The Role of Academia in Driving Post-Approval Innovation in Areas of Unmet Medical Need

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List of Abbreviations

ADME	Absorption, distribution, metabolism, and excretion
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AS	Active substance
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BNF	British national formulary
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus disease 2019
CTA	clinical trial application
CU	Compassionate use
EMA	European Medicines Agency
EPAR	European public assessment report
FDA	Food and Drug Administration
GCP	Good clinical practice
GLP	Good laboratory practice
GMC	General Medical Council
IB	investigator brochure
IIT	Investigator-Initiated trial
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
IND	investigational new drug (application) (US)
IRB	Institutional review board
MA	marketing authorisation
MAA	marketing authorisation application
MAH	marketing authorisation holder
MERS	Middle east respiratory syndrome
MRC	Medical Research Council
NCATS	National Center for Advancing Translational Sciences
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
OD	Orphan designation

OECD	Organisation for Economic Co-operation and Development
PK	Pharmacokinetics
PUMA	Paediatric-use marketing authorisation
PV	Pharmacovigilance
RTU	Recommandation temporaire d'utilisation
SARS	Severe acute respiratory syndrome
SmPC	Summary of Product Characteristics
STAMP	Commission Expert Group on Safe and Timely Access to Medicines for Patients
WHO	World Health organisation

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1 Introduction

Modern medicine relies on well characterized targeted medicines which have been proven to be safe and effective. These are commonly highly purified chemical or biological substances which interact at the molecular level with a human or pathogenic target.

1.1 Drug development and licensing

The development of medicines is highly integrated across many professions.
The traditional structure (figure 1) is that a doctor diagnoses a disease in a patient, scientists then study the underlying biological mechanism and discover a molecular target which is associated with - and potentially causative of the disease. Pharmacists in large, highly integrated pharmaceutical companies then engage a well-tuned machine to screen millions of compounds to find the most efficient, selective and save drug candidates. This describes the drug discovery phase.
To assure safety and efficacy in patients and the safety of trial participants a tightly regulated (pre-)/clinical phase of animal and finally human tests is executed. This generates substantial evidence that the drug is effective in treating, preventing or diagnosing the disease. Any risk to the future patients must be proportionate to the clinical benefit.
Based on this data and the totality of available evidence, the permission to market the medicine and thereby recoup the cost of its development, is made by experts at a government health authority, such as the European Medicines Agency (EMA). Finally, the medicine is subject to continuous pharmacovigilance observation to assure that if rare adverse events occur, they do not continue unnoticed. During this time industry and academia conduct additional clinical research to establish the optimal use of the medicine.

This system has proven highly effective in developing life-changing medicines for millions based on strong scientific evidence and the continuous learning approach to develop its guidelines.

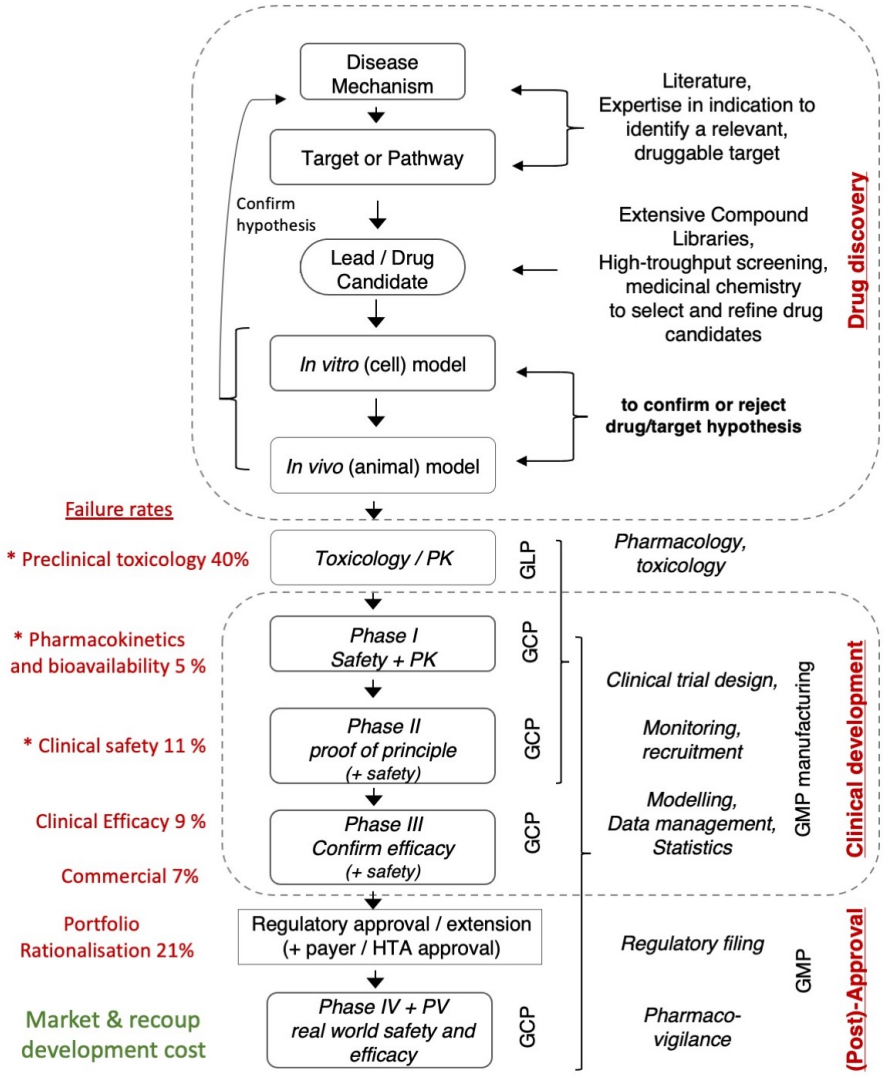

Figure 1 – Overview of the commercial drug development process

The process is shown from drug discovery (top, present chapter) to clinical development and approval / post-approval (subsequent chapters). Boxes in the centre show steps along the development pathway. These represent a common stem in subsequent figures. On the right, technology and purpose of the individual steps are stated.
Drug failure rates at each step of the (pre-)clinical development phases are given based on 812 development compounds during 2000 to 2010 from major pharmaceutical companies Astra Zeneca, Eli Lilly, Glaxo Smith Kline and Pfizer (Waring2015). (It is expected that many candidates are rejected in the discovery phase, therefore no failure rates are given.)

1.1.1 Areas still lacking effective medicines

Despite these advances many diseases still do not have an effective medicine and this represents a high unmet clinical need for many patients. Three areas where this is especially pronounced are complex diseases such as cancer where rarely a single drug on its own is transformative, the

diverse and many rare diseases that affect less than 5 and 10,000 of the European population (Art.3(1) of regulation EC/141/2000) and emerging and neglected infectious diseases.
Only 6% of rare diseases have an approved treatment, leaving other patients suffering from one of thousands of orphan diseases without an approved treatment option (Tambuyzer 2020). Half of all patients with rare diseases are children and 30% die before the age of five (Southall 2019). Orphan diseases are diverse but affect small population numbers, which is challenging the drug development process. Small patient populations mean that the design of clinical trials and recruitment of patients is difficult, that there are fewer clinical experts and that the understanding of the disease mechanism is limited.
For some diseases, scientific evidence may exist but financial incentives for commercial drug development may be lacking.

1.1.2 The challenge of *de novo* drug development

Pharmaceutical research expenditure has risen over the last decades (12% per year) (Munos 2009) but the number of approved new drugs has remained the same (Sleigh 2010), (Ashburn 2004). In clinical development programs between 2006 and 2015 just 20% of infectious disease and 5% of oncology candidate medicines were ultimately found to be effective and safe in humans (Alteri 2018).

Drug discovery is by nature highly experimental and it is expected that very few ideas finally result in a new drug. The discovery of a disease mechanism and identification of a potential molecular target or pathway for a future drug molecule may take decades of academic research. It may only happen when chance, expertise and perseverance come together. The ability to go from target to drug candidate in the other hand is one of the key assets of pharmaceutical companies. It involves their unique multidisciplinary expertise together with large compound libraries and high throughput screening platforms. Cellular models of disease may augment screening the process.

The first confirmation of a drug candidate and its target comes from highly specialized cellular *in vitro* models of disease and from *in vivo* animal models. In the animal model, a first experience of the bioavailability of the tissue- and cellular compartment is gained. At this stage, most drug

candidates fail or indeed the target hypothesis is rejected[1]. The focus of industry on proven drug targets, suggests that a (clinically) validated target may be one of the hardest to reach milestones.

Once the candidate drug-target pair is validated *in vivo* in an animal model, the hope is to validate safety and efficacy in the patient. For this, clinical trials are needed. To safeguard the well-being of trial subjects and to ensure data integrity, all further steps are performed under highly controlled GxP conditions. Prior to exposing trial participants to the drug, a defined battery of toxicology and safety pharmacology tests is performed in animals. Additional data on pharmacokinetics (PK) are collected. About 40% of medicines fail these preclinical toxicology studies. An additional 5% of medicines have unfavourable absorption, distribution, metabolism and excretion (ADME) in human PK. These drugs or their active metabolite will not reach required bioavailability at the site (and cellular compartment) of action.

Throughout clinical development, safety signals are collected and an additional 11% of drugs fail clinical safety studies. Phase II proof-of-principle clinical studies initially validate or disproof the treatment hypothesis in humans. Larger-scale confirmatory phase III clinical trials generate the data required for regulatory approval to market the medicine. Because of heterogeneity of some diseases, genetic differences in the patient population or comorbidities and comedication, a drug may only have a positive benefit-risk in a subpopulation of the target indication. Therefore, phase III clinical trials represent a balance (Sherman 2017) between inclusion criteria and trial designs in order to prove a positive benefit risk for the drug. The scope of those confirmatory clinical trials therefore defines in most part the indication and counter indication in the medicines label (SmPC).

Regulatory approval of the drug and its SmPC then allows the marketing of the drug and thereby the use in the general population as defined in its SmPC. Crucially, a pharmaceutical company must not market a drug for an off-label use, which is a use not described in the SmPC (Art.5 of directive 2001/83/EC). Therefore, to add new indications or patient groups to the label, additional phase II and III clinical trials are performed and approved via variations to the SmPC. Post-approval phase IV clinical trials observe real world use and safety of the medicine in a wider population or in a very specific subsets of patients of concern, *e.g.* who may receive comedications and have comorbidities. In addition to industry-sponsored phase IV trials,

[1] Science-based rejection of drug leads is essential for commercial success, to safeguard subjects of clinical trials or patients from effective or unsafe medicines and allocate resources to more promising targets. Losses to these leads are therefore not counted as part of the attrition rate. However, failures later in clinical development come at a high financial cost to companies and delay treatments for patients. (Naylor 2015).

investigator-initiated trials allow hospital physicians/medical researchers to test the medicine in a specific setting.

Because drug companies are in competition for markets and investment, they survive by being highly efficient in these steps and this assures innovation and speed from drug to market. A downside to this is that drugs may be abandoned for commercial or portfolio rationalization reasons (28%). It also means that economically unrewarding or scientifically challenging medicines may not receive funding.

1.2 Drug repurposing as an option to reduce development time, cost and risk

Due to these challenges, there may not be a new medicine for every (orphan) disease using the current approach in the foreseeable future. However, one option in a subset of conditions is drug repurposing. Reusing existing medicines that are either already approved or have already undergone preclinical and clinical safety testing, may shorten drug development times and reduce risk and cost (Ashburn 2004). Strong candidate drugs may have failed earlier efficacy tests or have been rejected for commercial reasons in another indication. Crucially, they should have positive safety data (Sleigh 2010). The underlying theorem is that some diseases share a common mechanism and a common drug target - or that a drug engages multiple targets. Secondary (off-target) effects may have already become apparent during development (*e.g.* in mandatory secondary pharmacology studies), in clinical use or through systematic screening (Pushpakom 2019).

A repurposing approach allows a company to skip certain development steps and have a higher certainty that others will be successful. In the simplest case, it requires a confirmatory clinical trial and extension of indications via an EU Type II variation (Annex II(2)(a) of regulation EC/1234/2008, which is common for pharmaceutical products. (Murteira 2014, Balogh 2016). In the most complicated cases (off-target repurposing and reformulation), an entirely new clinical development with the same active ingredient is required. (Oprea 2011).

In a survey of the most transformative drugs of the last decades based on a survey of physicians, one third were repurposed from a different indication (Kesselheim 2015). The definition of transformative included both innovative and ground-breaking in terms of patient care. The term innovation in the context of drug repurposing is applied to the discovery of a shared mechanism or target. However, offering the same incentives for *de novo* developed and repurposed drugs is

also seen as detrimental to the cost-effectiveness of orphan incentives (*e.g.* Art.8 of regulation EC/141/2000). A survey of drugs subject to US orphan provisions found that 73 out of 301 were repurposed drugs previously approved in other indications (Tribble 2017).

Drug repurposing efforts are common in the pharmaceutical industry in order to maximise the return of investment for a new drug by the originator. They have been subject of two previous MDRA theses (Papakrivos 2011 and Borsuk 2015). Regulatory strategies, requirements and the contribution from academia to commercial repurposing are discussed in chapter 4.

1.2.1 Types and terminology of repurposing

Drug repurposing is an increasingly common pursuit and numerous terms have been used including drug rescue, repositioning, reprofiling, redirecting, retasking, therapeutic switch (Sleigh 2010), (Ashbourn 2004), (Tambuyzer 2020). (Murteira 2013) Proposed the following terminology also used by the European Commission STAMP[2] group:
Drug repurposing is the umbrella term used to describe finding a new use for an existing drug. It may include: Drug repositioning is finding a new indication for an existing medicine. Reformulation refers to the change in dosage form which may be used on its own or to aid repositioning. Drug rescue exclusively refers to the rescue of previously terminated development candidates.
The umbrella term repurposing will be used here in order to remain open about possible reformulation. However, it is generally assumed that academia will attempt to use a repositioning strategy, whereby an existing medicine may be sourced from the hospital pharmacy. Commercial repurposing programs often require a reformulation in order to obtain additional intellectual property protection (Murteira 2014, Langedijk 2016). Fixed combinations will be out-of-scope of the present work.
In addition, extension of indication will be used exclusively to refer to the inclusion of a new indication in the marketing authorisation (MA) of an already approved drug, most commonly by the originator.
Repurposing may further be differentiated as on-target or off-target in relation to its original indication (see figure 2). Use of a medicine in a nearby indication or patient group is sometimes

[2] European Commission Expert Group on Safe and Timely Access to Medicines for Patients

included in the term repurposing, but it is often unclear if this represents a true innovation in terms of patent regulations. However, it would normally represent an off-label use in terms of the regulation of medicines. Off-target repurposing, which may come from a chance discovery or deliberate screening, is often considered more challenging as the required dose or formulation may have to differ and require additional preclinical and clinical testing (Oprea2011).

