study design

3.2.1 Standardisation of clinical endpoints and a focus on minimal clinically relevant outcomes

The main objective of phase III trials is to verify the therapeutic action of a new substance in a large number of patients, essentially to obtain the benefit-risk estimation required for market approval. However, in practice, the evidence needed to obtain market approval is often not sufficient to inform patients and health-care providers on whether or not a certain treatment will benefit a specific patient (see also section 4.1). This knowledge requires data on clinically and patient-relevant information, such as: conditions for monitoring treatment, dosing, the duration of treatment, modalities for discontinuing treatment and interactions with other drugs. These measures do not constitute an intrinsic part of trials.

The more frequently a disease has a serious outcome (high incidence), the easier it is to show an effect of treatment to reduce the occurrence of this outcome (see box 3.1). In case of rare and/or life-long progressive diseases or diseases with a remitting

course or preventive treatments, however, this can be much more challenging. The size and duration of a randomised clinical trial (RCT) depends on: i) the incidence of the disease in the general population; ii) the incidence of the targeted outcomes in patients and iii) the effectiveness of the medicine (see 3.1).

BOX 3.1 DEMONSTRATING AN EFFECT OF TREATMENT IN POMPE DISEASE.

Pompe disease (or glycogen storage disease type II) is a rare, progressive metabolic disorder that was first described in 1932 by the Dutch pathologist J.C. Pompe. The disease, caused by a deficiency of the lysosomal enzyme acid α-glucosidase, which results in the progressive intracellular build-up of glycogen, has a broad clinical spectrum dominated by skeletal muscle weakness. At the most severe end of the spectrum are patients with the classic-infantile form of Pompe disease (all of whom die within the first year of life). For patients who have the late-onset form of the disease, symptoms first appear in infancy, childhood or (early) adulthood.

Until the approval of enzyme replacement therapy (ERT) in 2006, there was no treatment available to stop the progression of this disease. The Dutch paediatrician Ans van der Ploeg at the Erasmus Medical Centre has been involved in the steps that ultimately led to the development of the therapy: from gene cloning to biotechnological production of recombinant human alpha-glucosidase in the milk of transgenic mice and rabbits and, in CHO cells; from the development of a knock-out model for Pompe disease; feasibility studies in mice to = the first clinical trial in infants, and finally the international multicentre placebo controlled trial that demonstrated the effects of therapy in adults (van der Ploeg & Reuser, 2008). This is a true success story of academic drug development all the way from scientific discovery to marketing approval (and the ongoing long-term follow-up studies). Small-scale interdisciplinary collaborations (involving patient organisations) were also key to this accomplishment. However, the substantial costs of the therapy showcase the need for an intense debate on fair pricing.

The showcase of ERT in Pompe disease also illustrates how the incidence of the targeted outcomes defines the sample size necessary to show the treatment effect. While all patients with the infantile form of Pompe disease die within the first year of life, the survival of patients with late onset Pompe disease greatly varies. This means that it is much more difficult to show a treatment effect on survival in patients with late onset Pompe disease as compared to patients with the infantile form; it requires a much larger study patient group and follow-up over a longer period of time. Moreover, for patients, other outcomes besides survival (e.g. effects on muscle strength, pulmonary function and daily life activities) are central to their quality of life. To determine the clinically meaningful effects of a new drug treatment, standardised tools to measure these outcomes should be used. In this case, the R-Pact score has been specifically developed to measure the effects of ERT in patients with adult-onset Pompe. Such standardised tools require insight into the course of the disease (i.e. an understanding of what would have been the outcome without treatment).

RCTs are most interpretable when they focus on so-called' 'objective' and 'hard' endpoints (e.g. overall survival in cancer). But where this is inappropriate, so-called surrogate endpoints might (temporarily) offer a solution. These endpoints might be more subjective, but they can certainly be relevant to patients. If this is done in, for example cancer research, it is still important to illustrate a strong causal relationship between the surrogate intermediate and the subsequent hard endpoints. For instance, scientists have assessed the clinical benefit of ninety-three cancer drugs that received accelerated FDA approval between December 1992 and May 2017 (see Gyawali et al, 2019). In the accelerated pathway, approval could be obtained by demonstrating an effect on a surrogate endpoint (or intermediate clinical endpoint) that was considered 'reasonably likely' to predict a real clinical endpoint. Confirmatory (post-approval) trials for nineteen out of ninety-three indications (20%) reported improvement in overall survival, twenty (21%) reported improvement in a different surrogate endpoint than the one used in the preapproval trials and nineteen (20%) reported improvement in the same surrogate endpoint used in the preapproval trials. Thus, after confirmatory trials, relatively few cancer drugs approved via the accelerated pathway were shown to have verified benefits.

What are the opportunities for science? Firstly, validation of surrogate endpoints that can be extrapolated to other study settings is needed. Secondly, standardisation of endpoints (long-term hard, objective outcomes as well as shorter term surrogate or subjective endpoints) will aid in the interpretability of RCT data. Thirdly, insight into the natural course of disease is crucial for clear definitions of endpoints. This requires collection and understanding of (standardised) high-quality data on the natural course of disease. While such data collection is not strictly related to pharmaceutical development, it deserves a central place in this chapter because it provides the necessary foundation for good RCT designs. Measuring whether a drug therapy alters the natural course of disease and making informed decisions on patient relevant effects requires knowledge about the clinical picture without treatment or (when no treatment is unethical) with the current, standard care treatment. Here, the development of mathematical models for data integration is key. Fourthly, attention should be paid to developing methods to measure outcomes in a way that is as standardised possible and to defining the minimally patient or clinically relevant difference. Especially for certain (rare) progressive diseases (e.g. ALS), meaningful treatment effects include not only reverting symptoms, but also function retention. Fifthly, research into finding early markers for response (biomarkers that indicate if a treatment is effective) and research investigating prognostic or predictive factors for treatment success can help with selecting the right patient for the right treatment (Riley et al., 2013; Steyerberg et al., 2013; Hingorani et al., 2013). Lastly, actively seeking scientific advice from the EMA or the CBG prior to trial design and early interaction with HTA and patient organisations will help with the selection and acceptance of the most important endpoints.

3.2.3 Novel trial designs

A randomised, double-blinded and placebo-controlled trial is the standard to demonstrate the efficacy and effectiveness of a drug. The advantages of this design are that:

i) the randomisation makes groups, according to expectations, comparable according to known and unknown prognostic and predictive factors;
ii) study procedures are performed prospectively, at regular time points;
iii) subjective interpretation by patients, researchers and health-care providers are accounted for.

BOX 3.2 CLINICAL TRIALS DURING A PANDEMIC

At the start of the global pandemic in early 2020, no approved treatments were yet available for COVID-19: the disease caused by the novel coronavirus SARS-CoV-2. There was a pressing need to evaluate the possible treatment options to determine whether any would be more effective than the hospital standard of care in helping patients recover from COVID-19. Therefore, researchers at Oxford University initiated the RECOVERY trial, an international, platform-based trial in collaboration with researchers across the UK and other countries. To improve efficiency, the platform trial was based on easy inclusion, simple — but clinically relevant — endpoints and the comparison of treatment with standard of care rather than a placebo. All of the possible treatment options involved approved medicines, so side-effects were well-known from other applications. In June 2021, well over 40,000 participants have been included at 183 participating sites.

In the Netherlands, the REMAP-CAP trial yielded an innovative approach to collecting clinical evidence on the COVID-19 treatments. The advantage of this so-called 'Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia', in comparison with a conventional trial, is that the adaptive design enables (see also: https://www.remapcap.org/what-is-an-adaptive-trial):

- Avoiding ambiguous results
- Drawing conclusions once sufficient data have accrued, rather than when a pre-specified sample size is reached
- Evaluating the effect of treatment options in pre-defined patient subgroups
- Increasing the likelihood that patients within the trial are randomised to treatments that are more likely to be beneficial
- Evaluating multiple questions simultaneously
- Incorporating new questions into the trial as initial questions are answered, so that the trial can be open-ended

Both RECOVERY and REMAP-CAP (with over 7,000 participants by June 2021) strongly contributed to the evidence about the treatments of COVID-19. These trials provided evidence for the effectiveness of certain treatments (e.g. corticosteroids) and the ineffectiveness of other treatment (e.g. Hydroxychloroquine).

Meanwhile, out of necessity, the pandemic also catalysed the use of virtual and fully remote decentralised clinical trials (trials@home), which might also practically enable future international studies on (very) rare diseases (Ledford, 2020).

Traditional randomised clinical trials may not be feasible after considering the characteristics of the treatment, its intended indication and the targeted patients, such as in rare diseases (due to a rare population and clinical heterogeneity). Science can help overcome these challenges by searching for alternative approaches that are acceptable to regulatory agencies and that do not follow the classic RCT paradigm. Examples of such approaches include:

- *Non-placebo controlled RCTs*
- *Non-randomised comparative studies* (pre-designed and RWD-based). Non-randomised study approaches may also contribute to generating evidence about the drug's therapeutic effectiveness. These range from quasi-randomised (or quasi-experimental) studies to controlled 'before-after' studies and cohort or case-control studies. These non-randomised studies are more prone to bias and present challenges related to the selection of study subjects, the choice of comparison group and adjusting for other confounding factors. When existing clinical databases or registries are used for data on the potential benefits and risks of a treatment, relevant information about other influences is often not — or only partially — available, which compromises valid inferences about its true benefits and risks.
- Sometimes *single arm trials* (SAT) can be an alternative when access to good quality (historical) 'controls' from clinical practice is available. This not only reduces trial costs but also guarantees that every patient in the trial receives the treatment, which is advantageous from the patient's-perspective. SATs requires fewer patients, but still has extensive screening, and it remains difficult to interpret results without a control group.
- *cmRCTs* (cohort multiple randomised control trials) offer a new way to combine real-world data with randomised trials, where the cohort serves as a pool for selecting patients eligible for experimental interventions, as well as a platform for multiple randomised comparisons according to the design of a cohort multiple randomised controlled trial. This means that you have access to parallel rather than historical controls.
- *Registry-based randomised trials*
  Existing patient registries can serve as a reusable component of the clinical trial infrastructure and assist in patient recruitment, randomisation and data collection. Compared to traditional RCTs, a registry-based randomised trial may offer opportunities to avoid data duplication, recruit patients more efficiently and reduce costs. Ideally, the registries should also be made suitable to collect data for regulatory purposes, for example to assist in analyses that aid decision-making on reimbursement of a novel therapy (see also CCTI recommendations for registry trials).
- *Pragmatic randomised trials*
  Pragmatic trial design is an emerging concept. While traditional 'explanatory' trials (like the RCT) are designed to evaluate the effectiveness of an intervention

in a well-defined and controlled setting, pragmatic trials are designed to evaluate the effectiveness of an intervention in real-life settings to maximize generalisability, or applicability, to a broad routine clinical practice. The combination of real-world evidence and randomisation is applied in pragmatic randomised clinical trials, which may also assist in regulatory decisions. A combination of a pragmatic trial and a registry based trial, involving real-world data, seems to offer high potential for future trials, specifically with regard to rare diseases. However, collecting more evidence applicable to real-life settings should not be at the expense of explanatory trials. As stated by Ford & Norrie (2016): 'A pragmatic approach to pragmatism would be to adopt the features of pragmatic trials whenever feasible and sensible and when such features do not compromise trial quality and the ability to answer the clinical question of interest.'