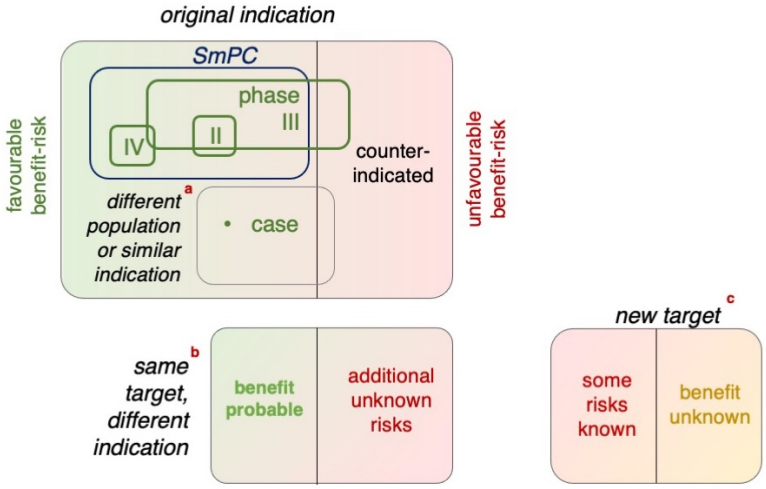

Figure 2 - Drug repurposing scenarios with respect to the original indication

The SmPC defines the approved patient group / indication within the original disease area. The SmPC is approved based on phase II and phase III trial data. The drug may be counter-indicated for some patients. Phase IV studies test the drug in a wider patient population that phase II/III studies cannot fully cover. Repurposing may cover the following scenarios:
[a] Repurposing may simply be to another patient population, or similar indication. The mechanism and potential benefit of the medicine could be expected to be the same but additional risks may be encountered. Bioavailability of the drug may be different in children. The rational may be obvious and such off-label use of the medicine might already be documented in individual case reports or health records. However, before general – and potentially unsupervised use, its benefit-risk has to be confirmed by additional (pre-)clinical studies, regulatory review and SmPC update.
[b] A second case may involve the same target in a new disease area (on-target, bottom left) where the benefit cannot be known beforehand. While the safety profile of the drug may already be well-established, the benefit and safety in the new indication would still have to be shown by scientific *in vitro* and *in vivo* experiments and in clinical trials. Bioavailability (extend and exposure) at the site of action might be different from the original indication.
[c] Repurposing (including possible reformulation) to a different target has less certainty about the efficacy, but the risk profile of the drug may partially be known. The effect may be identified as part of the original development effort or the result of deliberate screening. Such off-target repurposing requires preclinical and clinical development that may approach that of a new drug (Oprea 2010).

1.3 The role of Academia in drug discovery

Academia has traditionally contributed target hypotheses to fuel industry's drug discovery and pharmaceutical development. Small biotech firms often contribute innovative product types and technology platforms. Academia has unique and important insights from clinical practice, allowing it to discover disease mechanisms and develop the target hypothesis (Kesselheim 2015). But

academia has lacked the ability to rapidly synthesize and screen new compounds and therefore test the target hypothesis with an early lead compound in order to establish a proof of concept. Collaborations between industry and academic scientists have been responsible for major breakthroughs (Kesselheim 2015). One such example is Imatinib, a medicine that has revolutionized the treatment of chronic myeloid leukemia (CML) and spurred the development of similar medicines. Scientist Brian Druker[3] discovered a chromosomal translocation in CML that led to BCR-ABL protein kinase overactivity. Together with the pharmaceutical company Ciba Geigy (Novartis) that supplied its development library of tyrosine kinase inhibitors, the scientists selected a potent inhibitor of the BCR-ABL kinase and proved the treatment hypothesis. They thereby convinced Novartis to develop the compound into the drug Imatinib, which transformed CML from an untreatable, fatal disease to a chronic, manageable condition (Kesselheim 2015).

1.3.1 The push towards translational research in academia

The proximity to patients, closer integration of clinical and basic science and a policy push towards investing public money in translational research has led academia to engage in more early drug discovery. Additionally, many skilled scientists moved from pharmaceutical companies to academia in the 2000s. (Oprea 2011). Together, this has led to a strong base for drug development in academia, especially in a few highly integrated centres (Frail 2015, Corsello 2017). These drug discovery centres therefore gained the ability to validate the treatment hypothesis themselves before partnering with pharmaceutical companies that took the medicines through late-stage clinical development and to regulatory approval. The ability to overcome the translation gap from basic research to clinic also benefitted industry collaboration. The previous lack of proof-of-principle requirement led to a flood of poorly validated targets proposed by biomedical research, which presented a major obstacle for industry engagement (Jones 2016). Academic translational research centres uniquely benefit from close patient interaction and have available to them patient cohorts, clinical samples, patient data and patient trust. Therefore, academia has shown that it can contribute to drug development projects in a highly integrated manner throughout the drug discovery stage - and beyond.

[3] An interview about the discovery can be found in a New York Times article from 02.11.2009 “A Conversation with - Researcher Behind the Drug Gleevec“

1.3.2 A revolution in biomedical research

A revolution in biomedical research over the last two decades is a light at the end of the tunnel for many cases of unmet medical need where the disease mechanism is not yet fully understood. Aided by interdisciplinary approaches in physics, chemistry, mathematics and information technology, whole-cell level data can now routinely be collected from patients. Disease-associated perturbations in genomic or proteomic networks can be read (genomics, proteomics), simulated *in silico* and tested (*e.g.* CRISPR-Cas9 screens) in molecular detail at individual patient whole-cell level or at population level (Corsello 2020). Mechanistic hypotheses are thereby generated more quickly and can be tested in highly multiplexed cellular assays or in highly disease-specific patient derived cell lines or artificial organoids (Corsello 2020, Pizzorno 2020). Figure 3 summarises some applications of these recent technologies to drug discovery and repurposing and attempts to highlight likely key contributions by academia and industry. However, such technology may not produce meaningful results without the deep experience of experts in the disease area (Oprea 2011).

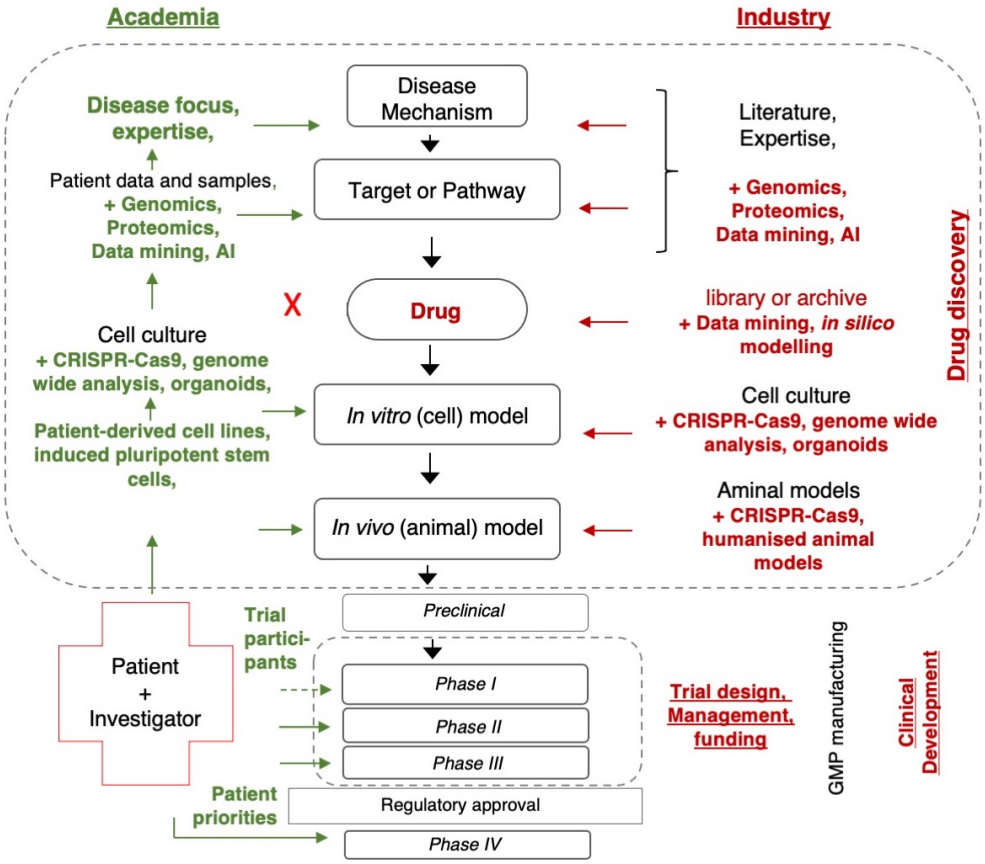

Figure 3 - New technologies being adopted by Academia and Industry

They aim to speed up understanding of disease, proposal of target hypothesis and *in vitro* and *in vivo* proof-of-principle. However, the need to confirm these in clinical research remains. See (Corsello 2020) for a recent example in repurposing discovery.

1.3.3 Academic drug repurposing platforms supported by new technologies

The continued growth in treatment hypothesis has therefore far outgrown the capacity to develop and test new candidate drugs. One option that has received renewed interest is therefore to repurpose existing medicines that are already on the market or have been abandoned during development. An example of a new discovery paradigm is that of system-wide correlation between drug and disease effects. Cell-signalling and expression networks from patient-derived models are compared to the effect on those systems by libraries of existing drugs. Such information is collected from experiments, clinical use and development data of the drug. A number of specific academic drug repurposing technology platforms have been set up as open collaborations (see Corsello 2017 for an example and Frail 2015 for a review). Some of these include funding for *in vivo* or clinical proof-of-concept studies.

1.4 Can academic drug repurposing address unmet medical need ?

To help patients with unmet medical needs in a safe and effective manner, robust clinical evidence of a benefit has to be generated and assessed. To make it universally available, regulatory approval is required. It is unlikely that clinical drug development can match the growing speed and number of scientific hypothesis generated. (Verbaanderd 2020).

In the context of this renewed enthusiasm for academic drug repurposing, it is therefore important to understand what role academia plays in drug repurposing, its clinical development, regulatory approval and/or routine clinical use.
Does the current regulatory framework support translation of academic research into new, approved treatments for existing medicines or where does it meet its limits?

It can be assumed that as with any drug development, initial treatment hypotheses do not in most cases translate to proven clinical efficacy (attrition). Secondly, while academia can take on most roles in drug development, it never replaces industry the as the final applicants or holders of marketing authorisations (Lincker 2014). Therefore, industry engagement is required to achieve the inclusion of a new indication in the product licence. On the other hand, it is known that (Pushpakom 2019) drug repurposing has yielded transformative treatments based basic and clinical research.

1.4.1 Aims and outline

The present work seeks to understand how successful examples of academic drug repurposing were translated from idea through clinical research, to what extend academic clinical research contributes to approvals and label extensions and where the current marketing authorisation framework meets its limit.

In the following chapters:

3) Provisions in the EU clinical trials regulation for academic researchers to perform proof-of-principle trials with known drugs in new indications are described. Investigator-initiated COVID-19 trials are explored to understand how researchers combined existing product knowledge and new indication-specific data to support clinical trials and to prove efficacy.

4) The regulatory pathways used by industry to extend indications and obtain new MAs for repurposed drugs are described. EMA public assessment reports (EPARs) from paediatric and orphan MAs approved between 2015-2019 and indication extensions from 2001-2018 were searched for academic clinical trials that directly or indirectly contributed to approvals. Two examples – propranolol and treosulfan are given as examples

5) The pathways and successful cases in which academic scientific evidence contributed to clinical practice through an update of the SmPC are discussed. Limits to the MA, the dilemma of off-label use and initiatives to achieve SmPC updates in the absence of commercial incentives are discussed.

2 Methods

2.1 In vivo / in vitro efficacy data used to support IITs

The requirements for investigator-imitated trials with repurposed (approved and rescued) medicines were analysed, see chapter 3 for results.

Because studies with an existing drug in a new indication require a clinical trial application based on a simplified IMPD (the SmPC and any data to bridge the gap to the new indication and trial protocol), examples were sought to analyse which data was available at the time such trial application is made.

Commonly, information preclinical and early clinical studies is only made public after approval in the EPAR. However, the 2020 COVID-19 pandemic resulted in publication of a multitude of different information at the same time. Therefore, an early IIT with Remdesivir, (Wang 2020 Lancet) and the RECOVERY trial (RECOVERY 2020-P) were chosen as two examples.

2.1.1 Example - Remdesivir

For Remdesivir the knowledge at the beginning of the trial and contribution from academic *in vitro, in vivo* and clinical studies was reconstructed from the trial publication (Wang 2020 Lancet) and a parallel CHMP compassionate use opinion (EMA/178637/2020). The references were followed and the originator of the preclinical and discovery studies along with a short description recorded. Were references were made to publications later than the initiation of the trial, the information separated. The results may or may not have been available to sponsor and it is unclear if such early information can be included in a trial application.
In chapter 4, the contribution of the IITs to the approval of the MA for Remdesivir were analysed starting from the EPAR (EMA/357513/2020) clinical efficacy section. Study type, sponsor, comedication, endpoint and result were taken from the EMA, confirmed by the respective publication or entry in clinicaltrials.gov. Interpretation of the trial results were taken from the discussion on clinical efficacy section in the EPAR and journal editorial comment (McCreary 2020) published along with the industry-sponsored trial publication (Spinner 2020).

2.1.2 Example – RECOVERY trial

For the RECOVERY trial, the study protocol (RECOVERY 2020-P) was downloaded from the trial website www.recoverytrial.net to understand the trial setup, and publications of individual trial arms were used to understand the prior clinical and preclinical experience.

2.1.3 Contributions of IITs to industry MAs

In chapter 4, the contribution from IITs to industry MAs and extensions of indication were investigated. MAs for orphan medicinal products and paediatric MAs (PUMAs) were chosen as examples because they are approved exclusively through the centralised procedure and because the use of existing medicines in a new indication is explicitly included in such provisions.

EMA annual reports are available from the EMA website at:
www.ema.europa.eu/en/about-us/annual-reports-work-programmes

For the years from 2015 to 2019, CHMP opinions are available in Annex 10.
The corresponding files were downloaded. From 416 positive CHMP opinions after initial EMA evaluation, the 85 that where subject to orphan designation at the time of CHMP opinion were selected.
Positive opinions according to each category were separated.
Hybrid application (Art.10(3)) (7%)
Known active substance (Art.8(3)) (13%)
New active substance (Art.8(3)) (78%)
Well-established use application (Art.10a) (2%)

Known active substance (Art.8(3)), Well-established use application (Art.10a) and three PUMA applications (taken from the 10-year report (EMA/231225/2015) on the paediatric regulation) were used for further analysis.
For those examples, the EPAR corresponding to the initial orphan indication approval were taken. The section on clinical efficacy was reviewed with respect to the main and supporting clinical trials. The trial sponsor, additional trial information and the trial publication if required were then retrieved from clinicaltrials.org (if available for the trial).

2.1.4 Contributions of IITs to industry extensions of indication

Contributions of academic research to extensions of indication were analysed by a similar EPAR search. The list of orphan-designation medicinal products and indications was taken from EURODIS www.eurordis.org/orphan-drug-designations-marketing-authorisations (version last update 30 April 2019).

All extension of indications (if not withdrawn) were taken and the EPAR for the original approval and subsequent Type II variations (Annex II(2)(a) of regulation EC/1234/2008) that match the second indication searched. Where the 2nd indication was applied for through a separate validation, the EPAR was analysed. Any academic study (clinicaltrials.gov: sponsor = NIH, US government, other) was noted.
All approval data are summarised in the Annex.

3 From science to clinic – investigator-initiated trials

The push for closer integration of basic and clinical sciences has allowed the lab scientists to elucidate the mechanisms of diseases and propose new treatment hypotheses for existing drugs (Oprea 2011). But most academic research units do not have the full experience and comprehensive set of expertise for drug development. Therefore, it is hoped that drug repurposing can allow even a small academic unit to propose a new treatment hypothesis, validate it *in vitro* or in *in vivo* animal models and test the repurposed treatment to address medical need in an indication, in which no medicine is yet approved. Such candidate drug would be sourced from the hospital pharmacy and its safety profile well established.

Alternatively, the treatment hypothesis itself may come from previous clinical research. The role of academic investigators is traditionally seen in post-approval (phase IV) studies, which study the use of the medicine in clinical practice (Suvarna 2012). Such observational studies, case reports and real word evidence[4] play an important role in the study of the safety and efficacy of approved medicines and may by themselves lead to new repurposing hypotheses being proposed by clinical investigators.

3.1 Regulatory and design aspects of clinical trials

Clinical studies aim to investigate the safety and efficacy of medicinal products. They study the clinical, pharmacological or pharmacokinetic properties of drugs or identify adverse reactions (Art.2.2(1) of the EU clinical trials regulation EC/536/2014). This includes the above observational studies.

If the use of the medicinal product in the study no longer follows clinical practice, but the decision to administer the medicine is made according to the trial protocol (*e.g.* randomization) or if additional diagnostic data are collected, the study is no longer observational and becomes a

[4] Real word evidence, such as post-hoc analysis of electronic health records is becoming a powerful tool to study the utility of a drug in clinical practice. Its potential lies in the study of potentially millions of patients and cross-correlation with additional data sets, such as genomic information. It has the potential to discover unknown adverse reactions and possibly discover new uses for drugs by capturing serendipitous events. Thereby RWE complements clinical studies. But it has been shown that currently RWE cannot fully substitute or replicate clinical trial evidence. (Bartlett 2019)

clinical trial (Art.2.2(2)). Thereby it is subject to the EU clinical trials regulation (EC/536/2014), subject to supervision by national authorities and ethics committees and subject to the principles of good clinical practice (GCP) Art.47 of regulation EC/536/2014.

In order to prove safety or efficacy of new medicines or of existing medicines in a new indication, such interventional clinical trials are usually required. Interventional trials follow a study protocol (rather than a physician's decision) to administer the drug based on preselected criteria designed to test the hypothesis. The gold standard is a controlled, randomized trial that compares the treatment effect against a control, such as the standard of care or placebo.
To reduce the effects of confounders such as disease progression or comedication and human bias, additional measures carefully matched to the trial and its purpose are taken. These can be inclusion/exclusion criteria, patient stratification, cross-randomisation of comedication, cross-over designs, blinding of patients and investigators to the study drug and/or trial results. Successful trial designs require expertise in both design principles (see Yordanov 2015) and the disease.

3.1.1 Risk-proportionate trial oversight

Completing a full clinical trial application (CTA) data package and implementing a complex trial monitoring system, even though the trial medication is approved and no additional risk is expected from the trial design, may represent an undue burden for academic sponsor-investigators. It may thus discourage trials that could have uncovered new risks or benefits.

Requirements for such trials may therefore be adapted. The level of regulatory trial oversight, monitoring by the (academic) sponsor and documentation required should be proportional to the level of risk from the trial design and the investigational medicinal product (IMP) (Art.48 of EC/536/2014). Such risk assessment in itself requires experience and is best performed within the existing framework of a trials unit (Tudur Smith 2014).

General risk classifications have been proposed that assess the risk against clinical practice. In clinical practice, prescription of medicines is intended to be done according to its approved SmPC. However, in areas of unmet medical need, off-label use (*e.g.* use in another indication or patient group) may be permitted (Art.5 or directive 2001/83/EC, see also chapter 5). The ultimate responsibility lies with the treating physician. National treatment guidelines, reimbursement by

payers and national law may guide this. Because such off-label use may already be common in clinical practice, clinical trial regulations take both on-label and off-label use into account when assessing the risk of an IMP.

An OCED recommendation (OECD 2013)[5] on the governance of clinical trials in 2013 proposed such a risk categorisation, see table 1.

Table 1 - OECD Clinical trial risk classification with respect to the SmPC

	Approved MP According to SmPC	Approved MP Off-label (evidence of common clinical use)	Approved MP Off-label (no evidence of clinical use)	New medicinal product
Repurposing scenario	Phase IV, Observational study, data collection, hypothesis generation	Evaluation of safety (efficacy) of repurposed drugs known to be widely used off-label	Clinical trial to test or confirm repurposing hypothesis	Rescue of development drug, or drug no longer licenced in any EU member state
OECD Risk category	A (usual care)	B1 (modified use)	B2 (modified use)	C (new product)
EU	Low-intervention trial (or observational study)	Low-intervention trial SmPC + new data for gaps	Clinical trial SmPC + new data for gaps	Clinical trial full IMPD
UK (MHRA 2011)	A no higher risk than standard of care	B – somewhat higher risk than standard of care - SmPC + new data for gaps		C Clinical trial, full IMPD
US IRB for all trials	Non-registration trial[a]	Clinical trial with IND and FDA overview, cancer-drug exemption [b]	Clinical trial with IND	Clinical trial with IND
Japan	Non-registration [c] trial, IRB approval	Registration trial, IRB approval and PDMA supervision		

(Table from (OECD 2013) recommendation with adaptations for repurposing, low-intervention trials according to Art.2.2(3) of regulation EC/536/2014, and US regulation)

[a] In the US and Japan, a tangential concept of registration and non-registration trials exist. If the drug is used according to its SmPC, the trial is considered a non-registration trial and only requires approval from the institutional review board. These trials are not intended to produce the data required for regulatory approvals. Trials outside the SmPC follow the registration-type and require an investigational new drug application (IND). Full IND requirements are found in US 21CFR 312.23 these contain IB (SmPC if available), detailed trial protocol for phase 2/3 studies, and detailed information on the investigational product: manufacturing and quality (CMC), pharmacology, toxicology and previous clinical experience.

[b] An IND exemption for sponsor-investigators was introduced in 21CFR312.2(b)(1) to allow clinical trials with approved medicines off-label in cancer, where there is no significantly higher risk due to change in duration, administration or patient population compared to clinical practice.

[c] In Japan off-label use or clinical trials outside the scope of the SmPC by academic investigators are not common (Imanura 2010).

[5] The OECD document predates the EU trials regulation, but it is useful to compare these categories between countries. The old EU trials directive 2001/20/EG already allowed a risk-based trial oversight but was implemented differently between member states (OECD 2013). The UK MHRA had already created a risk-based classification system (MHRA 2011). Some elements, such as low intervention trials were incorporated in the EU clinical trial regulation EC/536/2014.

3.1.2 Provisions for trials with approved medicines in the EU

A clinical trial application has to be based on scientific, preclinical safety and initial clinical data to demonstrate safety to the trial participants and make plausible the rationale for the expected efficacy (including bioavailability by suitable pharmacokinetic data.).

However, for active projects such data may already be held by the originator and for marketed products, health authorities' prior assessment in the SmPC may be referred to where appropriate.

3.1.2.1 EU product documentation requirements for clinical trials (IMPD and IB)

Documentation requirements for clinical trials are given in Annex I of the clinical trials regulation EC/536/2014. The investigational medicinal product dossier (IMPD) contains the product knowledge to be reviewed with the trial application (CTA) by the HA and ethics committee (EC). The IMPD contains all data on the IMP, its manufacturing and quality along with preclinical and clinical development and discussion of current literature knowledge of the product if available. The investigator brochure (IB) then summarises the information relevant to the investigator. IMPD and IB are therefore updated as product knowledge is gained[6].

When a clinical trial is performed with an IMP authorised in an EU member state, different requirements may apply with respect to the IMPD and IB. They may be substituted by the SmPC and supplemented with relevant nonclinical and clinical data that supports the use in the new indication (simplified IMPD). (Annex I G.1.2. of regulation EC/536/2014). This depends on how far the trial protocol deviates from the SmPC and the IMPD data package may be tailored to bridge the gaps with additional data.

The low intervention trial category introduced in the EU clinical trials regulation (Art.2.2(3) of EC/536/2014) is a formalised way for such risk-proportionate adaptation of requirements. It allows the use of a medicine according to published evidence of off-label use[7] and very limited

[6] The IMPD and IB are not publicly accessible. For research purposes, a summary of the product information is also be available in the trial protocol (if public), the trial publication (if published). At the time of approval, assessment of all preclinical data and clinical data is then summarized in the (EU) public assessment report (EPAR).

[7] *the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned".* Art.2.2.(3)(ii) of EC/536/2014.

(*e.g.* low-risk diagnostic) intervention[8]. The IB and the IMPD may be replaced by the SmPC and lower requirements exist for trial monitoring. Such trials can serve to gain knowledge about the safety and efficacy in known off-label uses. Low-intervention trials would not allow a new hypothesis to be tested. However, the beforementioned simplified IMPD requirements still apply to those.

Even if the trial is performed with a rescued development drug where no SmPC can be referred to, the benefit for the originator is that data is already available, the IMPD and IB may only have to be updated or an IMPD amendment filed to add the new data to a current project[9].

3.1.2.2 Provision of the study medicine and monitoring

Clinical trial monitoring can also be designed proportionate to risk to the patient while assuring the quality of the data collected. (Tudur Smith 2014) (Art.48 of EC/536/2014). Requirements for IMP tracing are reduced and an approved IMP may be sourced from hospital pharmacy, who may also perform label changes required for blinding. (BfArM 2009)

In the case of medicines in clinical development Industry may support investigator-initiated trials by providing documentation, study medicine, advice and scrutiny. Industry may also assume the role as a sponsor of the trial (Suvarna 2012).

3.1.2.3 Considerations with respect to on-target / off-target repurposing

In on-target drug repurposing the pharmacology of the drug-target pair is already known. The chosen dose, pharmacokinetic (PK), toxicology and secondary pharmacology data may be broadly applicable in the new indication. However, repurposing to a new patient group may still expose patients to additional risks due to differences in PK, comorbidity or comedication. Thus, high quality data supporting the new treatment hypothesis is minimally required, while additional clinical or preclinical studies may be required in a new target population.

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[8]A placebo control is not contrary to the concept of a low intervention trial *per se* as long as withholding the treatment in the control group does not represent a risk the patient.

[9]. A licensee (*e.g.* small biotech company) or collaborator (*e.g.* academia) typically obtains this information from the originator or obtains its permission to reference. It has been noted that while this is common for active development programs, it is a significant burden for programs that are no longer active (Frail 2017).

Entirely new (off-target) interactions for existing drugs are frequently found in screening experiments, but far higher obstacles exist for those cases. Oprea et al. (2011) noted that many such reports or even patent applications show micromolar affinities which are likely to be too weak to achieve physiologically relevant concentrations at the approved dose. (A finding that is likely to invalidate the repurposing hypothesis).
For older medicines it is also quite possible that safety has not been studied extensively prior to approval and that existing data would no longer meet today's regulatory requirements. Such cases are likely to require additional preclinical and clinical phase I and II studies. Overall, these approach the complexity of a new drug development program (Oprea 2012). Thus, these cases are likely to be outside the remit of academic drug repurposing.

3.1.3 Provisions for academic investigator-initiated trials

The EU regulation applies to commercial and non-commercial sponsors alike. However, academic sponsors may benefit from reduced financial burden. For example, in low-intervention trials, reimbursement and damage insurance (Art.76 of regulation EC/536/2014) in established clinical practice applies. Such provisions for other trial categories exist at national level (BfArM 2009). Scientific advice to seek to agencies agreement on required data packages and trial protocol may be fee-reduced or aimed specifically at academic investigators. Their early use is highly recommended (Pantziarka 2017)

3.2 Prevalence of academic clinical trials with known medicines

The majority of exploratory trials with approved medicines are expected to come from academic investigators (OECD 2013), while large industry phase III trials dominate in patient numbers. Only one third of trials registered between 2000 and 2010 were from industry (OECD 2013). IITs are dominated by small trials with fewer than 100 participants (Califf 2012). Many of such trials are too small to test or compare marginal treatments and contribute to indication extensions. But they may serve to test new ideas or validate biomarkers (Califf 2012). A systematic search of clinical trial activity after approval in the EU showed a similar time-distribution compared to industry-sponsored trials (Langedijk 2016).

A recent review/database of the state of current repurposing efforts lists 280 repurposed treatments in oncology of which 70 are in late-stage clinical trials. 95% of those have a non-commercial sponsor (Verbaanderd 2019).

3.3 Investigator-initiated repurposing trials for COVID-19

In late 2019, a new respiratory disease (COVID-19) emerged in Wuhan, China. It spread globally and was declared a pandemic on 11th of March 2020.
Already two months earlier, on 13th January 2020, the genomic sequence of the SARS-CoV2 virus had been published (Wu 2020). This led to an intense international search for medicines that may prevent SARS-CoV2 infection or treat the COVID-19 condition. Platform technologies in antibody (Weinreich 2020) and vaccine development (Voysey 2020) and drug repurposing were seen as options to bring medicines to patients faster than would be possible with other *de novo* drug development.

Similarities with other respiratory viral infections further supported drug repurposing. Proposed interventions were targeting 1) viral infection 2) viral replication 3) disease progression (e.g. strong inflammation, and acute respiratory distress syndrome, thrombosis). It was understood that antiviral drugs may act on 1) and 2), while host-targeted therapies may prevent damage to lungs due to inflammation. Therefore, it was likely that not one drug would be the solution, but that medical expertise was required to apply the right medicine or combination of medicines at the right stage of the disease.