Selecting the optimal trial design can be challenging; therefore, academic researchers should seek timely regulatory and scientific advice in trial design selection for pivotal registration studies.

More and more opportunities exist to use real-world data in decision making. Examples include several of the above-mentioned trial designs and the EMA's patient registry initiative (aiming to facilitate the use of patient [disease] registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines and promoting the dialogue between regulator, industry and registry holder to understand the barriers to using registries). Standardised, structured and stratified data collection in clinical practice can result in valuable real-world databases. This allows for the rapid identification of potential study participants for prospective studies (based on genomic alterations, see box 3.2). Such databases also hold significant potential for the identification of novel prognostic and predictive models, but require whole genome sequencing and collecting genetic and clinical data in large centralised databases with easy access for researchers.

BOX 3.2 FROM BIOPSY TO DATABASE

The database from the Centre for Personalised Cancer Treatment (CPCT) and the Hartwig Medical Foundation is an example of a database developed for better insight into the association between genomic alterations in tumours and the outcome of treatment. To obtain this database, from each patient with advanced disease, who starts a new line of systemic treatment genetic data and clinical information is gathered, irrespective of tumour type and or treatment. The standardised data collection includes: whole genome sequencing data from metastases (tumour and leukocytes), baseline characteristics and outcome to treatment. Currently, almost 7,000 patients are included (data on the first 2,500 patients is published in: Priestly et al., 2019). The database is accessible, and over 250 researchers have requested to use the data.

Indeed, prospective registries (phase IV studies) and standardised electronic real-world data and databases (RWD) can complement clinical trials when building an evidence base (Dreyer & Garner, 2009). Despite the tremendous potential, this requires a 'culture change' among physicians to follow patients and input data into electronic health records in a standardised way. In addition, the urgency for practical solutions that enable the usage and sharing of data from electronic health records between hospitals should be addressed. This comprises not only the technical limitations in the communication between different software systems, but also regulatory restrictions, particularly between different countries.

The growing role of real-world evidence (RWE), based on real world data (RWD), is also reflected by the recent Aetion report 'The role of real-world evidence in FDA approvals' that systematically reviewed FDA approval documents in 2019, of which 49% included a RWE study over nine different disease areas. However, many regulators are reluctant to use RWE. Randomisation and control remain preferable to eliminate confounding factors whenever possible, which is difficult in certain areas such as gene therapy, immunological therapy and rare paediatric diseases.

Science can contribute here by developing methodology to improve the scientific value of real-world data and to promote its usage and acceptance.

4. PATIENT ACCESS; PRICING, HTA, PHASE IV AND REGISTRIES

4.1 From approval to patient access

New medicines for the European market are typically authorised through the central route: the European Medicines Agency (EMA), which decides whether a medicine can be approved based on its benefit-risk ratio. Orphan drugs and biologicals will always need to be evaluated through this central procedure. Approval by the EMA, however, does not imply immediate access. EU Member States have their own system for scrutinising new medicines, as they will have to weigh not only the benefit-risk ratio, but also how the medicines will affect the national health-care budget (price), the relative effectiveness (i.e. the effectiveness of the medicine versus other treatments for the same indication) the cost-effectiveness (i.e. value for money) and the effect on the national health-care budget (the budget impact). In case of uncertainty about the long-term effectiveness of a medicine, there may be additional requirements for managed access.

The 'efficacy-effectiveness gap' refers to the difference in weighing the evidence from the 'ideal' setting of randomised clinical trials to the 'real-world' setting of actual clinical practice. Differences in analysing the effect of a new medicine may, in some cases, lead to a substantial issue when national authorities refuse to reimburse centrally authorised medicines. By way of example, the time between market authorisation and patient access and clinical use of new drugs varies greatly between the US and the various EU Member States (see box 4.1).

BOX 4.1 UNEQUAL ACCESS TO NEWLY REGISTERED CANCER DRUGS

A retrospective database study identified that the marketing approval for twelve new cancer drugs in the period 2011-2018 was granted, on average, 242 days later in Europe than in the US (Uyl-de Groot et al., 2020). The average time to market in Europe was 403 days, with significant variation between EU Member States; patients in Germany, the UK and Austria generally have the most rapid access (17, 22 and 31 days; respectively); in the Netherlands, this takes, on average, 128 days. In Greece and many eastern European countries, it takes, on average, two to three years. Several factors may contribute to this delay, including variability in the HTA requirements across jurisdictions in the EU (Wang, McAuslane et al., 2020)

In the Netherlands, a complex system of rules and regulations governs access and pricing. The National Health care Institute (Zorginstituut Nederland, ZIN) typically evaluates the relative effectiveness and cost-effectiveness of medicines, and then provides its recommendation to the Minister for Medical Care and the Ministry of Health, Welfare and Sport (MMC). The Dutch Health care Authority (Nederlandse Zorgautoriteit, NZa) is tasked with market regulation and sets the tariffs and treatment descriptions for the funding of health-care, including pharmaceutical care in the outpatient setting and the so-called 'add-ons' in the inpatient setting.

Outpatient pharmaceutical care and hospital-based inpatient treatment with medicinal products are evaluated differently. New medicines for outpatient pharmaceutical care are always evaluated by the National Healthcare Institute (ZIN, which follows this up with a recommendation to the Minister for Medical Care. The price is set as part of the internal reference pricing for the Netherlands' medicine reimbursement system (*Geneesmiddelenvergoedingssysteem*, GVS). In the event of a completely new indication, prices may first need to be negotiated. For hospital-based inpatient treatment with medicinal products, ZIN can advise the Minister for Medical Care and the Ministry of Health, Welfare and Sport to negotiate the drug price, based on cost-effectiveness studies (health technology assessment, HTA). During the health technology assessment and the negotiation, the medicine is placed in a temporary 'lock chamber' (*sluis* in Dutch). This is usually the case for very expensive medications. Either the price per patient is high or the budget impact is expected to be high. During this period, the medicine is generally not accessible for patients. Following the health technology assessment, advice is formulated as to whether the medicine fulfils the criteria of established medical science and medical practice and whether the medicine falls within the boundaries set for cost-effectiveness. A final recommendation is issued by the appraisal committee (Advies Commissie Pakket), who weighs the societal and ethical arguments for access and who may advise the relevant parties on pricing and/or ways to improve appropriate use.

In case of new medicinal products in hospitals with very low patient numbers or low budget impact, health-care insurers provide advice on reimbursement. Although an 'open system' exists for such new medicinal products, in practice, there is often no immediate access to patients. Hospitals may decide to pay for the treatment themselves, but high prices often preclude this. Health-care insurers have organised themselves within a committee to evaluate add-on medication (CieBAG), which provides advice on reimbursement. A recent rule for orphan drugs stipulates that unregulated, open access is no longer possible. The rule is not intended to be yet another obstacle to access; it is simply the consequence of the high number of new orphan products for very few indications that may have a high price and limited available information on effectiveness, and on which patients will benefit from treatment. Following from the above, the three main factors that impede and prolong the time to patient access which can be teased out are price, the relative effectiveness evaluation and uncertainty about appropriate use (van Lesse Kloeke, 2020).

BOX 4.2 ECULIZUMAB: THE LONG ROAD FROM MARKET APPROVAL TO PATIENT ACCESS

Eculizumab (Soliris®) is an expensive medicine for paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome (aHUS), two orphan (previously untreatable) diseases that involve red blood cell degradation. For eculizumab, the road from scientific development to patient access was long. The first scientific publications on eculizumab — the first drug to target the complement system — appeared in the mid-90s, followed by clinical evidence in the mid-00s and market approval granted in 2007 (for PNH) and 2012 (for aHUS). Subsequently extensive discussions on the balance between the effectiveness and the costs of eculizumab for PNH began in 2008 and additional data collection was requested, although this was not followed up. In 2017, a ZIN evaluation advised 'only providing reimbursement after price reduction', which resulted in the medicine being incorporated in 2020 into a *weesgeneesmiddelenarrangement* (a package of agreements to increase cost effectiveness, including personalised dosing). The trajectory was similar for aHUS. Initially, it was not evaluated. Then, in 2016, it was conditionally reimbursed and, in 2017, it was included in the *weesgeneesmiddelenarrangement*. The product's extremely high price hindered the approval and eventual patient access, which is an important reason to better understand the optimal treatment scheme. Research into the right personal dose and usage duration may minimise unnecessary usage, which is critical for patient benefit considering the burden that comes with recurrent intravenous administration, the risks of side effects and the significant variation in pharmacokinetics between individuals (Wijnsma et al., 2019). This type of academic research, so critical for patient benefit, illustrates that the drug development pathway is far from complete once marketing approval has been obtained.

4.2 Price

How new medicines impact the health-care budget is constantly debated. Although, in relation to other Member States, the total amount of money spent on medicines in the Netherlands is relatively low, the costs of inpatient treatment with medicinal products in Dutch hospitals in particulars has risen over the last years. According to the NZa, the costs in 2018 were 9.9% higher than in 2017 and 61% higher than in 2012. The total expenses of medical specialist care in 2018 concerned €23.96 billion. Pharmaceutical care accounts for an increasingly large proportion of these costs, from 6.8% in 2012 to 9.5% in 2018 (€2.27 billion). While the expenses for brand name medicines (*spécialités*) with available biosimilars have dropped 38.2% in the period 2017-2018; the expenses for newly introduced medicines without competition continue to drive expenditure growth. Indeed, according to the yearly forecast analysis in the US, the share of expensive orphan products is expected to be over 18% of overall prescription sales in 2024 (Evaluatepharma, 2020).