In the following, the example of an early investigator-initiated clinical trial with the rescued development drug Remdesivir and the large platform trial RECOVERY comparing approved drugs are given.

3.4 Remdesivir – repurposing of a rescued development drug

Remdesivir is a broad-spectrum antiviral adenosine analogue that targets viral RNA replication (wang 2020 Lancet). It was developed by Gilead Sciences for the treatment of Ebola but it was abandoned at the end of the outbreak.

Remdesivir is therefore not an approved medicine. However, it had been subject to a full development program including preclinical and clinical studies and only failed in comparative efficacy trials against another medicine in the initial Ebola indication one year before (Mulangu 2019)[10]. This made it a good repurposing (rescue) candidate for industry.

On 06.02.2020 an investigator-initiated controlled, randomized clinical trial of Remdesivir in 237 COVID-19 patients started in Hubei, China.

3.4.1 Data and product knowledge supporting an early IIT

The IMPD and IB that describe the product knowledge are part of the trial application that is not normally publicly available for analysis. However, both the trial publication (Wang 2020 Lancet) and a parallel EMA compassionate use opinion[11] from 03.04.2020 describe the product knowledge and data supporting the treatment hypothesis. Given the proximity of the compassionate use opinion and the clinical trial application, the same data sources may have been used for both. The CU references the IB for non-clinical aspects.

In the following, the role of the early investigator-initiated trial in Hubei, China and an NIAID trial in the repurposing of Remdesivir are investigated. In particular, (academic) *in vitro* and *in vivo* studies that supported the early trial will be described below.
(The full history of Remdesivir will be subject of a parallel MDRA thesis from another student.)

[10] The Ebola trial itself was led by National Institute of Allergy and Infectious Diseases (NIAID, USA) together with Institut National de Recherche Biomédicale (Congo) and Partners from Universities and the charity Médecins Sans Frontiers to compare efficacies of 1 NIH (US government) and 3 commercial treatments.
[11] On 26.03.2020, Estonia, Greece and the Netherlands requested a harmonized EMA opinion on compassionate use according to Article 83(3) of Regulation EC/726/2004. Given the pandemic situation, the CHMP adopted an opinion within one week. In line with the mandate of Art.83(2) to allow treatment in cases of unmet need in life-threatening disease, and proposed by the applicant, EMA gave a positive CU opinion for Remdesivir initially in mechanically ventilated patients and later extended to all severe-stage patients. (EMA/178637/2020)

3.4.1.1 In vitro and in vivo efficacy data

Table 2 - In vivo / in vitro evidence prior to the early Remdesivir IIT in Hubei

Study / publication	Model system	Result	Source	Cited in CU [a]
(Sheahan 2017) Purpose: Future pandemic preparedness	In vitro/in vivo (non-GLP) Human lung cells and animal model including toxicity	Inhibition of related coronaviruses **MERS-CoV** and **SARS-CoV**	Academic US, Poland, collaborators from Gilead Inc.	*yes*
(Warren 2016) Purpose: Protection from Ebloa	In vivo Animal model Rhesus Monkey	Protection from death from **Ebola virus** (original indication) 3 days after infection	US government (Army research institute and CDC), Gilead	
(Brown 2019) Purpose: Future pandemic preparedness	In vitro non-GLP) Human lung cells and animal model including toxicity	Inhibition of **Orthocoronaviruses**	Academic US, collaborators from Gilead Inc.	
(Sheahan 2020) (accepted 2019)	In vitro/in vivo (GLP unknown) Human lung cells and animal model including toxicity	Therapeutic efficacy against **MERS-CoV** compared to lopinavir/ ritonavir and interferon beta	Academic US	*yes*
(Wang 2020 Cell Res.)	In vitro, VERO (monkey) cells	Inhibition of **SARS-CoV-2** EC50 of 0.77 µM [b]	Academic, Wuhan, China	*yes*
Studies published after start of IIT (NCT04257656)				
(de WIT 2020) (13.02.2020)	In vivo Animal model Rhesus Monkey	Reduction in disease severity in **MERS-CoV** infection Higher protective effect than therapeutic effect.	US government (NIH) Academic US	*yes*
(Pizzorno 2020) (pre-published 02.04.2020)	Innovative In vitro model using **human 3D cell culture** from biotech Epithelix SARL.	Suppression of **SARS-CoV2**	Academic, France	
(Williamson 2020) (pre-published 22.04.2020)	In vivo Animal model Rhesus Monkey	Reduction in disease severity in **SARS-CoV2** infection	US government (NIAID) Gilead Inc.	
Additional studies cited in EMA CU (EMA/178637/2020)				
EMA CU citing Gilead IB, not published	In vitro, VERO (monkey) cells	Inhibition of **SARS-CoV-2** EC50 of 0.137 µM	cited as China CDC in the CU	*Yes, CU only*
EMA CU citing Gilead IB, not published	In vivo Animal model (mouse)	Prophylactic effect of SARS-CoV with Remdesivir given 1 day prior to exposure	only IB referenced	*Yes, CU only*

[a] Study results were cited as *IB from 21.02.2020 in the CU*

[b] The authors also reported such effect with Chloroquine (EC50 = 1.13 µM)

Available data prior to the trial in Hubei is shown in Table 2. In February 2020, Remdesivir (and chloroquine) had been shown to inhibit SARS-CoV2 infection in monkey cells (VERO E6) (Wang 2020 Cell Res.)[12] The investigators also cited individual case studies (Wang 2020 Lancet).

[12] Later studies then confirmed this finding in human 3D cell culture (Pizzorno 2020) and rhesus monkeys (Williamson 2020) but these had not been published at the time of the start of the trial.

Supporting evidence was given from the development history. Academic researchers had tested Remdesivir on related SARS-CoV and MERS-CoV Coronaviruses *in vitro and* in *vivo* to prepare for future pandemics.[13]

In animal models of earlier pathogenic SARS-CoV and MERS-CoV viruses it had shown superiority to interferon-beta and lopinavir/ritonavir. However, in SARS-CoV2, the efficacy rested on the bridge of the VERO cell assay that showed similar EC50 values as for SARS-CoV and MERS-CoV (as was concluded by the CU (EMA/178637/2020).

3.4.1.2 Toxicological, PK and safety data

The EMA CU describes comprehensive toxicology studies: Secondary pharmacology, safety pharmacology and pharmacokinetics, drug-drug interactions and toxicology are mentioned in the CU and include representative human cell line models and rat and cynomolgus monkey models. These are presumed to be proprietary Gilead data from the earlier development. Studies involved both the Remdesivir prodrug and the GS-441524 metabolite.
PK and safety in human trial participants were shown in Gilead-sponsored phase I clinical trials performed between 2016 to 2019 (pre-COVID-19). Additional safety data was provided based on the NIAID sponsored phase 2/3 Ebola study (Mulangu 2019).

3.4.2 Trial outcome

The study was ended due to rapid control of the pandemic in China. At 28 days, no significant benefit was seen for Remdesivir in the primary endpoint of time to clinical improvement. The authors noted that earlier treatment may be more effective[14], but the result was not significant. The trial was included in the discussion on clinical efficacy during EMA eventual MAA assessment. A later further NIH-sponsored trial in the US gave a clearer result. (Beigel 2020) (see chapter 4 for both).

[13] „Given its broad activity, this antiviral could be deployed to prevent spreading of a future coronavirus outbreak, regardless of the specific virus that jumps over“ Science translational medicine editorial comment accompanying (Sheahan 2017)
[14] Similarly, the EMA CU noted that the *in vivo* data support a prophylactic use better than a therapeutic use and finds that data available only cover treatment regimens starting prior to infection and up to 1 day after infection at the latest. Given similar insights from other acute viral disease, they note that late-stage COVID-19 may not represent the best use of Remdesivir.

3.5 COVID-19 repurposing trials with approved medicines

Other repurposing efforts focussed on approved medicines. Repurposing of approved medicines was seen as one of the ways to get help to patients early and universally. In an early survey of 201 trials on the 25th of March only 8.7% of interventions were new molecular entities. 55% of trials were sponsored by hospitals, 9% by government and 18% by industry (Mehta 2020).

3.5.1 Overview of repurposing trials for COVID-19

Many trials were considered unlikely to yield meaningful results. They either contained no clinical endpoints, fewer than 100 patients or were open label (Mehta 2020). The authors noted that overstretched frontline clinicians should not be required to set up such trials.

On the 16th of March 2020 EMA issued a call to pool resources into large scale multi-center multi-arm clinical trials in order to generate comparative knowledge. EMA noted that this would require comparable endpoints, and common robust study scale and study designs across the proposed treatments. [15] As at the time no treatment had been shown to be effective, the inclusion of a negative control was recommended. Further, EMA recommended to consider the inclusion of children or adolescents and that adequate paediatric PK and safety data should be collected.

Three large global repurposing trials were set up: SOLIDARITY (WHO), DISCOVERY (France) and RECOVERY (UK) (Naci 2020).
In the following, the principles of the trial design, knowledge of the IMP prior to the trial and results of the RECOVERY trial will be explored as an example.

[15] „The CHMP is concerned about the amount of planned small studies or compassionate use programmes across Europe that are unlikely to be able to generate the required level of evidence to allow clear-cut recommendations“ (EMA/136815/2020)

3.6 RECOVERY – an example of a large phase 2/3 platform trial

RECOVERY is a large phase II/III multicentre, adaptive randomised controlled trial set up as investigator-initiated platform trial by the University of Oxford. It was rolled out to 176 sites across the UK. The reasoning was that it was better to enrol as many patients as possible in a simple trial than leave physicians to prescribe unproven treatments in the longer term (Maher 2020).

Therefore, in order to include less well-equipped hospitals and staff who may be stretched by the epidemic, the study protocol and consent forms were kept short. A single set of data was entered at diagnosis and at release/after 28 days. Randomization was done via the same web interface that was used to collect patient data and report adverse events to the central coordinating office[16] (RECOVERY 2020-P). Additional patient data was added centrally from laboratory and electronic health records to reduce workload and complexity of GCP and monitoring requirements at the trial site[17]. A high proportion of central data management thus enabled a high level of central monitoring. The setup was based on an electronic trial and health record platform established in the UK in the preceding years (NHS Digitrials) (Maher 2020).

The adaptive design of the trial used large numbers of patients (12'000 in the first 3 months), the same method and endpoint for treatment arms. It then allowed treatment arms to be opened or closed during the trial. Thereby, comparative efficacy data could be generated on a common primary endpoint using a simple controlled, randomized design without prior stratification of patients. Additional insights came from analysis of patient subgroups (RECOVERY 2020-P).

Analysis of efficacy and safety were performed by an independent data monitoring committee (DMC) throughout the trial, thereby allowing arms to be halted and closed or new arms opened as new treatment hypotheses emerged while initially blinding investigators from trial results (RECOVERY 2020-P).

[16] Assessment and possible expediated reporting of unexpected events were then done centrally. Additional safety monitoring of patients was established for later treatment arms with development IMP, such as antibody therapy.

[17] While the core trial design was simple, additional exploratory data could be collected. Smaller numbers of better-equipped trial-centres could add additional diagnostics e.g. electrocardiograms collected during routine practice or laboratory assays. In later iterations of the trial factorial design allowed for the overlapping combination of treatments (e.g. +/-treatment, +/- aspirin) while avoiding bias. (RECOVERY 2020-P).

Table 3 - Initial IMP study arms in the RECOVERY trial

Lopinavir/Ritonavir (1616 patients, 70% of whom were on oxygen support) (RECOVERY 2020-L)	
Hypothesis	Off-target repurposing of antiviral drug from HIV to SARS-CoV2 main protease
Prior *in vitro* / *in vivo* data	*In vitro* data showed inhibition of related SARS-CoV, SARS-CoV2 and MERS-CoV proteases. Reduction of symptoms but not viral load in a COVID-19 ferret model. Reduction of clinical symptoms and viral load in marmoset monkey MERS model
Prior clinical data	Reduced risk of adverse outcome and viral load historic in a controlled study of ARDS patients. Inconclusive evidence from observational studies. Inconclusive evidence from a small 199 patient controlled trial. The treatment had been tested in a small controlled trial during the 2002-2003 SARS outbreak and in earlier studies of acute respiratory distress syndrome (ARDS) but the evidence was not conclusive.
Outcome	**No reduction in 28-day mortality, duration of hospital stay, disease progression to ventilation or death.**
Additional comments:	No meaningful benefit was found in the RECOVERY trial. Therefore, the DMC recommended that principle investigators be unblinded to the effect of the drug and the treatment arm was stopped [a]. It cannot be excluded that another use of Lopinavir/Ritonavir, such as earlier application or a different formulation of this antiviral drug may benefit COVID-19 patients. Questions remained about bioavailability due to high plasma protein binding.
Hydroxychloroquine (1561 patients) (RECOVERY 2020-H)	
Hypothesis	Host-cell targeting, prevention of virus uptake, likely on-target with respect to approved 2nd indication.
Prior *in vitro* / *in vivo* data	In vitro activity against SARS-CoV and SARS-CoV2. Inhibitory concentration required likely higher than plasma- concentration. No effect in animal models.
Prior clinical data	Inconclusive benefit in observational studies. No benefit in mild-moderate COVID-19 in an earlier RCT.
Outcome	**No reduction in 28-day mortality, longer duration of hospital stay**
Comment / outlook	Though negative, the outcome solved a clinical dilemma. Hydroxychloroquine was used early-on in the pandemic, but studies were inconclusive. Laboratory cell culture experiments and data from small clinical trials had suggested that it may shorten the time to recovery. Because some of the small early studies were widely publicized and the benefit exaggerated, 1 in 6 of the first 1000 COVID-29 trials included (hydroxy)chloroquine (Naci 2020), despite warnings about the lack of evidence. Patient demand for chloroquine trials soared, left trials for other drugs without participants or forced changes to trial design to include the drug (Ledford 2020).
Dexamethasone 2104 patients (RECOVERY 2020-D)	
Hypothesis	On-target, host-cell targeting. Approved in similar indication (inflammation) but counter-indicated in viral infections
Prior *in vitro* / *in vivo* data	n/a
Prior clinical data	Proinflammatory biomarkers were found in COVID-19 patients in a retrospective study (Ruan 2020). Improved clinical outcomes in a small trial of a similar drug, methyl-prednilsolone. Evidence from the 2002-2003 SARS outbreak showed reduced viral clearance (negative effect) in patients treated early. (Lee 2004).
Outcome	**Lower 28-day mortality in patients receiving either oxygen or mechanical ventilation**
Comment / outlook	The repurposing case is on-target and in a near indication. But the use of corticosteroids had been counter-indicated in viral infections and in early COVID-19 guidelines (Dagens 2020). Because of this conflicting evidence for or against the use, the trial results were clinically important. The study authors caution that the result is likely to be dependent on the right dose at the right disease stage in the right patient and caution against the use at an (early) stage when the control of the viral replication is paramount. EMA CHMP opinion according to Art.5(3) of EC/726/2004 recommended an update of the SmPC. (EMA/509632/2020)

[a] press-release with RECOVERY 2020-D) available at www.recoverytrial.net

In the initial iteration of the trial, the three treatments (hydroxychloroquine, lopinavir/ritonavir and dexamethasone) were compared in a 2:1:1:1 ratio against standard treatment. The patients were enrolled at UK hospitals and were receiving no oxygen, receiving oxygen (majority) or if applicable were on ventilator support.
The primary endpoint was 28-day mortality. Additional endpoints were duration of hospital stay and progression to mechanical ventilation. Those parameters were thus clinically meaningful. The study was optimized to confirm/refute the different treatment hypotheses, rather than select the best use for a particular drug.

All three medicines were well-established and off-patent. They are used extensively in clinical trials and off-label in clinical practice against COVID-19 and have a well-established safety profile. The study medication was supplied by the hospital pharmacies.

Results are shown in Table 3. The RECOVERY trial was able to show that both hydroxychloroquine and lopinavir/ritonavir had no positive effect on mortality and hydroxychloroquine had a potential risk of harm. In patients receiving either oxygen or mechanical ventilation, 28-day mortality was reduced in the dexamethasone arm. Therefore, the anti-inflammatory drug benefited the patients most at risk of death. Both lopinavir/ritonavir and hydroxychloroquine had been included in national treatment guidelines (Dagens 2020), while the use of corticosteroids had been counter-indicated in viral infections.
This led to a change in national treatment guidelines and the revocation of an FDA emergency use authorization[18].
Dexamethasone was validated as an effective treatment, allowing it to be included in clinical practice. EMA took an unusual approach propose an update to the SmPC for this out-of-patent medicine via a CHMP opinion according to Art.5(3) of regulation EC/726/2004 requested by the EMA executive director (see chapter 5).

[18] „Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate“ FDA, 15.06.2020

4 Academic contributions to Industry MAs

4.1 Commercial rationale for drug repurposing

Drug repurposing is a common strategy for the originator of a new medicinal product. The originator owns all development data and patents for the drug substance, use and likely manufacturing. For a recently approved product, development data includes toxicology, safety pharmacology and pharmacokinetic data, existing human PK data from phase I trials and the initial safety profile developed from cumulative phase I-III. Therefore, additional regulatory requirements and risk of failure in the second indication are reduced (Ashburn 2004).

As a result, post-approval extension of indication are routine lifecycle strategies for pharmaceutical companies aiming to maximize a drug's return on investment. The first years after granting of the marketing authorization are the most valuable (Balogh 2016, Langedijk 2016). The originator commonly seeks to extend the indications of the drug through variations to the MA. Alternatively, a new MA may be applied for in case of an (ideally) reformulated product in a paediatric or orphan indication in order to benefit from additional market protection.

4.2 Marketing approval pathways and initial exclusivity

The EU directive 2001/83/EC and subsequent regulations encourage post-approval innovation in additional indications:
The originator receives 10 years market exclusivity for the product in its initial indication under a full Art.8(3) application. All subsequently added indications are covered by the same exclusivity period as part of the global marketing authorization, Art.6(1) of the directive 2001/83/EC. An additional 1 year of market exclusivity is added to the global MA if a new indication is approved within the first 8 years. This is subject to a test of "a significant clinical benefit in comparison with existing therapies" Art.14(11) EC/726/2004. Thereby, not only is the market of the product increased but a significant benefit in a small indication can enable another year of overall peak sales in the main indication. Such incentives based on the global MA are therefore highly valuable

incentives for industry. Art.8(3) applications may include the use of literature to fulfil some of the requirements (mixed application).

Generic Art.10(1) or biosimilar Art.10(4) applications do not allow for a change in indication. Hybrid applications Art.10(3) contain limited additional data that commonly cover formulation changes. They are not common routes used for (Langedijk 2016, Papakrivos 2011). Well-established use (Art.10a, literature only) applications are extremely rare.
Full applications according to Art.8(3) are therefore the main route to obtain a new MA for a repurposed drug. Additional indications, including the first repurposed indication for a new drug are then added via an EU Type II variation (Annex II(2)(a) of regulation EC/1234/2008) or included in a line extension.

4.3 Market incentives for industry beyond initial exclusivity

Once the initial patent, its supplementary protection certificate and exclusivity periods have expired, the market is open for competition by generic manufacturers. From thereon, there is limited scope for the protection of additional indications by themselves[19].
Therefore, if an existing drug is to be redeveloped commercially during the generic period, it has to be able to be protected from generic competition and have a large enough market that supports a premium pricing. (Ashburn 2004) (Murteira 2014).

4.3.1 Orphan and paediatric incentives for repurposed medicines

Orphan and paediatric medicinal products can apply for a marketing authorization which is independent from the global MA and covered under new exclusivity terms. The Paediatric-use marketing authorisation (PUMA) (Art.30 of EC/1901/2006) establishes a new 10-year market exclusivity term for the paediatric MA only. The orphan designation (Art.8 of regulation EC/141/2000) establishes a new 10-year market exclusivity term (12 years for paediatric medicines) for the first-in-indication medicine or for one that shows a significant benefit over existing treatments.

[19] The intention of the intellectual property system is to allow a pharmaceutical company to recoup the cost of development during the exclusivity period. In the following generic period, market competition lowers the price of the medicine close to its production costs. This is essential for the sustainability of health care systems, but this limits commercial options to repurpose medicines.

4.3.2 Other incentives for repurposed medicines

For other indications, Art.10(5) of 2001/83/EC offers one year of data protection (during which no application is accepted from a competitor), where a well-established medicine was repurposed to a new indication and substantial additional preclinical and clinical data were generated.

At the same time an additional patent may be sought to protect the use of the medicinal product in a new indication. However, publication of the invention in case reports, entries in public (trial) databases or scientific publications may precede the commercial development and invalidate the patent (Oprea 2011).

4.3.3 Applicability of provisions to repurposing

In the above cases, there is uncertainty if the new indication can be protected from off-label use. If an additional exclusivity term or patent is obtained for the new additional indication, only this MAH may include such information in the SmPC. However, as will be discussed in chapter 5, physicians may prescribe an alternative generic medicine off label, when there is good scientific basis for such a decision. There is considerable controversy if this includes the prescription of a generic in the proprietary indication for cost saving reasons. This is a risk that may have prevented repurposing in many cases where the original patent and exclusivity had expired (Langedijk 2016).

An option to create additional protectable exclusivity is reformulation into a dosage form specific to the new indication. Medicines containing the same active ingredient, but the original formulation would then not be a generic substitute to the new product.
Thus, there exist few market incentives for either originator or competitor to add a new indication to the label once a drug has become generic. Exceptions are orphan designation and PUMA. To succeed commercially, these are ideally combined with a reformulation when appropriate.

4.4 Prevalence and timing of drug repurposing in industry

Post-approval addition of indications is common in industry and a number of comprehensive studies exist. A first study by Ashburn and Thor in 2004 described a growing trend in industry to

find additional uses for their drugs and a booming biotechnology field that had developed either based on a strong indication-knowledge or an innovative screening technology platform.
Murteira *et al.* (2013) performed a systematic literature search of repurposing cases and proposed a unified nomenclature for repurposing and reformulation cases.
Langedijk (2016) compared EMA approval and clinical trial data bases to track clinical trial activity and approval proceeding and following introduction of generic competition. Clinical trials with approved medicines by both industry and academia are common but drop to half after the end of the exclusivity term.
84 percent of the top 50 best-selling medicines had at least one indication added after approval (Sleigh 2010). An analysis of product authorized by the EU centralized procedure (Balogh 2016) showed a peak of additional indications early during product lifecycle (2-3 years after MA), consistent with expected return on investment.

In these studies, very few non-originator approvals of new indications were noted. This is to be expected given the ownership of data, intellectual property and product expertise. In addition, such cases may in part be masked because public databases may not cover an observation window past the 10-15 years of patent and market protection (Langedijk 2016). On the other hand, a number of individual success stories have been described (Langedijk 2016, Pushpakom 2019).
Such known examples may serve illustrate regulatory paths, academic contributions, hurdles and bases of HA decisions.

4.5 Analysis of contributions from IITs to Industry approvals

As academia is not the MAH of new drugs (Lincker 2014), a search of all (commercial) recent approvals of existing drugs with a new orphan designation (non-orphan to orphan repurposing), extensions of indication (orphan-orphan) and paediatric-use marketing authorisations was performed to identify academic contributions to clinical efficacy in the form of investigator-initiated trials in their European public assessment reports.

4.5.1 EPAR search of IIT contribution non-orphan – orphan repurposing

Orphan designation medicinal products that received a positive CHMP opinion were retrieved in Annex 10 of the EMA annual reports from 2015 to 2019, see figure 4. Of those, only those approved according to Art.8(3) with known active substance or Art.10a well-established use or through a (non-orphan) PUMA were included. (A full evaluation and references to the EPARS are shown in the Annex.)

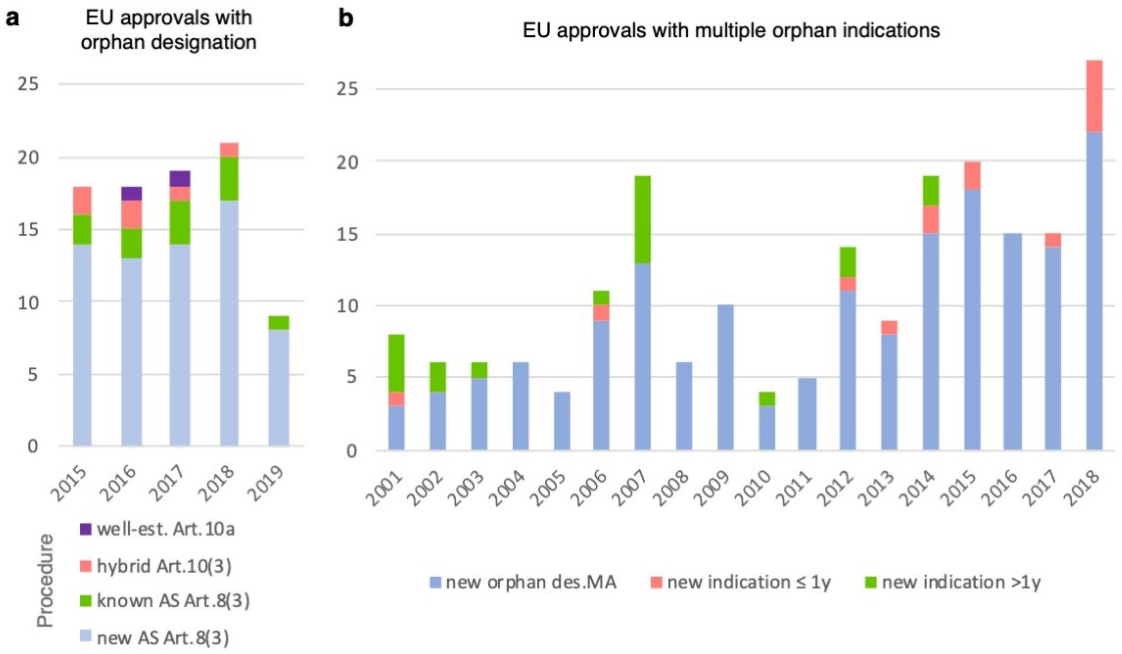

Figure 4 - Approvals and extensions of indication of drugs with orphan designation in the EU

a) Positive CHMP opinions from the EMA annual report Annex 10
b) Numbers of new approvals of orphan medicinal products and new indications for those medicines if approved prior to 2019 in the EURODIS list of orphan-designation medicinal products (based on EMA approvals).
Examples for Art.8(3) with known AS, Art.10a well-established use and extensions of indication where 2nd indication > 1 year after the initial MA were used for further analysis.

From eleven approvals according to Art.8(3) with a known active substance (AS) three contained references to IITs or literature in the clinical efficacy section of the EPAR:
Cystadrops, a stable formulation of mercaptamine for the treatment of corneal cystine crystal deposits was based on formulation development by academia (Tsilou 2003). Three small randomised, placebo-controlled IITs at the US National Eye Institute and the University of Leeds (UK) support the main phase II and III studies by the MAH.
The clinical efficacy package of trientine in Wilson's disease is based on a retrospective study of patient records by the MAH and 133 literature references dated from 1958-2017.

The use of mexiletine in the symptomatic treatment of myotonia adult patients with non-dystrophic myotonic disorders was approved based on a main phase III IIT trial in France.

Two well-established use applications (Art.10a), the PUMA for glycopyrronium in the treatment of chronic pathological drooling in children with chronic neurological disorders - and pentosan polysulfate In bladder pain syndrome were based on extensive scientific literature, but also on published industry-sponsored clinical trial data.
In addition, the diagnostic agent gallium edotreotide for tomography imaging was approved on literature alone for the clinical efficacy section.

Two additional examples - a PUMA and an Art.8(3) application that were based on a collaboration of academia and industry - are given below.

4.5.2 Example - proof of principle for propranolol in infant haemangioma

Despite the more systematic approaches mentioned in chapter 1, many academic repurposing IITs follow a chance discovery. It may then be the initiative of a single investigator or hospital to organise additional proof-of-principle trials and successfully seek collaboration with industry to make the new indication universally available to patients. Given that small-scale investigator-initiated trials are far more common than new MAs, such successful cases are expected to be rare. However, one case is the use of propranolol in the treatment of infants suffering from haemangioma which was identified in the search of PUMAs:
The chance discovery resulted from infants suffering from haemangioma being co-medicated with propranolol. The haemangioma in two children had started to impact function of the heart and the children were treated with the beta-blocker propranolol. This led to a rapid remission of the haemangioma. The physicians then treated an additional nine children with severe disease with the parents' consent (Léauté-Labrèze 2008). Two small, controlled IITs were then performed to establish the use of propranolol as an effective treatment (Léauté-Labrèze 2013).
The researchers then collaborated (Léauté-Labrèze 2015) with Pierre Fabre Dermatologique who developed a paediatric formulation and sponsored a phase 3 trial with 460 patients to confirm its

efficacy and safety. The new product was approved through a PUMA according to Art.8(3) with a known active substance[20].

Propranolol has since been proposed for the treatment of vascular sarcomas in the adult population and has been proposed as a test case for academic repurposing in STAMP meetings (see chapter 5). The authors have published a summary of the scientific advice given by the MHRA (Pantziarka 2017). However, the evidence in the adult population is still not conclusive and the use under debate (Wagner 2018). An investigator-initiated phase II proof-of-principle trial funded by private donations is underway to clarify the scientific question (Heinhus 2020).