A significant number of new cell, tissue and gene therapies have been approved within the past decade. Specifically, these advanced therapy medicinal products (ATMPs) will create a challenge to providing access, since the current system, as outlined above, will not always be suitable for a fast and appropriate reimbursement assessment. For example, with the traditional value-based HTA approach, the maximum price for a devastating disorder is set at €80.000 per quality adjusted life year (QALY). A hypothetical curative treatment that is life saving and extends a life with optimal quality for, say, 40 years, could cost €3.2 million per patient. Indeed, for some gene therapies, such as for the treatment of spinal muscular atrophy (SMA), the requested price per patient approaches €2 million (ZIN, 2021), see box 4.3. Therefore, the concept of value-based pricing is not sustainable for certain therapies (e.g. if lifetime reductions in medical expenditure or very high QALY gains from curative treatments are included in the pricing). The HTA model may include, as a comparator, other high-priced medicines, for which the officially negotiated prices are unknown. Along with uncertainty about the long-term outcomes, this creates an almost impossible situation as regards advising on reimbursement.

BOX 4.3 THE MOST EXPENSIVE DRUG IN THE WORLD

Spinal muscular atrophy (SMA) is a rare, hereditary and progressive neuromuscular disease. The most common forms of SMA are caused by defects in the SMN1 gene, the primary gene that encodes for the survival motor neuron (SMN) protein. Insufficient levels of SMN protein lead to irreversible loss of the nerve cells that control muscle movement (motor neurons), resulting in weakness and skeletal muscle wasting. SMA can be classified into different types based on the age of onset and severity of muscle weakness. The majority of children with the most severe type of SMA will not reach the age of two without permanent ventilator support (Finkel et al., 2014).

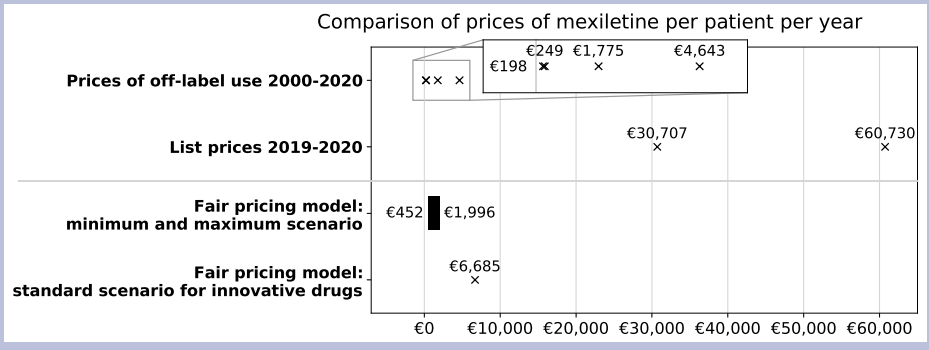
For years, SMA treatment consisted of managing symptoms and preventing complications, but recently, new gene-based therapies for the treatment of SMA have been developed.
Zolgensma® (onasemnogene abeparvovac), a one-time gene-replacement therapy for the paediatric treatment of SMA, is currently the most expensive drug in the world at a cost of around €1.9 million per treatment. The price of the drug should represent its potential value to save children's lives as well as improve their quality of life. Although the current data are promising, the long-term outcomes are unknown and there is no evidence yet to confirm that Zolgensma® offers a life-time cure. In addition, within the SMA spectrum of phenotypes, it is not certain which patients will benefit optimal from this drug. Interestingly, in the HTA model, a comparison is made to the costs of yet another very expensive drug: nusinersen (Spinraza), which may drive the price of Zolgensma even higher. In view of these issues, the Zorginstituut Nederland recommended to only include the drug in basic insurance if the price is reduced by half. In addition, a pay-for-performance agreement with Novartis must assure that reimbursement is based on actual treatment results.

It is important to understand that the value-based pricing (VBP) system and international reference pricing was initially created sometime around 2000 in response to the high costs of innovative new drugs. Most European countries now apply the VBP system, but it has its limitations as illustrated above. For companies, the disadvantage of this system may be that market access is delayed due to time-intensive HTA. In addition, fierce price negotiations or demanding managed access agreements may de-incentivise companies to invest in orphan drug development. Interestingly, the use of VBP contrasts with the call for transparent pricing: greater transparency in the research and development costs, patents and clinical trials and when declaring how much public funding has gone into medicines development. Such transparency would be required for a 'cost-based pricing' approach. However, this may prove difficult as commercial companies are not always willing to disclose their investments and profit margins, and the high attrition rates and associated cost of capital are difficult to incorporate in cost-based pricing models for innovative drugs. Commercial companies may refer to high R&D costs as a causal factor to justify extremely high prices, even though there is not always a clear relationship between the pricing of medicines and the costs of R&D (Uyl-de Groot & Löwenberg, 2018).
A special subgroup concerns old medicines that have been redeveloped for a new indication. For these 'repurposed medicines', it might be feasible to make reliable assumptions on investment costs, as recently shown for Mexiletine (see box 4.4). This is where science could make a real difference, by further developing new pricing models, such as the model developed by Uyl and AIM.

BOX 4.4 MISUSE OF ORPHAN DRUG LEGISLATION

European orphan drug legislation was enacted in 2000 to encourage medicinal product development for rare diseases, which is not considered commercially attractive under normal market conditions. Sponsors who obtain orphan designation benefit from protocol assistance and ten-year market exclusivity once the medicine is on the market (https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview]. While this legislation has indeed resulted in newly developed (often high-priced) treatments for rare diseases, it has also facilitated the authorisation of old drugs for new indications. This has led to a situation where it is possible to abruptly sell widely used and previously low-priced drugs at monopoly prices. A striking example of which is Mexiletine.

Mexiletine, a sodium channel blocker originally developed in the 1960s, has long been known for its life-saving properties in patients with ventricular arrhythmias. The drug has also been repurposed and used off-label in neurology for patients with non-dystrophic myotonia (NDM) (Statland, 2012), a rare neuromuscular disorder. In December 2018, however, when the EMA gave marketing authorisation for Mexiletine (under the brandname *Namuscla*) as an orphan drug for NDM, its price shot up outrageously, ranging from €30,707 to €60,730 per patient per year in European countries (van den Berg, 2021). Strikingly, this increase applied not only to patients with NDM but also for the treatment of patients with arrhythmias, for which the drug has been used since the 1970s (Postema et al., 2020]. In addition, the authorisation of Mexiletine blocked the legal possibility for continuing its import to most countries, thereby critically endangering patient access to the drug (Postema et al., 2020).



Cost-based pricing may provide a suitable alternative for repurposed orphan drugs like Mexiletine. As illustrated in the figure from van den Berg et al. 2021, the current list price for Mexiletine in Europe is much higher than any scenario of the cost-based models. Research into calculating a fair cost-based price based on detailed information for development costs may aid in the discussions on fair pricing and reimbursement.

4.3 Relative effectiveness evaluation and appropriate use

As indicated above, the current system requires evaluations by the payers of each EU Member State, who apply their own system for assessing relative effectiveness. For some medicines, again specifically for orphan diseases, uncertainty may exist about a drug's effectiveness because trials were either short or have only shown benefits on surrogate outcomes. Most of these kinds of products are conditionally authorised, which implies that the marketing authorisation holder should fulfil post-marketing commitments. This could entail conducting additional studies or creating a registry to collect real-world data. Unfortunately, these post-marketing registries (as mandated by the EMA) are frequently not suitable for answering questions about relative effectiveness. This 'efficacy-effectiveness gap' could cause serious delays in access. In some cases, the company registries may even be used as marketing instruments rather than evidence-generating systems (Hollak et al., 2020).

Besides the uncertainty on clinical effectiveness, there is also frequently uncertainty on appropriate use: i.e. which patients benefit most from the treatment. Multiple factors can influence this. In rare genetic syndromes, there can be a wide range of phenotypes, not all of which will benefit from a treatment. In addition, the co-morbidities of, or advanced disease stage in, some patients may limit the added benefit of the new medicine. Often, the trials have been performed in selected patient groups, leaving the evidence generation for appropriate use to post-marketing studies.
Several instruments are under development in the Netherlands, including the oncology drug-access programme (DAP) as well as the orphan drug-access protocol (ODAP). The aim of such a protocol is to support controlled access for patients in the Netherlands (based on a set of key principles), to include conditional reimbursement (pay for performance, price negotiations) which is to be discussed between the pharmaceutical company and regulators or payers, to formulate start-stop criteria and to establish an indication committee, with regular updating of criteria and structured data collection for future analysis.

Science could especially contribute in the area of regulatory science and HTA: to evaluate the use and value of post-marketing instruments and appropriate use, such as DAP and ODAP, to validate these instruments against real-world outcome data, to identify success and failure factors and, *in ultimo,* to help reshape post-marketing instruments for improved evidence generation. We suggest that independent disease registries for the pre-and post-approval of novel treatments should be supported. These should function independently from commercial interests and be maintained by health-care professionals and patients alike. Additional requirements would include the early establishment of (international[5]) registries; ideally well before novel treatments are introduced.

5 in the case of orphan diseases

In conclusion, a long and difficult pathway to access may exist once marketing authorisation has been granted. The processes involving the assessment of clinical application and reimbursement can be long, vary greatly between countries and have become increasingly complex for innovative (often expensive) therapies for rare diseases. Science could help shape the post-marketing landscape by offering critical evaluations of existing tools and by developing new models for pricing and post-marketing evaluation with the aim to speed up access to novel medicines, in combination with societal responsible pricing and appropriate use.

5. NECESSARY CONDITIONS TO SUSTAIN SCIENTIFIC FINDINGS

5.1 The ecosystem: a problem shared is a problem solved

An efficient medicines development ecosystem entails sustainable mutual partnerships between all parties involved (academia, research institutes, (academic) medical centres, clinicians, pharmaceutical companies, regulatory agencies, government, etcetera) throughout the trajectory (see figure 2). The call for such a medicines development ecosystem is nothing new. The challenge is to shape the current partnerships in a more structured way. In this chapter, we offer several suggestions for realising a more efficient ecosystem based on collaboration, trust building and dialogue.

5.1.1 A patient-centred approach

To attain their common goal of improving patient health, ecosystem stakeholders must understand that active patient involvement is important and, indeed, even crucial at various stages of the R&D process. Collaboration with patient experts and patient representatives and/or organisations should be a consistent thread running through the process. This collaboration is relevant to better understand patients' unmet needs and the impact of both disease and treatment's undesirable side-effects on their daily life. A patient-centred approach also aids in selecting the clinical endpoints and patient-relevant minimal clinical difference, including quality of life outcomes.