4.5.3 Example - Treosulfan as part of conditioning treatment for stem cell transplantation

Treosulfan is an anticancer alkylating agent used since the 1980s (Beier 2013). In 2019 it was approved as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in adults and in children with malignant diseases.
The EPAR search performed here identified only industry-sponsored trials. The background was then only identified after additional literature search:
A prospective earlier phase II trial MC-FludT.8/MDS (NCT01062490) sponsored by the MAH (Medac, Hamburg) was published by authors including the MAH and clinical investigators at the University of Rostock and the East German Study Group for Hematology and Oncology (Ruutu 2011). The references in the paper were then followed back to the same investigators as in MC-FludT.8/MDS who had proposed the treatment and performed initial proof-of-principle trials involving 30 patients 15 years earlier (Caspar 2004). In the meantime, several IITs and long-term follow-up studies Beier (2013) had been performed. The safety aspects of this medicine and indication are complex.

4.5.4 EPAR search of IIT contribution to orphan-orphan extensions of indication

EURODIS rare diseases Europe maintains a list of orphan-designation medicinal products approved in the EU. Both initial approvals and extensions of indication are listed. Figure 4 showed

[20] The investigator described this as a long and challenging process. “Comment faire du neuf avec du vieux...en médecine“, Christine Leauté-Labrèze, TEDxBordeaux

the distribution of new drugs with orphan designation and the addition of indications with orphan designation (orphan-orphan repurposing).

20% of drugs have since had a second indication added. After 2014, there were no longer any indications added through a subsequent variation. Instead, a similar number of additional indications were included in the initial submission. This is in part due to the limited observation window (such cases may be submitted in the future). But it may represent a trend in industry to either collaborate earlier with academia or characterise additional uses of a new drug earlier-on.

Where such a new indication was added as a subsequent Type II variation, the clinical efficacy section of the European public assessment report (EPAR) was inspected to find evidence that was provided by non-industry sponsored trials[21]. The table containing the combined information from EURODIS and the EPAR search and all EPAR references is shown in the Annex - EU orphan designation – extensions of indication 2002-2019.

Of 12 additional indications for which an EPAR was available, 4 mentioned at least one IIT.

4.5.4.1 Examples of IIT contribution to extensions of indication in EU orphan drugs

Miglustat was first approved in 2002 for the treatment of mild to moderate type 1 Gaucher disease. An extension of indication to include patients with Niemann-Pick type C disease was supported by phase I/II studies from the US National Institute of Neurological Disorders and Stroke and the US National Eye Institute. The main study was a phase II trial sponsored by the MAH. In parallel, a phase III study of 5 patients in the new indication was performed by the National Taiwan University Hospital. However, a more complete picture of the clinical trial activity of the drug in this indication is given by a review in 2018, which lists 31 clinical studies and case series since approval (Pineda 2018).

Notably for all active substances, tens or hundreds of phase II/III interventional clinical trials were registered in clinicaltrials.gov. About half of trials were from industry. But it would not be useful to compare these numbers without additional analysis. In many cases the drug was used as the standard of care by other MAHs (e.g. only 40 out of 238 industry studies with sorafenib came from its originator).

[21] Sponsor information corresponding to the clinical trials in the EPAR was obtained from clinicaltrials.gov

Most commonly, IITs serve to provide supporting information to the main MAH phase III trial. This was the case for sorafenib, in its third indication of thyroid carcinoma and lenalidomide in the second indication of transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes. In trabectedin, both in the initial indication of advanced soft tissue sarcoma and the second indication of ovarian cancer, supporting studies were sponsored jointly by the MAH and the NIH. In the case of eculizumab only the first indication, treatment of paroxysmal nocturnal haemoglobinuria, data was supplemented by a phase II trial sponsored by the Jonsson Comprehensive Cancer Center.

In rare genetic disorders, Carglumic acid was approved in 2003 for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency based on a retrospective series of 20 patients. In 2010, the MAH submitted further retrospective data to comply with Art.46 in the then new paediatric regulation EC/1901/2006 to submit all current paediatric data for review. This resulted in an extension of indication in the EU to include hyperammoniemia due to different genetic variations (isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia).[22]

4.6 Example – EMA approval of Remdesivir in COVID-19

In chapter 3 an early IIT in performed in China was described. The drug Remdesivir was an abandoned development candidate, had passed preclinical and clinical development and only failed comparative efficacy trials in its original indication. In early 2020 both investigator-initiated and industry sponsored trials studied the efficacy of Remdesir in COVID-19 patients. On 3.7.2020, EMA granted a conditional MA for Remdesivir for the treatment of COVID-19 (EMA/357513/2020).
In the following, the relative contribution of investigator-initiated and industry trials is described. Results from four phase 2/3 clinical trials with Remdesivir in COVID-19 patients from February to June 2020 were listed in the (EMA/357513/2020) (see Table 4).

[22] However, the new indications were not added in the US as of the last SmPC from 23/12/2019 listed on Drugs@FDA. Four additional phase II/III IITs are ongoing in the US and in Saudi Arabia for this indication (clinicaltrials.gov).

Table 4 - phase II and III clinical trials with Remdesivir listed in the EPAR

Study	Sponsor/location	Study type	Endpoint	Result
NCT03719586 (Mulangu 2019)	US government (NIAID)	Treatment of **Ebola** disease Randomised, controlled trial against comparators	Death from Ebola at 28 days	Remdesivir showed higher cumulative incidence of death.
NCT04280705 phase III Adaptive COVID-19 Treatment Trial (ACTT) 21.02.2020-21.05.2020 (Beigel 2020)	US government (NIAID) International multicentre trial	1062 patients hospitalized with COVID-19 and had evidence of lower respiratory tract infection double-blind, randomized, 10 days Remdesivir 100mg+100mg/day placebo-controlled trial	Time to Recovery, no longer hospitalised or no longer requiring supplemental oxygen	Higher likelihood of recovery at day 15 compared to placebo
NCT04292899 Phase 3 5 day v.s. 10 days (Goldman 2020) (preliminary) 06.03.2020-30.06.2020	Gilead International multicentre trial	4891 patients hospitalized with SARS-CoV2 and reduced oxygen saturation Randomised open-label: (397 patients in Goldmann2020) 1:1 5 days or 10 days Remdesivir 100mg+100mg/day (+ standard of care)	Clinical improvement according to predefine 7 point at day 14	*No significant difference between 5-day and 10-days of treatment*
NCT04292730 Phase 3 15.03.2020-26.06.2020 (Spinner2020)	Gilead International multicentre trial	1113 patients hospitalized with SARS-CoV2 and reduced oxygen saturation and radiographic evidence of lower respiratory tract infection Randomised open label 1:1:1 none 5 days or 10 days Remdesivir 100mg+100mg/day (+ standard of care)	Clinical improvement according to predefine 7 point at day 11	10-day course no significant difference *5-day treatment group had a better status at day 11 compared to standard of care. 10-day treatment group was inconclusive.*
NCT04257656 Phase 3 06.02.2020 to 10.04.2020 (Wang 2020 Lancet)	Capital Medical University (Academic, China) PR China Multicentre	237 patients Hospitalized Adult Patients with Severe COVID-19 (by predefined criteria) Randomized, Double-blind, Placebo-controlled 10 days Remdesivir 100mg+100mg/day (+Concomitant use of: lopinavir–ritonavir, interferons, and corticosteroids)	Primary endpoint: Time to clinical improvement up to day 28	Remdesivir was not associated with statistically significant clinical benefits, however the study was underpowered. Exploratory comment: clinical improvement in those treated earlier requires confirmation in larger studies

Additional information have been added from the respective publications and entries in *clinicaltrials.gov*

As discussed in the journal editorial (McCreary 2020) and the EPAR, there was considerable disagreement between the trial results.

4.6.1 Early IIT from China

The first study was an IIT in China which involved 237 severe-stage patients in a randomized, placebo-controlled trial (Wang 2020 Lancet). However, the study was ended due to rapid control of the pandemic in China. At 28 days, no significant benefit was seen for Remdesivir. The authors noted that earlier treatment may be more effective, but the result was not significant. This study may be considered unplanned evidence to industry that risks to prevent the drug being approved. However, the EPAR noted that the study was underpowered and unlikely to provide evidence.

4.6.2 NSAID study of Remdesivir in COVID-19 patients

An international randomized, placebo-controlled phase 2/3 study was sponsored by the US government National Institute of Allergy and Infectious Diseases (NSAID), and this was considered the primary evidence by the EPAR. Patients receiving a 10 days course of Remdesivir were more likely to recover by day 15.

4.6.3 Company-sponsored studies of Remdesivir in COVID-19 patients

A study sponsored by Gilead to compare 5 and 10-day treatment periods showed no difference. Finally, a further phase 3 study sponsored by Gilead showed a clinical improvement against a 7-point scale at day 11 with 5 days but not 10 days of treatment.

An editorial (McCreary 2020) explains the complex issue of conflicting trial outcomes. Some confounders may have been the wish of doctor or patient to complete 10 day open-label treatments of Remdesivir[23] thereby delaying hospital discharge and the use of standard of care that may have included corticosteroids[24]. However, a more fundamental point remains the stratification by disease severity (*e.g.* as inclusion criteria). The understandable focus on severe

[23] The study authors note that the hospital discharge peaked at 1 day after the end of treatment of the open-label study. Given that hospital discharge is 1 point on the scale, this may have biased results if doctors finished the intravenous treatment course in the interest of the patient.

[24] The standard of care that was permitted by the trial design included the use of corticosteroids in some cases and as (McCreary 2020) has pointed out, appropriate cross-randomisation would be required given the treatment effect shown by the RECOVERY trial.

COVID-19 patients is difficult to achieve if Remdesivir may need to be given early for optimal use as had been noted in the EMA compassionate use opinion. (McCreary 2020) argue that this creates an issue with choice of primary endpoint. The 7-point scale[25] contains clinically measurable outcomes. However, they are not necessarily linear (*e.g.* low flow/high flow oxygen *v.s.* hospitalized or not, dead or alive) and this makes statistical averaging less meaningful.
The study authors also note that in the ACTT-1 (Remdesivir) and RECOVERY (other treatments, see chapter 3) trials, outcomes were strongly dependent on the disease status at randomization. The authors conclude: "*Future trials should consider studying individual severity strata incorporating further clarification and refinements in their definitions." (McCreary 2020)* Here the lack of detailed knowledge of the disease at the time may have impeded study design. It thereby highlights the importance of detailed understanding the disease physiology by clinical experts for the design of successful clinical trials.

4.6.4 Conditional marketing approval of Remdesivir in the EU

In addition to the above clinical studies, additional toxicity tests to complete the approval data package were performed by Gilead. On 3.7.2020, EMA granted a conditional MA for Remdesivir for the treatment of COVID-19 in patients age 12 or older requiring supplemental oxygen following a new drug application according to Art.8(3) of directive 2001/83/EC. The CHMP noted that major objections with respect to the available data prevented the inclusion of patients not requiring oxygen as originally proposed by Gilead.
As indicated in the EPAR, long term carcinogenicity studies have not yet been performed, which was judged acceptable for the approved short-term use. Together with still unclear questions about hepatoxicity and nephrotoxicity mentioned in the EPAR and the high cost, this could currently prevent repurposing to an earlier indication suggested in the CU (EMA/178637/2020), such as prevention of SARS-CoV2 infection.

[25] clinicaltrials.gov/ct2/show/NCT04292730 - The scale is as follows (: 1. Death 2. Hospitalized, on invasive mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices 4. Hospitalized, requiring low flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (coronavirus (COVID-19) related or otherwise) 6. Hospitalized, not requiring supplemental oxygen - no longer required ongoing medical care (other than per protocol Remdesivir administration 7. Not hospitalized.

5 Discussion

5.1 Knowledge generated in academic drug repurposing

In the present work, the contributions of academic investigators to repurposing projects aiming to resolve unmet medical needs was investigated. A focus was on the regulatory questions in clinical development and contribution to marketing authorisations (extensions) that would then be sought by industry (Lincker 2014). Figure 5 shows a drug repurposing-specific development flowchart with highlighted key contributions of industry and academia.

5.1.1 Hypothesis and target validation

In chapter 3, prior product knowledge and *in-vitro* and *in-vivo* research data that supported investigator-initiated trials in COVID-19 were analysed. Substantial pre-COVID-19 data from academia for similar viruses was available prior to IITs for Remdesivir and Lopinavir/Ritonavir. New virus-specific data was then available within a few months using highly specialized *in vitro* assays, such as a 3D human airway cell culture model from start-up company Epithelix (Pizzorno 2020) or early SARS-CoV2 models of infection from an academic laboratory in Wuhan (Wang 2020 Cell Res.).
Of note is that several listed Gilead as collaborator, thus giving the academic laboratory access to the experimental drug and Gilead access to data from such specialized model systems.
These examples show relative contributions from academia and industry in drug rescue and repurposing. They also show rapid laboratory validation of treatment hypothesis by academia. A possible limit to those collaborations can be absence of quality systems which impacts reliability - and in some instances regulatory status (*e.g.* GLP for drug-safety studies) (Bolon 2019).
The quality of evidence in drug/target validation is important (Jones 2016). Given the early development stage, reliable research is expected to reject a hypothesis more often than it validates it. Repurposed or rescued drug candidates that are successful *in vitro* but fail *in vivo* safety or PK profiling may serve as chemical probes[26] for further discovery research instead of proceeding to the clinic.

[26] The structural genomics consortium proposed the open distribution of well-characterized probes from development pipelines for *in vitro* research to any academic lab that may have the appropriate disease model.
(see www.thesgc.org/chemical-probes)

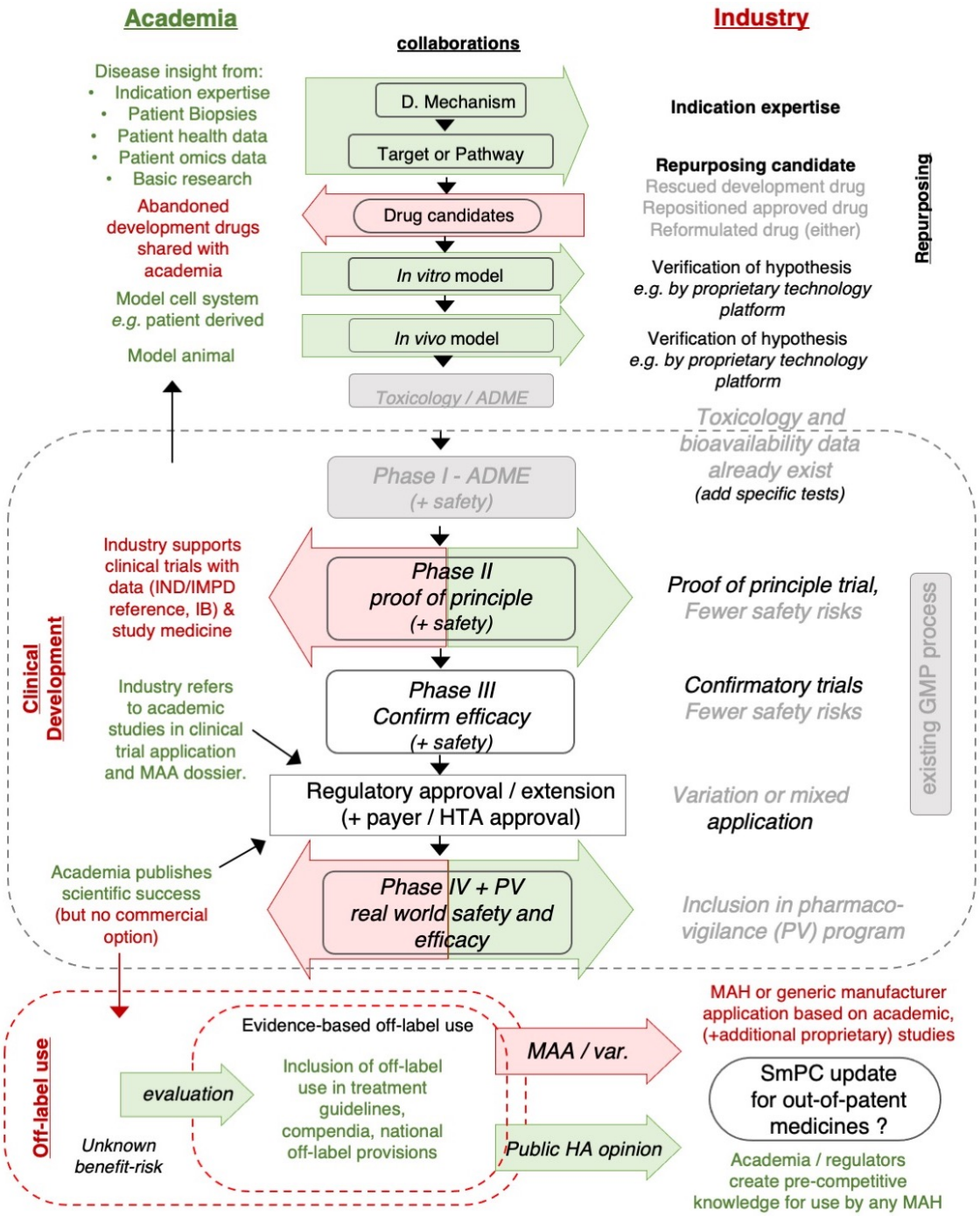

Figure 5 – Repurposing-specific adaptations in drug development

Grey boxes highlight steps that may be skipped or have data available. Green represents possible collaborations with academia or contributions from the academic literature. Red shows possible support from industry to academic programs.

5.2 Clinical evidence generated

5.2.1 Support for investigator-initiated trials in the EU regulation

Regulatory requirements for IITs are described in Chapter 3. One of the advantages that drug reproposing promises is that some clinical trials can be carried out with existing medicines without the need to repeat preclinical work, PK and possibly dose finding and to start at phase II. The examples of COVID-19 clinical trials showed that the majority of the data required to support clinical trials came from existing product knowledge (development, SmPC and clinical practice). Provisions such as the simplified IMPD in the EU regulation are applicable to all sponsors. However, academic sponsors may benefit from additional scientific advice and the reimbursement of the IMP and insurance may follow clinical practice (BfArM 2009).
A new formalised low intervention trial category applies to new uses of a drug outside of its SmPC but subject to evidence of clinical use. In the US a similar but not identical prevision is made for IITs in cancer drugs where no greater risk compared to clinical practice is expected. Thereby the FDA does not want to impede a trial where it represents no greater risk than clinical practice and new insights can be obtained. Contrary to requirements in the US and in Japan, all clinical trials in the EU under regulation EC/536/2014 are intended for inclusion in MA applications, while a risk-proportionate approach is made for IMPD and GCP requirements, such as monitoring.

5.2.1.1 Examples of product and disease knowledge that supported COVID-19 trials

Examples in which clinical trials were supported by a combination of prior knowledge and data on efficacy in a new indication were found for current COVID-19 IITs. An EMA CU for Remdesivir listed available preclinical and clinical data with reference to the IB. Additional data was found in timely publications of clinical trial results.
The EMA CU (EMA/178637/2020) for Remdesivir and publication for the RECOVERY trial arms of lopinavir/ritonavir, hydroxychloroquine and dexamethasone (RECOVERY 2020 D,H,L) referred to a well understood safety profile. However, specific risks due to *e.g.* treatment of stages with high viral replication with corticosteroids were discussed (RECOVERY 2020-D). The RECOVERY trial was open-label and included an option to opt-out of randomisation based on individual decisions by physicians. At the same time the medicines were already used widely in clinical practice or even included in national guidelines on COVID-19, despite of poor evidence of efficacy (Dagens 2020).

Therefore, in these publicly available documents, the safety aspects of the trial were described without major concerns.
Preclinical evidence for efficacy appeared weak for hydroxychloroquine. Evidence for the antiviral drugs lopinavir/ritonavir (RECOVERY 2020-L) and for Remdesivir were primarily based on similar viruses. For Remdesivir, a standard in vitro cell model (VERO E6) provided a bridge to earlier non-COVID-19 data (EMA/178637/2020). Support for the use of dexamethasone came from biomarkers, a nearby-indication hypothesis and a small earlier trial (RECOVERY 2020-D).
It is unclear if similarly low levels of evidence would be accepted in a less acute and life-threatening situation. However, ascertaining the acceptable level of indication-specific evidence to perform a clinical trial in a new indication may frequently be unclear to smaller academic groups and could be subject to scientific advice from an HA. (Pantziarka 2017)

5.2.2 Enablers of academic clinical research

Concerns remain about the burden placed on academic sponsor-investigators (Bergmann). While risk-proportionate approaches are important to enable academic research, such risk assessment in itself requires experience (Tudur Smith 2014). Institutional, structured support for clinical investigators is likely to both reduce burden on the sponsor/investigator and assure quality.
The technical coordinators (Maher 2020) described the RECOVERY trial as a trial and technology platform that can be applied to other diseases and other countries. The adaptive design allows the successive testing of alternative and conflicting treatment hypotheses and this is shown by the success of the first trial arms. The administrative simplification for investigators afforded by centralising the control of the trial and the established infrastructure to link sponsor (central), investigator (site) and data from routine health records creates administrative and GCP simplifications. It may bridge the concepts of clinical trials and real-world evidence (Bartlett 2019) by allowing more patients to be routinely included into trials, thereby closing evidence gaps in clinical practice (see below). The concept of not losing evidence – to include rare disease patients in disease registries (Tambuyzer 2020) or to include more cancer patients systematically in clinical trials mirrors current regulatory thinking (FDA 2004).

The majority of IITs are likely to remain the smaller-scale proof-of-principle trials, as shown in the example of propranolol. They can confirm a new treatment hypothesis and catalyse industry engagement. Here help may come from integrated initiatives such as the MRC-Astra Zeneca

collaboration or the NIH-NCATS funding programs (Frail 2015) which both provide access to repurposed and rescued study medicines, financial and regulatory support to clinical researchers.

Industry has established procedures to support IITs based on defined quality standards and may supply the IMP, regulatory documents and product knowledge as in the case of the Hubei Remdesivir trial (Wang 2020 Lancet) and earlier preclinical studies described in chapter 3.

5.2.3 Evidence obtained from investigator-initiated trials in COVID-19

The large ITTs set up by the NIAID (ACTT) and the University of Oxford (RECOVERY) were highly effective at confirming or rejecting treatment hypotheses that were already part of national treatment guidelines (Dagens 2020).

This contrasts with experience from the earlier SARS outbreak in 2002-2003, an early test case in which investigator-initiated trials tested existing medicines against an emerging coronavirus disease. The SARS-CoV virus is similar to SARS-CoV2 (90% in RNA sequence, Wu 2020) and similar treatments were proposed at the time. These included corticosteroids and Lopinavir/Ritonavir. In 2003, the WHO SARS treatment study group recommended a systematic review of treatment effects. An analysis of 54 clinical trials found no reliable evidence of patient benefit in any of the treatments/trials but potential for harm to trial participants (Stockman 2006). The authors noted that frequently, antiviral activity had been shown *in vitro* but this could not be translated into patient effects. The use of corticosteroids was empirical and insufficient evidence was generated to prove their effectiveness[27].

The high mortality and speed of the 2002-2003 outbreak left little time for controlled trials. This is understandable as doctors would not want to risk withholding a treatment that they saw promising. This ethical dilemma in the execution of a trial may also be resolved by an adaptive trial design supported by a data monitoring committee as was done for (RECOVERY 2020-P). Should one treatment arm show an extreme benefit / disadvantage, the investigators may be unblinded to this effect, the arm halted and the medicine included or removed in future arms. Alternatively, a physician may decide against the randomisation on a per-patient level. Therefore, the blinding of investigators to the study medicine can be a difficult choice.

[27] Some data in a small randomized-controlled trial showed possible improvement in patients suffering from acute respiratory distress syndrome. But another study showed delayed viral clearance, a clear risk.

The RECOVERY trial invalidated the treatment hypothesis for hydroxychloroquine and Lopinavir-ritonavir (RECOVERY 2020-H,L), at least under the proposed treatment regimens. This in itself is an important achievement as it allowed patients to be included in more promising treatment regimens/trials[28]. Such situations of established poor evidence may be true for many off-label uses of drugs (Radley 2006). They do not benefit the patients and delay research into more promising alternatives.

The positive effect shown for the dexamethasone arm (RECOVERY 2020-D) (reduction in 28-day mortality), in patients receiving either oxygen or mechanical ventilation, is a second success of the RECOVERY trial. While small trials may be successful in more clear-cut situations, the small effect size and large number of confounders such as age or comorbidity required a larger patient population. It shows how a large publicly funded[29] phase III trial can generate high quality pivotal evidence. Such published evidence may represent the majority of the data required for an extension of indication and is available to any manufacturer. However, given that dexamethasone is an off-patent medicine, was used off-label in the indication (if not in trials) and is produced by multiple generic manufacturers, it was not obvious who should fund, assemble and submit the variation dossier to update a reference SmPC.

5.2.4 CHMP Art.5(3) opinion on label update for dexamethasone

Therefore, EMA itself acted in community interest. Because dexamethasone is not indicated for the use in COVID-19 and may be counter-indicated in viral infections, an update of the SmPC would clarify its use and benefit patients in the EU. To perform a rapid public benefit-risk assessment, the executive director of EMA requested a CHMP opinion according to Art.5(3) of regulation EC/726/2004. Notably, this procedure had never been used to recommend a label extension before[30]. EMA evaluated the use of dexamethasone based on the data from the recovery trial (EMA/509632/2020) as the main study and supporting data from a WHO rapid

[28] This had been highly anticipated for (hydroxy)chloroquine. One physician interviewed pointed out that "Researchers might have settled some of these issues weeks ago if there had been a rapid international effort to develop a rigorous chloroquine clinical trial" (Ledford 2020), [even if the sole outcome may be to close this chapter].
[29] The RECOVERY trial was funded primarily by the UK government, the Wellcome Trust (UK) and the Melinda Gates Foundation (www.recoverytrial.net)
[30] Previous procedures listed on the EMA website referred to safety and quality aspects. (www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions)

evidence appraisal based on a meta-analysis of the other big COVID-19 studies. Additional evaluation of previous clinical research and meta studies was done by the CHMP[31].
In summary EMA recommended an SmPC update to include treatment of COVID-19 in patients 12 years and older requiring supplemental oxygen. A generic template to update the SmPC was provided.
Such public assessment presents way of promoting an update the SmPC from an off-label use situation (see Figure 5). It created a precompetitive evaluation that may be picked up by any MAH. However, it presents a soft opinion rather than an obligation to an MAH[32]. Therefore, it is unclear if it will not simply promote off-label use (as has previously been argued by Verbaanderd *et al.* (2019)).

5.2.5 Quality in the design of investigator-initiated trials

A point raised in early summaries of COVID-19 trials and by an EMA call (EMA/142322/2020) was that of insufficient trial size and design shortcomings (Mehta 2020). While this is made worse by the shortage of time during the pandemic, it may occur more frequently where clinical researchers lack regulatory training and support.
Characteristics of a trial, intervention and disease will require different approaches, e.g. cross-over designs will only be applicable if the effect of the drug is reversible, blinding will be required for patient-reported outcomes and more subjective endpoints. But it may be less acceptable in a pandemic or emergency. Often small details in the design of a trial can make a big difference in the reliability of the results (Yordanov 2015). Thus, successful trial designs require detailed expertise in both the disease and trial design principles and therefore an input from clinicians and multiple professions.

5.3 Contributions made by academia to industry MAs

[31] The CHMP opinion noted the limited quality of evidence and poor control confounders in earlier small trials. Additional safety data were provided by the trial sponsor provided upon EMA request. EMA noted that the safety profile of dexamethasone is generally well understood. However, any future applicant should consider additional safety studies and a risk management plan to cover missing safety aspects.
[32] *"The CHMP's scientific opinion can be taken into account by EU member states and EMA when evaluating dexamethasone medicines for the treatment of COVID-19"* (EMA/483739/2020).

5.3.1 Frequency and types of contribution

Three of eleven (27 %) of new orphan MAs between 2015 and 2019 that were based on a known active substance according to Art.8(3) (*i.e.* those repurposed from a non-orphan to an orphan MA) used at least in part an academic study to support clinical efficacy claims in the EPAR. All three PUMAs and two additional well-established use applications referred to academic data.
In only one case was a phase 3 industry trial replaced by an academic phase 3 trial as the sole or main evidence of clinical efficacy. More common contributions from academia were a number of smaller trials together with a meta-analysis, retrospective analysis of patient data or extensive literature reports. (see chapter 4 and Annex). There were only three cases where mainly academic data was used: one a phase III trial, one an MAH retrospective analysis supported by an academic data package as an Art.8(3) application and a literature data package of an Art.10a well-established use application.

The figure for extension of indication is similar to that of known active substances with four out of twelve relying in part on data from academia.

Those numbers are somewhat higher than those for new molecular entities. 11 % of orphan an 18.5% of non-orphan products approved in the EU between 2010 and 2012 originated from academia (and another 6 / 8 % from collaborations). The MAH of the final approved medicine was industry in all cases (Lincker 2014). However, the sample size in the present study is small.