Whereas individual patients fulfil an important role as research participants, patient experts and patient representatives and/or organisations contribute to the

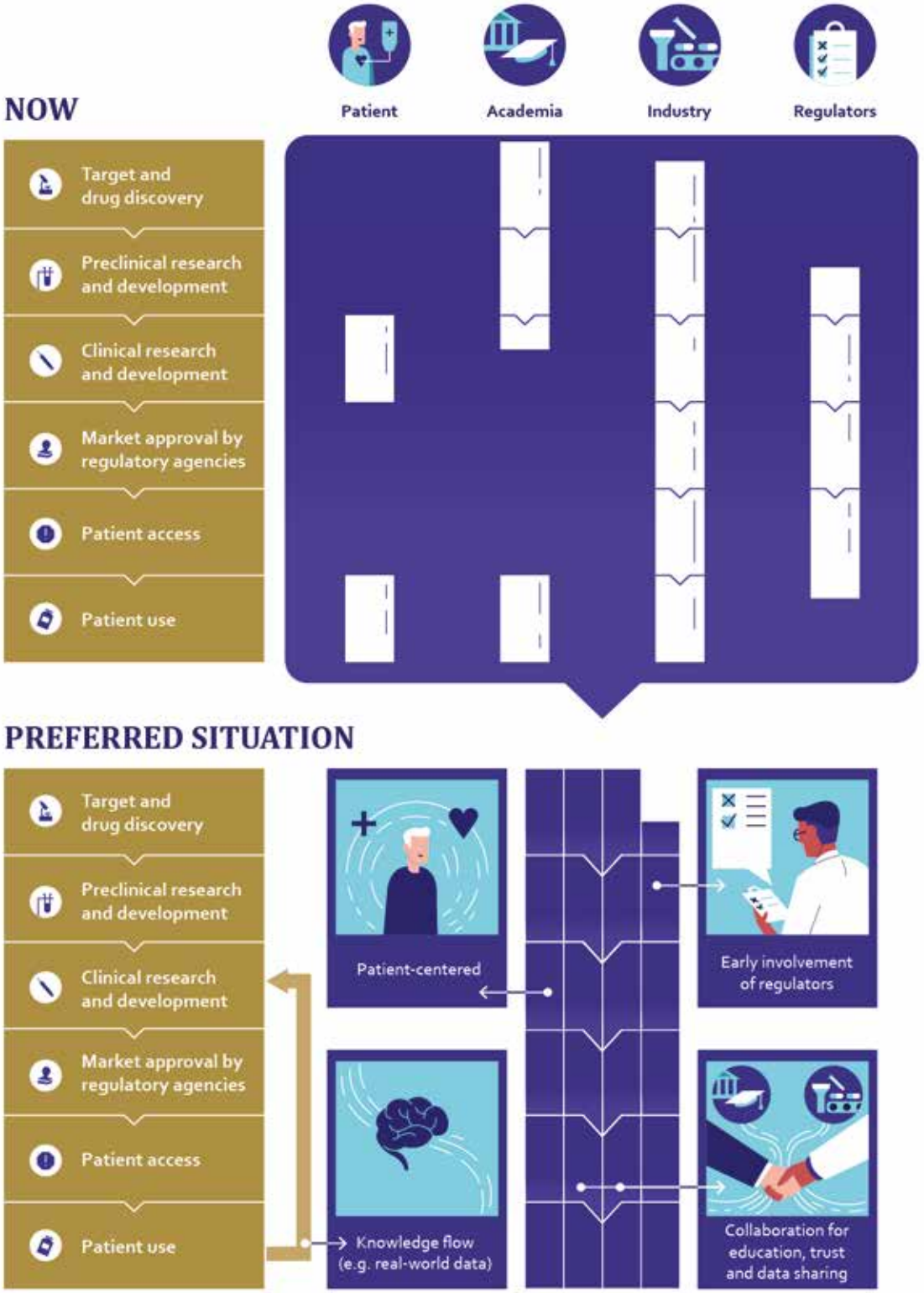

NOW
Patient
Academia
Industry
Regulators
Target and drug discovery
Preclinical research and development
Clinical research and development
Market approval by regulatory agencies
Patient access
Patient use
PREFERRED SITUATION
Target and drug discovery
Preclinical research and development
Clinical research and development
Market approval by regulatory agencies
Patient access
Patient use
Patient-centered
Early involvement of regulators
Knowledge flow (e.g. real-world data)
Collaboration for education, trust and data sharing

Figure 2

various phases of the R&D process as advisors (Is the study protocol feasible?), reviewers (Is the patient information clear?), co-researchers (help defining relevant outcome measures; judging the feasibility of the protocol), commissioners, initiators and driving forces. These diverse roles call for different profiles and background knowledge. The European Patients Academy on Therapeutic Innovation (EUPATI) provides theory and skills training for expert patient representatives to fully enable them to understand and contribute to the R&D process for medicines and to improve the availability of medical information for patients and other stakeholders.

5.1.2 True partnership between academia and industry

In medicines development, academic researchers have traditionally focussed on the upstream basic science: the research needed to understand pathophysiology and underlying disease mechanisms and to identify potential targets for therapeutic intervention. The downstream, applied research to develop new drugs and bring them to the market has been mainly performed by industry researchers. Nowadays, academia has taken on a more prominent role in applied research. When analysing the relative contribution of pharma's and biotech's home-grown projects to new molecular entities (NMEs), the increasing role of academic innovation becomes apparent. The EMA reported that roughly 45% of the 94 NMEs approved during the period 2010-2012 originated from academic institutions, small companies, public institutions and public-private partnerships (Lincker et al, 2014). This highlights the importance these sources hold for the European medicines market. Assessment of the research conducted in industry, academia and biotech that led to FDA-approved NMEs reveals that 55% of the FDA-approved drugs (801/1,453, per 31 December 2013) were first reported by academia (Patridge et al, 2015). Academia, in particular, promotes a rich environment for high-risk, high-novelty projects, such as the development of small molecule drugs with no immediately obvious commercial value or drugs like ATMPs that require unique and highly specialised biological manufacturing. Indeed, university medical centres play a major role in the initial and ongoing development of ATMPs, as they have the necessary disease-specific expertise, the capacity for innovative research and the direct access to donor and patient material (de Meij et al., 2019). Further strengthening their role (as suggested by de Meij et al., 2019) could help increase the number of ATMPs that are further developed and reach the patient.

The major involvement, however, of industry (either established or venture-funded start-ups) remains essential to complete the path from scientific insight to approvable therapy. In large part because industry possesses the infrastructure, skills, (regulatory) expertise and the significant financial resources required to perform human proof-of-concept studies and clinical trials. In recent years, the realisation that mutual academia-industry partnerships throughout the whole R&D process are vital to success, has created space for all sorts of new joint approaches,

open innovation models and public-private partnerships. A study by Takebe et al. (2018), investigated 798 drug discovery projects performed between 1991 and 2015 at thirty-six academic institutions in the US. The success rates for academic drug discovery and development turned out to align with the corresponding common success rates of pharmaceutical industry, biotech, non-profit and academia together: 75% vs 63% at phase I, 50% vs 31% at phase II, 59% vs 58% at phase III and 88% vs 85% at the new drug application/biologics license application (NDA/BLA) phase. Importantly, academic drug discovery was shown to benefit from collaboration with the pharmaceutical industry. The nonclinical success rate was 36.7% for collaboration projects and 29.5% for noncollaboration projects. Yet only a small proportion of early R&D is performed in such collaborations. The need for collaboration is even more prominent at later stages of development than earlier ones. All academic projects that succeeded at phase III or the NDA/BLA stage involved academic-industry collaboration (success rates for collaboration vs non-collaboration projects: 78.2% vs. 71.4% in phase I, 54.4% vs. 36.8% in phase II, 63.0% vs. 0% in phase III and 87.5% vs. 0% at NDA/BLA. Academia and industry's complementary roles highlight the importance of maintaining a good partnership (equilibrium) between them. Although academics and small biotech companies (often academic spin-offs) play an important role in the early phases of drug development, continuing their involvement further down the pipeline turns out to be a real challenge. A true partnership is different from opportunism for the in-licensing of newly developed products as well as the involvement in clinical trials.

A European study (van den Bogert et al., 2014) demonstrated that many drug candidates are transferred to larger companies during their development. Of the 172 new active substances (NASs) issued by the EMA in the period 2009-2013, 69 (40%) were acquired by companies. There was no difference in approval success rates between acquired and self-originated NASs, but stratification for company size suggested that small companies have higher approval failure percentages for both acquired and self-originated NASs. Significantly, the failure rates in case of partial license agreements (19%) and whole company acquisitions (9%) were much lower than those involving whole product acquisitions (38%) (van den Bogert et al., 2014]. According to the researchers, this indicates that, 'The continued involvement of the development team, or access to its expertise, contributes to the subsequent success.'

Which pathways can facilitate a collaborative and interdisciplinary drug discovery landscape where creativity and the fundamental knowledge of academia combine with high-quality drug development paradigms of pharma? How can Dutch academia contribute? For a variety of reasons, Dutch academic culture struggles to establish intellectual partnering with industry. Several suggestions for improvement encompass new partnerships with a stronger, continuous role for academia, e.g. by including anti-shelving clauses, respecting principles of socially responsible licensing (NFU, 2019) and pricing, all while maintaining scientific integrity and independence.

In academia, drug development is driven by scientific curiosity or opportunity, and the patients' unmet medical needs, frequently involving rare diseases. The academic environment places emphasise on knowledge generation (and publications) and less on bringing a product to the market. Indeed, the time between the first publication of the discovery and the approval of a new substance is very different for substances discovered by industry (twelve years, on average) and those discovered by academia (twenty-four years, on average) (Patridge et al, 2015). The twelve-year difference in this so-called 'gap to approval' can be explained, at least in part, by the fact that academia is quicker to share results (while industry delays publishing them until later in the development process) and likely by inadequate funding of academic drug development. Therefore, aligning public investments to experiments with novel, true public-private partnerships is needed to investigate how innovation and affordability can go hand-in-hand, while celebrating the patient-centred approach. A well organised, collaborative Dutch academic environment is a prerequisite to realise this approach for aligning public funding (FAST, 2020).

In medicines development, the ultimate objective is to improve patient health. While academia and industry alike share this goal, a key stumbling block in public-private partnership remains the misalignment of their incentives. For pharma, drug development starts with the question: 'What will likely be a major medical need in ten to fifteen years?' Opportunities are then explored based on the available science, the needs and the population. The business case serves as the starting point of the journey. Pharmaceutical companies are largely market driven, with ties regarding publications, royalty payments and IP rights. Pharma's core mission, to bring a profitable product to market, comes with a long-term strategy, advanced infrastructural organisation, a razor focus and a product-oriented approach to project management, including financial project valuation (de Visser et al., 2020).

5.1.3 Less bureaucracy and earlier stakeholder involvement

A. Regulatory burden

The growing number of regulatory requirements, sometimes in response to social factors, sometimes initiated by regulators or industry themselves, is one of the biggest hurdles in the R&D process for medicines. To better deploy innovative solutions, we should reduce the long bureaucratic procedures. The growing regulatory compliance burden relates to every phase of the development process: from working with genetically modified materials (GMO) to performing animal experiments (CCD) and setting up clinical trials (ECTR, GCP).

For example, using animals for research purposes to study pathophysiology or to test the efficacy and safety of drugs is tightly regulated for good reasons, not least of which is animal welfare. However, researchers have warned that the

implementation of new regulations over the past few years has dramatically increased the administrative burden required to conduct animal experiments. This involves increased financial investment, as submission of each required approval and amendment costs money, as well as increased investment of time, since the processing of ethical approval takes longer and is required for small adjustments to experiments (Genzel et al., 2020). In addition, the Dutch government's expressed ambitions to reduce animal experimentation seem to have created unrealistic expectations among the general public that this can take place in the short term.

In the Netherlands, the process to set up clinical trials is slowed by the inefficient execution of laws and regulations and inadequate harmonisation among institutions. For example, because local approval differs between institutions and is scattered within institutions (beyond the approval of Board, the approval of i.e. scientific advise committees and privacy officers are needed). What's more, the professional support to draft and review research contracts between sponsors and hospitals is often lacking.

The Dutch Ministry of Health, Welfare and Sport initiated a programme to address the increased regulatory burden in clinical research in the Netherlands. Addressing this issue is urgent, as the EU clinical trial regulation (ECTR 536/2014) will change how clinical research is performed. This regulation may speed up approval of clinical trials carried out in multiple Member States, but it may also lead to more bureaucracy for national trials. If the regulatory burden is reduced in the Netherlands, it will become a more attractive partner for clinical trials carried out on the international stage.

B. Open minded regulators and better alignment with HTA bodies

To speed up marketing authorisation, regulators must adopt a more open attitude towards alternative trial designs and new procedures. An example of the success of such a new approach is Larotrectinib (Vitrakvi), where a single arm trial with N=102 led to conditional marketing approval with an agnostic indication (solid tumours with an NTRK fusion gene). However, early alignment with HTA agencies is also key to avoid long and cumbersome HTA procedures and price negotiations that slow down patient access.

Conditional marketing approvals provide a tool to retract a drug from the market until full access is obtained and thereby allow marketing authorisation before long-term evidence is obtained. Once a drug is approved, however, it is difficult to retract it based on real-world data. An action like this calls for research on how to combine rapid market access with pragmatic randomised studies in clinical practice and regulatory decision-making.

Regulators can (and do) assist with making the approval process more efficient by providing: i) rapid scientific advice, ii) accelerated assessment and; iii) rolling reviews (e.g. Covid vaccines: the approval procedure takes one-and-a-half years on average; the Pfizer Covid-19 vaccine only took two months due to this approach).

In addition, providing better alignment of different stakeholders and regulators throughout the development process is key for the translation of research from bench to bedside (see figure 2). The regulatory framework should be better equipped to keep up with the enormous technological and scientific developments that are rapidly changing the medicines development landscape (Roadmap EC, 2020). The misalignment of technological and scientific development with regulatory steps may hamper optimal patient access to state-of the art therapies based on, for example, gene therapies, regenerative medicine, personalised medicine, smart health applications and medical technologies, including AI. To solve this, regulators should adopt a more flexible attitude toward new research designs, and academics should be more proactive about informing policymakers and regulators at an earlier stage in the process. Ongoing dialogue between all parties is crucial to facilitate rapid drug development. Efforts must be made to encourage industry and academia to interact earlier with regulators, as well as HTA to understand what is required and what is possible. But the parties involved must also try to understand each other's language and needs. The European STARS project to strengthen the regulatory science training for academia can help here (Starokozhko et al., 2021).

5.1.4 A complementary instead of a competitive international mindset

It is self-evident that advances in drug development take place on the international stage. While this report primarily focusses on the drug development infrastructure in the Netherlands, this represents but a (very) small part of a much greater whole. Most academic researchers operate in international consortia (e.g. IMI, Horizon2020, etc.), further improving overall international collaboration, in particular during the clinical development stage is crucial to support a faster evidence generation on a medicine's potential (this may involve i.e. input into trial design, sharing data on natural history and setting up a registry). Across Europe, but also within the Netherlands, there are multiple examples of academia connecting and integrating (e.g. in COMBACTE [European networks aimed at fighting antimicrobial resistance]; Clin-net; lab-net; epi-net; stat-net; EORTC [European Organisation for Research and Treatment of Cancer] etcetera). It remains key to continue support for international collaborations and for the establishment of international disease registries (particularly for rare diseases). In addition, further strengthening our academic environment as a node in international hubs, such as EATRIS (the European infrastructure for translational medicine), BBMRI (a European biobanking infrastructure) and ECRIN (the European Clinical Research Network) facilitates new opportunities within (and beyond) the European landscape. Internationally, it may be

valuable to collectively decide on focus areas to realise a more complementary rather than a competitive international mindset.

5.2 A look in the mirror

5.2.1 Academic culture

Let's take advantage of the growing movement in the Netherlands to redefine the recognition and reward systems for academics ('Erkennen & Waarderen', see also position paper, 2019). Traditional quantifiable output indicators (e.g. the number of publications, first and last authorships, the h-index and journal impact factors) have long been used as the primary performance metrics for academic excellence. Researchers must fulfill these to obtain research funding and tenured positions. But these metrics do not accurately reflect the important role of academics who are primarily motivated by the development of new therapies.

To generate broader career perspectives for those academics interested in medicines development, the overall assessment of academics should be modernised. Fortunately, this is already taking place. The assessment should include achievements in translating research from bench to bedside and the creation of IP and entrepreneurial initiatives. Medicines development also requires a team effort and a long-term strategy to bring a novel therapy to patients. Therefore, we need to foster an academic environment where these elements are better structured and more highly valued. Solely acknowledging individual performance does not do justice to the fact that scientific and drug developments are actually team efforts. Furthermore, academic environments should not only value the researchers aiming to bring their discoveries to the clinic, but also provide them with better assistance by, for example, supporting technology transfer and regulatory affairs and by helping them to find and establish solid industry partnerships.

Preventing the continuous loss of trained researchers from the academic environment in the Netherlands will require a change in culture. While the number of PhD students has grown tremendously over the last twenty years, 70% of those who obtain a PhD do not go on to pursue an academic career. As discussed in section 5.1, successful medicines development requires experienced researchers who remain active in the development team. Therefore, academic culture needs to let go of the idea that working in or with industry means leaving academia. Instead, we should encourage career paths that are able to transition smoothly between academia and industry.

Along the same lines, we should support and further stimulate academia's changing opinions on public-private partnerships, as reflected in: i) the development of

concerted grants to bundles of projects and research collaborations, as well as awarding grants to individual researchers; and ii) the formation of a partnership as requirement for funding (e.g. the Gates foundation, the international AIDS vaccine initiative), while safeguarding the balance between collaboration and academic independence.

5.2.2 Education and awareness

A. Focus on education
It is equally important to sustain gained knowledge and expertise, and prepare for a future active role of academia in medicines development, by ensuring an academic training and education in medicines development and evaluation research. An important aspect of such education involves training on how to find, use, integrate, visualise and interpret the wealth of currently available data and methods/ approaches.

Academia is rich in focused disciplinary experts, but lacks experts to oversee the whole trajectory of medicines development. In the end, today's training determines the quality of tomorrow's lab technicians, trial-specialists, regulatory science experts. This underscores the importance of high-quality research-oriented education programmes that cover the full trajectory of medicines development: from basic cell biology and target identification, medicine synthesis, optimisation, safety and efficacy testing to marketing approval and cost-effectiveness analysis. Importantly, these multidisciplinary programs should not only be available to students in pharmaceutical, (bio)medical and health sciences but also for undergraduate medical students, specialists and academic researchers (e.g. chemists, (micro)biologists and geneticists) interested in a career along this line.

B. Literally bringing the world of academia and industry closely together
The standout places for quality education bring the worlds of academia and industry (literally) closer together. Bioscience parks encompassing universities, research institutes, industry and medical centres, such as in the cities of Leiden and Utrecht in the Netherlands, form the hubs where research and education meet industry and patient care and where interdisciplinary collaborations can sprout and flourish. See box 5.1 for an example illustrating how the dialogue between fundamental scientists and clinicians can help to connect the dots and generate solutions to fulfil patients' unmet needs. This example highlights how curiosity-driven research can lay the foundation for highly practical clinical implications.

BOX 5.1 CURIOSITY-DRIVEN RESEARCH: THE FOUNDATION FOR CLINICAL IMPLICATIONS

Synthetic glucocorticoids (e.g. dexamethasone) are commonly prescribed to treat inflammatory and immune diseases. They are not only very effective, but are also considered relatively safe in low doses. However, some medical conditions, such as acute childhood leukaemia, require long-lasting high dose dexamethasone treatment. This treatment is associated with undesirable side-effects in a substantial number of patients, such as psychosis, mood disturbances and/or sleep problems.

Conversations between clinicians who were confronted with these side-effects and fundamental scientists who have a deep understanding of the mechanisms of action formed the basis for a rather simple solution: abolishing the side effects through co-administration of the naturally occurring glucocorticoid cortisol (see Meijer & de Kloet, 2017). Albeit simple, the solution seemed so paradoxical that it had not come to mind in clinical practice.

The solution was based on receptor pharmacology, which is different for naturally occurring glucocorticoids (e.g. cortisol) and synthetic glucocorticoids (e.g. dexamethasone). The brain has two types of receptors that bind naturally occurring glucocorticoids (the glucocorticoid receptor [GR] and the mineralocorticoid receptor [MR]). Cortisol activates the MR at low levels and the GR at higher levels; synthetic glucocorticoids primarily activate the GR. Due to a negative feedback loop, GR activation potently suppresses the production of naturally occurring cortisol. Thus, while the MR is almost always occupied by endogenous cortisol, long-term high-dose dexamethasone treatment leaves the MR empty. Supplying exogenous cortisol normalises its levels and likely serves as a 'refill' for the brain MR. This was shown to substantially alleviate the side-effects concerning emotional symptoms, conduct and the impact of stress. '*For some children, cortisol treatment sometimes meant the difference between "unbearable" and "bearable."*

Next to science parks, specialised disease centres that bundle multidisciplinary expertise enormously stimulate innovative treatment solutions. The Netherlands is privy to an optimal environment for such centres, considering the relatively short distances and the existing collaborations between medical centres. A successful example of a specialised expertise centre is the Centre for Lysosomal and Metabolic Diseases at the Erasmus University Medical Centre, where geneticists, bench researchers, paediatricians, clinicians and pharmacologists collaborate on innovative therapies for rare disease. Evidently, bringing together various experts *into* one centre is not only a valuable approach to encourage the translation of scientific discoveries into the clinic. Ultimately, coalescing knowledge *between* institutions is vital to shepherding discoveries faster from bench to bedside. In the Netherlands, one example of this approach is the Oncode Insitute, which gathers the top fundamental cancer researchers in the Netherlands, supported by a valorisation team that facilitates the translation of the scientists' research findings into new diagnostics,

medicines and treatments. Supporting such centres is essential to keeping pace with innovative treatment development and ensures the highest quality patient care. Such hubs can also help raise awareness among academia about the opportunities to create public-private partnerships and about the different medicines development pathways.

C. TT requires expertise, focus, manpower and alignment with principles of socially responsible licensing

Dutch universities have three core tasks: education, research and knowledge valorisation (academic medical centres have patient care as a key fourth task). Valorisation concerns the application of scientific knowledge for society. One aspect of valorisation is commercialisation, which may require knowledge and/or patents protected by law (intellectual property (IP) (KNAW, 2014). Although patent utilisation is only a small part of valorisation, the creation of IP and generating revenue from it, has become an extension of academic research, where potential profit from licensing revenues can be reinvested into new research. Apart from monetising academic discoveries, the technology transfer (TT) process first and foremost is an essential step in bringing new discoveries to the patient. TT contributes to building public-private collaborations, protects new developments from being shelved and creates the conditions which ensure that a discovery translates into patient value. The backbone of (academic) TT should be NFU's ten principles of socially responsible licensing.

Technology transfer is key to successfully implementing new therapies, but it is no trivial task. It demands thorough expertise, (thematic) focus and manpower. Dutch universities and academic medical centres have their own technology transfer offices (TTOs). Although they vary in quality and lack uniformity, several TTOs have a sufficient mandate to help academia bring its discoveries to the patient. TT should be thoroughly embedded into the R&D process; therefore, TTOs should be visible and accessible to researchers. Next to financial valuations based on expectations regarding development time, costs and future revenues, scientific considerations regarding the specific candidate therapy and its indication are also critical to defining the most optimal development trajectory for a new therapy and to help define the project's value (necessary for investment decisions and licensing deals) (de Visser et al., 2019). Ideally, entrepreneurial biomedical researchers should attain a basic understanding of financial valuation (de Visser et al., 2019).

Bundling TT expertise at a national level, as previously suggested (KNAW, 2014; RVS, 2017), is a strategy to ensure thorough expertise and socially responsible patenting and licensing of the therapies developed with public funding. In certain specific and strong fields (e.g. cardiology and oncology), the TTO role could be scaled up to the national level, following the positive example of some national TTOs in other countries (e.g. Flemish Institute for Biotechnology VIB), expanding on national

initiatives to fund thematic technology transfer (e.g. RegMedXB, DCVA) and recent successes in individual university medical centres.

5.2.3 Collaborative data collection

As we have seen throughout this report, biobanks, registers, databases and electronic health records are a valuable resource of information-rich and patient-focused data. As mentioned in chapter 2, technology platforms, albeit critical for success, are very difficult to sustainably maintain with project-based (short-term) funding. Therefore, long-term investments are needed to organise and maintain such platforms and databases.

Provided that they are collected and used within the applicable ethical and legal boundaries, real-world data is key to more efficient development of new (personalised) medicines. See chapter 3 for several examples. In addition, concerted careful patient registries are needed to monitor the (cost)effectiveness of new therapies, for which a Dutch framework is currently being developed by the ZiN project *Regie op registers voor dure geneesmiddelen*. Greater uniformity between registries (also a goal of the Dutch Institute of Clinical Auditing DICA, which currently facilitates twenty-three registries) will further facilitate insight into available data.

In the Netherlands, the Health-RI initiative aims to form a national health data research infrastructure with strong data protection support and quality governance. However, it is currently very problematic to use and share data from electronic health records between hospitals (due not only to technical limitations concerning the communication between different software systems, but also due to regulatory restrictions). Even when it is technically possible, researchers and medical specialists often lack the training, time, willingness or permission to collect data in a standardised, structured and stratified way and to make these easily accessible. Optimal use of (available) data requires concerted action by researchers, health care providers and information specialists *and* support from their institutes. This support is also necessary to push for a 'culture change' to motivate physicians to follow their patients and enter data into electronic health records in a standardised way. We should strive toward a practical, feasible national guideline on the standardised, structured and stratified data collection in daily clinical practice and remove the practical limitations of sharing data from electronic health records (EPDs in Dutch). As previously suggested by the Dutch Federation of Medical Specialists (FMS), Chief Medical Information Officers can help realise these ambitions. National standardisation of data collection in electronic health records and making the systems truly interoperable between research systems and between institutions will increase the data available for registries and other research purposes. This is also important from a patient's perspective, as he or she might suffer from various types of disease during the course of their life and shifting each time from a registry is not optimal.

6. RECOMMENDATIONS

A coordinating expertise centre for medicines development

This report identifies areas where science can contribute to greater efficiency in the development of and access to new medicines, while retaining the quality of the development and adequate effectiveness and safety of the medicine. We hope scientists will be supported by their institutions, policymakers and funding agencies to seize the various opportunities mentioned in this report. Although there are wonderful examples of successful medicines development and evaluation initiatives that sprouted from academia, the overall the landscape is scattered. It is vital to foster dialogue among and collaboration between (fundamental) scientists (e.g. chemistry and biology researchers, clinical epidemiologists, statisticians, bioinformaticians, cheminformaticians, clinical pharmacologists, cost-effectiveness modellers and data scientists), (pre)clinical drug development scientists, health-care professionals, the pharmaceutical industry, patient advocates, regulators and HTA bodies. This could be better achieved by establishing a coordinating expertise centre for medicines development that bundles the strengths of its three sections: discovery and preclinical research and development, clinical research and development and regulatory science, patient access, and responsible pricing and appropriate use.

The core task of the expertise centre is to nurture a collaborative, full-fledged environment for drug development research and education in the Netherlands by: creating the infrastructure and supportive facilities for preclinical and early clinical drug development, as well as supporting collaborations and guiding decision-making (see figure 3). Below, we have listed the most important tasks for each of the expertise centre's three sections. The coordinating expertise centre for medicines

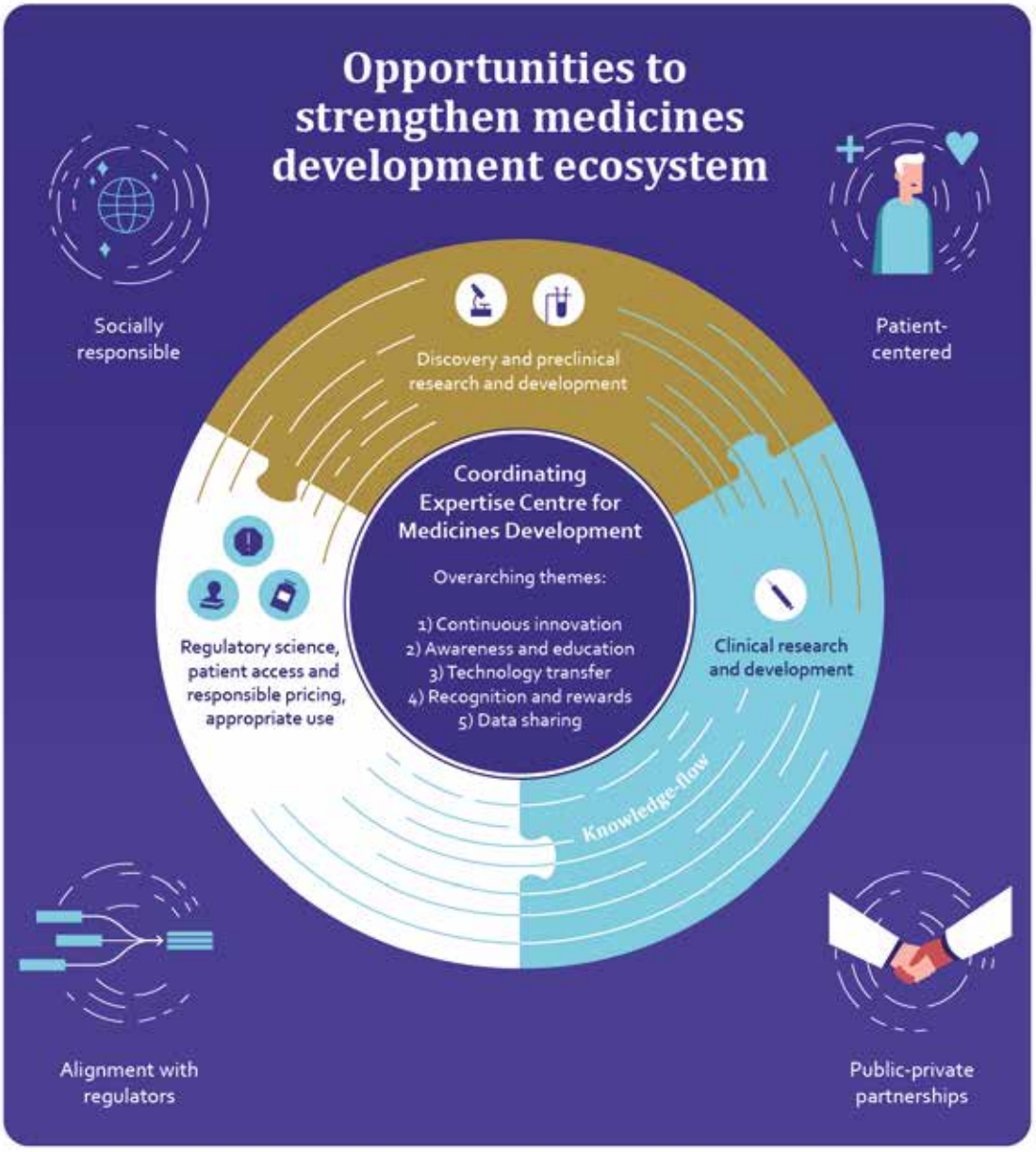

Opportunities to strengthen medicines development ecosystem
Socially responsible
Patient-centered
Discovery and preclinical research and development
Coordinating Expertise Centre for Medicines Development
Overarching themes:
1) Continuous innovation
2) Awareness and education
3) Technology transfer
4) Recognition and rewards
5) Data sharing
Regulatory science, patient access and responsible pricing, appropriate use
Clinical research and development
Knowledge-flow
Alignment with regulators
Public-private partnerships

Figure 3

development could be a joint initiative of the Dutch UMCs (united in the Dutch Federation of University Medical Centres, NFU) and universities (united in the Association of Universities in the Netherlands, VSNU), but this would require further definition and structuring by a specialised taskforce. The coordinating expertise centre would benefit from expanding FAST, the well-received ZonMw initiative that focusses on more coherent funding of R&D for medicines and underscores the importance of adopting an integrated approach, mutual partnerships between stakeholders, timely recognition of hurdles and the essential role of education.

Section I: Discovery and preclinical research and development

Section I is concerned with stimulating the development, validation and implementation of new methods or models to test preclinical efficacy and safety. Four critical tasks would include:

- Stimulating access to public funding for the preclinical phases of medicines development.
- Organising and maintaining technology platforms in a sustainable way (currently, this is often difficult with project-based (short-term) funding).
- Contributing to the development of *functional* assays (e.g. it helps to select the right treatment for the right patient).
- Carefully investigating alternatives to the design, conduct, analysis and interpretation of studies currently required for market approval (e.g. QT studies, testing a drug in two types of animal species).
- Engaging preclinical scientists in a timely manner with regulators to discuss how to qualify new methods and models.

Section II: Clinical research and development

The main task of section II is to create an environment that stimulates clinical research in the broadest sense and overcomes the challenges related to research on (and therapies for) rare diseases.

Three main tasks would include:

- Supporting clinical research into the natural course of disease with a clear focus on patient-relevant health outcomes by using so-called real-world databases. Although this is not strictly related to the clinical drug evaluation phase, it is required as a reference for making informed decisions on potentially relevant effects of the drug on these outcomes.
- Supporting methodological research on alternative randomised (and non-randomised) trial designs that are valid, effective and in alignment with regulatory requirements

- Supporting the development of methodology to improve the scientific value of real-world data to evaluate the intended and un-intended effects of a drug by creating a guideline for standardised collaborative data collection, stimulating sustainable funding of patient registries and aiming for national standardisation of data collection in electronic health records for a real-world national database of patient information that is necessary for drug evaluation.

Section III: Regulatory science, patient access, responsible pricing and appropriate use

The main task of section III is to help shape the post-marketing landscape by critical evaluating existing tools and developing new models for pricing and post-marketing evaluation. The use of real-world data plays a pivotal role here as well. All with the aim to speed up the access of patients and health-care providers to novel and sufficiently effective and safe medicines, in combination with socially responsible pricing and appropriate use. Four important tasks would include:

- Developing new fair-pricing models, which should stimulate both accessibility and innovation
- Supporting the development of drug access protocols
- Evaluating the use and value of post-marketing instruments and appropriate use; validating these instruments against real-world outcomes; identifying success and failure factors and reshaping post-marketing instruments for improved evidence generation
- Modernising public-private partnerships

Overarching themes

The strength of the coordinating expertise centre for medicines development would be the inter-sectional flow of knowledge while maintaining a focus on five crucial overarching themes:

1. Continuous innovation by creating infrastructure and facilities for model and systems laboratories (i.e. encourage researchers to develop new methods or models for evidence building, pricing and a public-private dialogue).
2. A focus on education and awareness**.** We need to train pharmaceutical, (bio) medical and health science students and develop research-oriented education programmes that cover the entire drug development pathway: from basic cell biology and target identification, drug synthesis, optimisation, safety, efficacy and effectiveness testing to marketing approval and cost-effectiveness analysis. It is important to note that these multidisciplinary programmes should not only be available to students in pharmaceutical sciences, but also for undergraduate (bio) medical and health science students, specialists and academic researchers (e.g.

chemists, (micro)biologists, geneticists, clinical epidemiologists, statisticians and data scientists) interested in a career along these lines. These researchers require education to find, use, integrate, visualise and interpret the wealth of available data and methods and/or approaches and training to aid their understanding of the different pathways for medicines development.

3. Supporting technology transfer for all these different researchers, the academic TTO role could be scaled up to the national level, following the example of successful TTOs in other countries (e.g. Flemish Institute for Biotechnology VIB), expanding on national initiatives to fund thematic technology transfer (e.g. RegMedXB, DCVA) and recent successes in individual university medical centres. This is designed to make academia more aware of the opportunities for forging public-private partnerships and should ensure the professionalisation and improved alignment of TT with principles of socially responsible development pathways, including licensing.
4. Capitalising on the growing movement to redefine the recognition and reward systems for academics given that traditional quantifiable output indicators (e.g. the number of publications, first or last authorships, the h-index and journal impact factor) do not accurately reflect the important role occupied by academics who are primarily motivated to develop new therapies.
5. Sharing data: smart decision-making requires knowing what has or has not worked. This may call for mandatory registration of research in an open repository for greater transparency and to avoid unnecessary duplication.

The medicines development ecosystem

While scientific advances and technological innovations may greatly contribute to progress in the development and evaluation of new medicines, this alone will not be sufficient to enhance medicine R&D efficiency. This also requires a strong basis formed by the ecosystem as a whole. Opportunities to strengthen the ecosystem include:

- Adopting a patient-centred approach. To reach the common goal of improving patient health, all stakeholders in the ecosystem must understand that active patient involvement is important during the various stages of the R&D process.
- Enabling a true partnership between academia, industry and regulators by protecting scientific independence and integrity while creating PPP; reshaping PPP to keep academia better aligned to prevent shelving and or high pricing.
- Striving for less bureaucracy and earlier involvement of regulators and medical ethics committees regarding new methods, models, designs, conditional approvals, etc. This will require better alignment of the EMA or the CBG in medicine evaluation (efficacy-effectiveness gap) and will require that EMA or CBG, industry and academia learn to speak each other's language and address their respective needs.

- Fostering a complementary, international mindset. Medicines development and evaluation is clearly an international matter. Having a Dutch coordinating expertise centre for medicines development would strengthen the Netherlands' role in the international landscape, but it is only a small piece of a large international puzzle. It is vital that international collaborations are supported and international disease registries are established, which may prove valuable for joint decision-making on focus areas.

In conclusion, we hope that scientists will be supported by their respective institutions, policymakers and funding agencies in seizing the opportunities mentioned in this report. This will require easier access to public funding for research on dosing, combinations of medicines, (very) rare diseases and the natural course of disease, as well as investigating alternatives for the design and conduct of studies currently required for approval. A coordinating expertise centre for medicines development that provides professional assistance, supports collaborations, guides decision-making and maintains an overview of (inter)national initiatives can optimally support scientists in this, thereby creating room to *gain efficiency through innovation*.

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DEFINITIONS

Academic research: all research conducted in universities, academic medical centres and non-profit research institutes. Academic researchers involved in drug discovery and development span a wide range of disciplines and include chemists, bioengineers and biomedical scientists in the early phases of drug discovery with clinicians and biostatisticians in later stages

Academia: the community of academic researchers

Drug target: A drug target is a molecular structure, in most cases a protein, that is intrinsically associated with a particular disease process and that could interact with a drug to produce a desired therapeutic effect.

Health-related quality of life (HRQL): the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being.

Lead discovery: the process of identifying a molecule with activity at the drug target

Medicine (or medicinal product):

'(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.' (definition from article 1(2) of Directive 2001/83/EC)

Industry (or *pharma*): the for-profit drug discovery and development, manufacturing and sales sector

Orphan drugs: Drugs intended for the diagnosis, prevention or treatment of life-threatening- or chronically debilitating conditions that affect not more than five in 10 000 people in the European Union

Personalised medicine: 'personalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.' (Definition from the European Council Conclusion on personalised medicine for patients (2015/C 421/03)). Often used interchangeably with related terms such as 'stratified medicine' and 'individualised medicine'.

Patient-reported outcome (PRO): Any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s)

Pharmacovigilance: science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Registry: an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).

ABBREVIATIONS

AI	Artificial intelligence
ATMP	Advanced Therapy Medicinal Product, i.e. innovative and complex medicines based on somatic cells, genes or tissues.
CBP	cost-based pricing
CAT	EMA's Committee for Advanced Therapies
CHMP	EMA's Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ERT	enzyme replacement therapy
FDA	US Food and Drug Administration
HTA	Health technology assessment a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner
HTS	High throughput screening
ICH	International council for harmonisation of technical requirement for pharmaceuticals for human use
IP	intellectual property
MMC	Ministry for Health, Welfare and Sport
NME	new molecular entity
NZa	Nederlandse Zorgauthoriteit, Dutch health care authority
PROM	Patient Reported Outcome Measure
QALY	quality adjusted life year
RCT	randomised controlled trial
R&D	research and development
RWD	real-world data data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as electronic health records, disease and product registries
RWE	real-world evidence the evidence derived from analysis of RWD
SMA	spinal muscular atrophy
TTO	technology transfer office
VBP	value-based pricing
ZIN	Zorginstituut Nederland, Dutch national health care institute

REVIEW

At the request of the academy's Board, a draft of this report was reviewed by the following:

- Prof. Anna Akhmanova, university professor of Cell Biology at Utrecht University
- Prof. Hans Clevers, university professor in Molecular Genetics at Utrecht University and PI at Hubrecht Institute and the Princess Máxima Centre, Utrecht
- Prof. Pancras Hogendoorn, university professor of Pathology and dean of the Leiden University Medical Centre (LUMC)
- Prof. Peter Mol, university professor of Drug Regulatory Science at University Medical Centre Groningen, EMA scientific advice working party, Dutch Medicines Evaluation Board (CBG-MEB),

In addition, the report was reviewed by:

- The academy's Council for Medical Sciences
- The academy's Council for Natural Sciences and Engineering

The reviewers are not responsible for the final report.

ANNEXES

Annex 1. Resolution inaugurating a committee for more efficient medicines development

Remark: an edit has been made in the original resolution, this is marked by an *.

The Academy Board has decided to set up a committee for the more efficient development of medicines, hereafter referred to as 'the committee'.

Article 1. Assignment

The committee's task is to make an inventory of scientific techniques and methods that can contribute to a more efficient development of medicines, and to make recommendations for the further development of these techniques and methods. The term 'medicines' should be understood in a broad sense and also includes advanced means such as stem cell and gene therapy.

These may include techniques and methods relating to:

1. preclinical and clinical research prior to the admission of new medicines;
2. post-admission examination and surveillance;
3. health economics and other approaches that can help bring about systemic improvements.

As a second step, the committee is being asked, on the basis of this inventory, to further analyse the highlighted techniques and methods (or a selection thereof) regarding their potential to make the development of new medicines more efficient, and to indicate what follow-up steps are necessary for them to reach optimal maturity.

The committee is being asked to involve the research and scientific community in the drafting of this report, for example, by organising a sounding board or expert meeting.

Article 2. Composition and appointment period

The following individuals will be appointed to membership on the committee in their personal capacity:

Chair
Prof. J. (Jaap) Verweij, emeritus, Erasmus University Medical Centre

Members
- Prof. C.A. (Carin) Uyl-de Groot, Erasmus University Rotterdam
- Prof. H.J. (Henk-Jan) Guchelaar, Leiden University Medical Centre
- Prof. C.E.M. (Carla) Hollak, Amsterdam University Medical Centre, AMC location
- Prof. H.G.M. (Bert) Leufkens, Utrecht University
- Prof. K.G.M. (Carl) Moons, Utrecht University Medical Centre
- Prof. C.L. (Christine) Mummery, Leiden University Medical Centre

International member of the committee
Prof. George Griffin, emeritus, St George's, University of London and FEAM president
The committee is appointed for the duration of the advisory process.
The committee will be assisted by Dr Eva Naninck (Academy Bureau).*
* Until 1 August 2020 the committee was assisted by Dr Jack Spaapen, interim secretary (Academy Bureau)

Article 3. Integrity and quality
Prior to the committee's first meeting, the committee members familiarised themselves with the *Code of conduct to prevent inappropriate influence owing to conflicts of interests* and submitted a written statement as confirmation. The committee members have familiarised themselves with the Manual for Academy Advisory Opinions (*Handleiding adviezen KNAW*) as adopted by the Academy Board on 18 September 2017. The policy set out in that manual will be followed when assessing the draft advisory report.

Article 4. Work plan
The committee will draw up a work plan specifying its working methods and its communication and implementation strategy.

Article 5. Travel allowance
The Academy will cover the travel costs of the committee members, but it will not make any other form of payment to them.

Article 6. Confidentiality
The committee members will treat as confidential any information that can be construed as such to which they become privy while implementing this resolution.

Adopted in Amsterdam on 18 February 2020 by the Board of the Royal Netherlands Academy of Arts and Sciences.

On behalf of the Academy Board, Mieke Zaanen
Director General of the Royal Netherlands Academy of Arts and Sciences.

Annex 2. Individuals consulted

- Albert van den Berg, University of Twente
- Peter Bertens, Association of Innovative Medicines (VIG)
- Haiko Bloemendal, RadboudUMC
- Ton de Boer, Dutch Medicines Evaluation Board (CBG-MEB), Utrecht University
- Jan-Willem Boiten, Lygature, Health-RI
- Stefan Braam, Ncardia
- Hans Clevers, Hubrecht Institute, Utrecht University Medical Centre, Roche, Genentech
- Olaf Dekkers, Leiden University
- Kors van der Ent, Utrecht University Medical Centre
- Pauline Evers, Dutch federation of cancer patient organisations (NFK)
- Fred Falkenburg, Leiden University Medical Centre
- Joop van Gerven, Central Committee on Research Involving Human subjects (CCMO) and Leiden University Medical Centre
- Wim Goettsch, National Healthcare Institute (ZIN) and Utrecht University
- Berend van Meer, Leiden University Medical Centre, University of Twente and Dutch Organ-on-Chip Consortium (hDMT)
- Peter Mol, EMA scientific advice working party, Dutch Medicines Evaluation Board (CBG-MEB), University of Groningen
- Ans van der Ploeg, Centre for Lysosomal and Metabolic Diseases, Erasmus University Medical Centre
- Annemiek van Rensen, PGOsupport, EUPATI-NL
- Maureen Rutten-van Mölken, Erasmus School of Health Policy & Management, Erasmus University, Institute for Medical Technology Assessment (iMTA)
- Stefan Sleijfer, Erasmus University Medical Centre
- Thijs Spigt, Erasmus University Medical Centre
- Lonneke Timmers, scientific advisory board (WAR) National Healthcare Institute (ZIN)
- Saco de Visser, advisor for Future Affordable Sustainable Therapies (FAST), ZonMW
- Carla Vos, Association of Innovative Medicines (VIG)
- Gerard van Westen, Leiden University

Annex 3. 'Truly predictive models' expert meeting programme

What:	Online expert-meeting (over Zoom)
Format:	Five-minute pitches (with slides) by experts addressing the central question, with time for questions, followed by a round table discussion with six to eight experts and a committee
When:	28 January 2021, 1.00-3.00 PM
Moderator:	Prof. Christine Mummery

Central question: If we can find or develop models, assays or methods with a far greater predictive value for the clinic than we currently have, a lot of 'clinical waste' can be avoided. This would greatly improve the efficiency of drug development. Based on your expertise and perspective, do you have suggestions on how to realise this? What should the Netherlands' knowledge infrastructure do to boost the development (and implementation) of models with higher predictive value?

Introduction by Prof. Jaap Verweij, *chair of the Committee Development of New Medicines*

Pitch by Prof. Hans Clevers
PI at Hubrecht Institute and professor in Molecular Genetics at UMC Utrecht/Utrecht University and board member of Roche and Genentech
Disease modelling in stem-cell derived 3D organoid systems (CF)

Pitch by Prof. Kors van der Ent
Paediatrician, professor in Paediatric Pulmonology, chair of the child health programme, UMC Utrecht
Clinical implications of organoid models to select the right drug and the right patient.

Pitch by Dr Berend van Meer
Leiden University Medical Centre, University of Twente & Dutch Organ-on-Chip Consortium hDMT Postdoctoral
Using hPSC cardiomyocytes as a model for heart toxicology as an alternative for rabbit cardiomyocytes normally used by the pharmaceutical industry

Pitch by Dr Stefan Braam
CEO of Ncardia, Leiden
Human iPSC solutions for drug discovery

Pitch by Prof. Albert van den Berg
Professor on Miniaturised Systems for (Bio)Chemical Analysis, University of Twente
Organ-on-chip systems and digital twins

Pitch by Prof. Gerard van Westen
Professor Artificial Intelligence & Medicinal Chemistry, University of Leiden
How deep learning (AI) can be applied to screen libraries for new targets and/or molecules

Pitch by Dr Jan-Willem Boiten
Programme manager at Lygature dedicated to Health-RI, former lead of the Data4lifesciences programmes of Dutch university medical centres
Optimal usage of all available data in genomic, clinical and biological databases

Pitch by Prof. Peter Mol
Professor of drug regulatory science, Groningen University
How to support regulatory decision-making regarding new models and/or methods and knowledge transfer between regulatory authorities, health-care professionals and lay people

Discussion

Annex 4. 'Clinical trials in the era of personalised medicine' expert-meeting programme

What:	Online expert-meeting (over Zoom)
Format:	Five-minute pitches (with slides) given by experts addressing the central question, with time for questions, followed by a round table discussion with six to eight experts and the committee
When:	Wednesday, 24 February 2021, 9.00-11.00 AM
Moderator:	Prof. Henk-Jan Guchelaar

Central question: The clinical phase is critical in the development of a new therapies. It is a great challenge to design and carry out clinical trials efficiently, dealing with i.e. the increased regulatory burden and small patient populations (for rare diseases and/or personalised medicines for which traditional trial designs may not be suitable). Based on your own expertise and perspective, what is required to make the clinical phase of therapy development more efficient?

Introduction by **Prof. Jaap Verweij**, *Chair of the KNAW Committee Development of New Medicines*

Prof. Stefan Sleijfer, *Head of the Department of Medical Oncology. EMC, chair of the Centre for Personalised Cancer Treatment (CPCT) and Chair of the 'Personalised Medicine route' of the Dutch Science Agenda.*
Clinical trials in the era of personalized medicine

Prof. Ans van der Ploeg, *Head Lysosomal and Metabolic Diseases, Sofia Children's Hospital, EMC*
Challenges in paediatrics and related to rare diseases

Prof. Olaf Dekkers, *Professor Internal Medicine, in particular the methodology of clinical research (Leiden University) and Chair METC*
A METC perspective

Prof. Joop van Gerven *chair of CCMO and Professor Clinical Neuropsychopharmacology, University of Leiden*
A CCMO perspective (pre-registration)

Prof. Ton de Boer *Chair of CBG and Professor of Pharmacotherapy, UU*
A CBG perspective (e.g. rolling reviews, Covid-19 vaccines being an example)

Dr Annemiek van Rensen *PGO-support/ EUPATI-NL, CBG*
A patient perspective

The aims of this session are:

1. to address the central question from the perspective of the various stakeholders
2. to discuss where can we take advantage of the Dutch knowledge infrastructure, and where it can and/or should be improved
3. to collect showcases for the KNAW report of achieved successes and initiatives currently undertaken by the field

Annex 5 'From development to patient access' expert-meeting programme

What:	Online expert-meeting (over Zoom)
Format:	Five-minute pitches (with slides) by experts addressing the central question and time for questions, followed by a round table discussion with six to eight experts and the committee
When:	Monday, 29 March 2021, 1.00-3.00 PM
Moderators:	Prof. Carla Hollak and Prof. Carin Uyl-de Groot

Central question: When market approval for a new therapy is obtained, the therapy is not yet accessible (available and affordable) for each patient. What are the major challenges in the step from developmental phase to patient access? From your own expertise and perspective, what is needed to make this process more efficient?

The aims of this session are:

1. to address the central question from the perspective of the various stakeholders
2. to discuss where can we take advantage of the Dutch knowledge infrastructure, and where it can/should be improved
3. to collect showcases for the KNAW report of achieved successes and initiatives currently undertaken by the field

Introduction by **Prof. Jaap Verweij**, *Chair KNAW Committee Development of New Medicines*

Prof. Peter Mol
EMA scientific advice working party, Dutch Medicines Evaluation Board (CBG-MEB), University of Groningen

Dr Wim Goettsch
National Healthcare Institute (ZIN) and Utrecht University

Dr Lonneke Timmers
Secretary scientific advisory board (WAR) National Healthcare Institute (ZIN)

Prof. Haiko Bloemendal
Professor of Networks in Oncology at RadboudUMC

Prof. Maureen Rutten
Professor Economic Evaluation of Innovations for Health at the Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Scientific director iMTA and involved in HEcoPerMed (Healthcare- and pharma-economics in support of the International Consortium for Personalised Medicine)

Pauline Evers
Patient advocate medicines at the Dutch federation of cancer patient organisations (NFK)

Dr Carla Vos and Peter Bertens
Association of Innovative Medicines (VIG)