5.3.2 Limits - Academic contributions not observable in the EPAR:

The EPAR discussions on clinical efficacy focused on the main study and some elements of the supporting study. Additional literature that is likely to have been submitted by the MAH was only identified in cases where it represented the core evidence of efficacy.
One such example, where the present analysis would underreport the contribution of clinical investigators is Trecondi (treosulfan) as conditioning agent in stem cell transplantation. Here, the background was only identified after additional literature search around the main industry-sponsored trial.
Thus, it is often difficult to ascertain the role of academic researchers in the eventual MA. Systematic reviews of the literature or interviews could yield better information. In the current

analysis, it is likely that the role of academia is underreported and that many such histories hide behind the commercial approvals and extensions of indication.

5.3.3 Contribution of publicly funded trial to the MA of Remdesivir

The both Gilead and NIAID sponsored phase III trials were included in the MA application for Remdesivir in COVID-19, but there was disagreement between the trial results. In this case, the NIAID trial contributed positive evidence to a limited pool of data. However, industry may see academic trials as a risk to approval, especially if a negative result or safety concern is the result of poor trial design.

In July 2020, EMA granted a conditional MA for Remdesivir for the treatment of COVID-19 in patients age 12 or older requiring supplemental oxygen. This may not represent optimal use of Remdesivir, insufficient data presently preclude the inclusion of (earlier stage) patients not requiring oxygen in the MA (EMA/357513/2020). So far neither NIAD nor industry trials had answered crucial questions on the optimal use of Remdesivir in clinical practice (Hsu 2020). Additional phase III and IV studies are therefore needed to answer open questions about efficacy, clinical meaningfulness of study endpoints and optimal use of Remdesivir.

5.3.4 Industry uptake and limits

Clinical trials with new uses for development or approved medicines are more likely to result in label changes or new MAs during the patent and exclusivity period. This has been shown in the work by (Langedijk 2016) and (Balogh 2016).

The above examples showed that academia contributes to industry drug repurposing efforts through the generation of a treatment hypothesis and by performing investigator-initiated trials to prove this hypothesis. Work by (Langedijk 2016) have shown that investigator-initiated trials are performed in a similar time window as industry trials: primarily in the exclusivity period after the drug has come to market. The example of propranolol and remdesivir showed that published investigator-initiated trials contribute to the total evidence discussed in the clinical efficacy section of the EPAR in an extension of indication or new MA application. Therefore, it is essential to both industry and regulators that academic phase II and III trials are well designed. As to whether industry or academia should fund and act as sponsor in these trials, there is a thin line between academic performing obvious industry work (which industry may even see as unplanned

evidence) and discovery of genuine new unexpected disease-treatment pairs that go on to benefit patients.

5.4 Adding up the evidence – risk-benefit assessment outside an MA

The above positive examples should not serve to underestimate the difficulty in translating the clinical proof-of-principle to a label update. Often scientific (unclear evidence) and/or commercial (unclear incentive for off-patent drugs[33]) considerations hold back essential industry engagement. The lack of investment and MA-oriented approach that industry contributes and the absence of structured review by health authorities then contribute to the lack of clear evidence. For those medicines that are out of exclusivity and which are frequently target of repurposing efforts, this has created a second academic translation gap – from clinical science to clinical practice (Verbaanderd 2019). Some have questioned the entire utility of drug repurposing and ethics of clinical research in cases where no approval can be expected for commercial reasons. (Giovannoni 2015).

Thus, the final question is one that is currently being discussed by regulators, law makers and several initiatives. Can a pathway be created to allow for evidence appraisal and (ideally) marketing authorisation based on scientific data even in the absence of a commercial incentive?

5.4.1 Uptake of innovation in guidelines and clinical practice

The SmPC is the manufacturer-proposed and health authority approved prescription guidance intended as the (primary) source of information for physicians. However, innovation cannot always be reflected in the SmPC in a timely manner. New research may show an improvement in patient care by better prescription and this may be outside of the SmPC (off-label)(AMRC 2017), (GMC 2013).

Therefore, additional prescription information is available to doctors: Treatment guidelines give disease-specific guidance (Muhrad 2017). Drug information resources such as the British national

[33] For industry, simply once the incentives mentioned in chapter 4 run out and there is no longer an exclusivity or an option for its extension, the drug leaves the innovation stage and enters the generic stage (Langedijk 2016). The market is then split between generic competitors and thereby any potential return on investment in the new indication is split between all competitors (AMRC 2017).

formulary[34] or commercial drug compendia such as IBM Micromedex[35] provide drug use information including off-label evidence (Radley 2006).
National health system guidelines, such as NICE evidence summaries (see UK section below) may directly influence reimbursement decisions. Guidelines such as the US NCCN[36] compendia also guide reimbursement of off-label use by payers (Shea 2018).

In addition, individual doctors may be involved in research and may have sufficient knowledge to allow off-label prescription. Within the scope of Project Renewal (Kluetz2020) (update of cancer drug labels, see below), the FDA conducted interviews with oncologists to assess which additional sources of information is used in clinical practice. The use of drug compendia and current literature was concentrated in urban, hospital or large practice settings. Therefore, unless the label is updated or the information available elsewhere, innovation only partially translates to clinical practice.

5.4.2 Off-label use in clinical practice

If a licensed medicine is used outside its licenced indications, patient group, dose or route of administration, such use is considered off-label. The dilemma in off-label use is the lack of thorough evidence appraisal that would have taken place during MAA review. Off-label use occurs in is common in areas of high unmet need. In US non-hospital settings in 2001, 21% of all prescriptions were off label, 75% of those with no or little scientific evidence based on the DrugDex (IBM Micromedex) compendium (Radley 2006). Especially high levels of off-label use occur in paediatrics (up to 70%, Weda 2017) and oncology[37] (ca.50%, Shea 2018).

When a licensed medicine is used off-label, additional risks may exist[38] similar to those described in chapter 3 for the clinical trial categorization. However, clinical practice does not have the safety

[34] (www.bnf.org/about) BNF guidelines are developed by the British Medical Association and the UK Royal Pharmaceutical Society.Off-label use guidelines are to be included as part of the UK repurposing framework (AMRC 2017).
[35] (www.micromedexsolutions.com) IBM Micromedex
[36] (www.nccn.org) National Comprehensive Cancer Network
[37] Shea et al. (2018) investigated the number of off-label indications for 43 approved cancer drugs. 79% of drugs had additional uses, often multiple. Of these 91% were supported by high quality evidence. The authors noted off-label use were far higher for off-patent drugs, 13.7 per drug, as there are fewer incentives to update the label. Oxaliplatin, which had 38 off-label indications listed has been included in FDA project renewal (Kluetz 2020).
[38] Higher incidence of adverse events in off-label has been documented by many studies. In a Canadian 2005-2009 study based on electronic health records of 46’000 patients in primary care (non-specialist care), despite a low level of

nets of an institutional review board, ethics committee or health authority. This leaves the patient exposed to a higher risk and the doctor to exposed to legal liability. Even if a doctor has all the data available, reimbursement may not be possible if the drug is not (yet) included in a national provision.

5.4.3 Provisions for evidence assessment in off-label use

While the marketing authorization is the route of drug regulation foreseen in EU directive 2001/83/EC, physicians should be able to prescribe the best medicine for the patients' need. Therefore, physicians may prescribe a medicine off-label based on a per-patient decision (Art.5 of directive 2001/83/EC) with the patients informed consent. National law, reimbursement and professional guidelines further regulate off-label prescription. The UK general medical council guidelines for example, recognise that off-label prescription may be necessary if no licensed medicine is available and that this is frequently the case in paediatric medicine (GMC2013). Crucially, the physician must be satisfied that sufficient evidence exists to support their decision.

In the EU, off-label use is regulated at the national level. Regulations in Germany and France have been part of a recent EU report (Weda 2017) and another MDRA thesis (Obermann 2013). A new framework has been created in the UK (AMRC 2017). Such national regulations aim to assess the available evidence, regulate off-label use and potentially enable extensions of indication by MAHs (see table 5). All three countries rely on a public assessment of the available evidence from (often academic) literature by regulators (ANSM, BfArM) or HTA (NiCE). However, they differ in scope. In France, medicines included in the RTU are those likely to achieve an update to the SmPC, in the UK those with little change of commercial development are included.

off-label prescription (11.8%) much of it was without strong evidence (9.5%) (Eguale 2015). Such use led to significantly higher incidence of adverse events (21.7 per 10'000) than evidence based off-label (13.2) or on-label (12.5) prescriptions.

Table 5 - National off-label use provision in Germany, France, UK

Germany - BfArM off-label expert group (Weda 2017)	
Risk-benefit assessment	The German health authority (BfArM) has established an off-label expert group which may perform a risk-benefit appraisal on request of the state/payer representative (GBA). The expert group commissions a review of evidence from the literature and clinical trial databases. Positive opinions allow reimbursement.
Provision to update SmPC	No formal provision, but it is expected that the evidence appraisal also lowers the barrier for a MAA.
Cases with subsequent approval [b]	Colchicin Tiofarma for the treatment of Familial Mediterranean fever 5-Fluorouracil as adjuvant in several cancers
France – RTU (Weda 2017)	
Benefit/risk assessment	A medical stakeholder may refer an off-label option for an unmet patient need to the ANSM for evaluation. A formal pathway (RTU) is intended to facilitate health authority (ANSM) risk-benefit assessment and allow off-label use to be reimbursed.
Provision to create MA	An RTU may then be issued for 3 years initially. During this time, data is to be collected to allow the application for a marketing authorization.
Cases [a]	RTUs approved within the first 5 years and since halted were either approved (Stelara,Truvada,Xalkori) through the centralised procedure within 2 years out approval. Another RTU for Roactemra was stopped but no report was provided. A current RTU is for Hemangiol. The paediatric formulation of propranolol is approved through a PUMA (see chapter 4) in a new indication (haemangioma). The RTU extends the use in children back to the 1st indication.
UK – NiCE Evidence summaries: unlicensed and off-label medicines (AMRC 2017)	
Benefit/risk assessment	Twice yearly, key stakeholders in drug repurposing including organizations representing children's doctors or rare disease patients, pharmacists and industry are invited to propose new topics for evidence evaluation. The NHS then commissions NiCE (UK HTA) to carry out the review. Taking into account information from manufacturers, regulatory agencies and a scientific literature search, NICE produces Evidence summaries: unlicensed and off-label medicines. These are communicated to the NHS, which commissions the new treatment for reimbursement and includes this in the continued learning curriculum for doctors. The report clarifies that the level of evidence would be expected to be similar to that for licensing, thus include a good quality phase III RCT.
Provision to update SmPC	Not foreseen, It is understood that the pathway is primarily intended for situations that are unlikely to gain an MA. It explicitly recognises that off-label use of medicine identified by new research presents a potential to address unmet medical needs and that physicians need to be systematically informed about benefit and risks of off-label uses. (But a label change is still considered the primary route for new indications to be included in clinical practice.) Off-label use of medicines is to be tracked in a national data base[c]. Commercial and academic sponsors are encouraged to contact the MHRA for scientific advice on closing the evidence gap.
Cases with subsequent approval	Not yet available or foreseen. NiCE to provide systematic prescription recommendation for off-label medicines. The British National Formulary initiated a review of 200 off-label indications that may be added to the drug compendium if they meet the evidence criteria.

[a] see list "Recommandations Temporaires d'Utilisation (RTU)" provided on the ANSM website: www.ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/

[b] see Expertengruppen Off-Label, Sachstandstabelle / Bewertungen www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/Zugelassene_Arzneimittel/Expertengruppen_OffLabel/_node.html

[c] UK House of Commons - Access to Medical Treatments (Innovation) Act 2016 c.9

5.4.4 Initiatives to update the SmPC based on public assessment of literature

The number of off-label indications included in the update of the UK BNF drug compendium (200) under the new UK framework (AMRC 2017), by far exceeds those found in the search for academic contributions to extensions of indication and new MAs in chapter 4. This underlines that the search uncovered only a small picture. However, there is a general understanding that product labels may not always reflect the evidence (Shea 2018). Additional initiatives have therefore attempted bring the additional uses on-label.

An example is the Art.5(3) CHMP opinion for dexamethansone in COIVD-19. Here the EMA executive director acted as a champion of the drug, the CHMP assessed the evidence and issued an opinion to update the SmPC. This is not a common route. However, it is a similar in intention and mechanism to the French RTU and a proposal by the EU STAMP group.

5.4.4.1 EU STAMP proposal

The proposed EU repurposing framework (STAMP2019) is targeted at high-impact late-stage repurposing cases without commercial interest. These would be picked up by a non-commercial champion and an EU or member state health authority would invite stakeholders to submit evidence for assessment in the form of a public scientific advice including a gap analysis of the data missing for an MA.

This creates precompetitive knowledge that reduces the scientific (but not commercial) risk of bringing the indication on-label. Thereby it is hoped that the threshold is lowered to such an extent that even generic companies will pursue such marketing authorization. It is hoped that the champion can engage a commercial developer or obtain further funding to close the evidence gap through additional academic research.

In a stakeholder feedback however, the concern from generics representatives remained that in cases of multiple competitors, all would have to agree to share the development cost as all would benefit. Potential champions also expressed concern about the high amount of work and little incentive for the champion (STAMP 2019).

5.4.4.2 FDA Project renewal

A more systematic approach is taken by the current FDA Oncology Center of Excellence pilot *Project Renewal*, which aims to update the label in off-patent cancer medicines through FDA review of the scientific literature supported by external stakeholders (Kluetz 2020). Additional indications would be added if the current scientific data from published studies meets FDA's regulatory standards of substantial evidence of effectiveness.
The FDA works with private contractors and the American Association for Cancer Research (AACR) and gathers input on clinical practice from clinical, clinical pharmacology and scientific experts. These gather evidence from the scientific literature and evaluate clinical trials on behalf of the FDA according to FDA criteria. The FDA then performs the assessment. Currently, the FDA then invites the MAH of the reference listed drug to submit a variation to update the label based the FDA finding.

5.4.4.3 Proposals to mandate SmPC updates

The above initiatives thereby provide precompetitive evidence to lower the requirements for (generic) manufacturers to seek updates to the SmPC. But the last step of industry engagement remains unclear, and multiple incentives have been proposed including finding non-pharmaceutical private investors[39]. These are comprehensively reviewed in (Pushpakom2019, Verbaanderd 2019). In additional, law makers have taken up the case and proposed provisions in national law.

The (rejected[40]) UK off-patent drugs bill of 2015 (AMRC 2017) proposed to require a government agency, such as Innovation UK to act as an MA applicant in the case of off-label use of a drug and absence of a commercial developer.

On 17 November 2020, the US house of representatives voted to pass the *"Making objective drug evidence for new labelling act (MODERN)"* act (Matsui 2020). The legislative initiative intends to

[39] The system proposed by a UK rare diseases charity generates a dividend from cost otherwise spend on supportive medical care in the absence of an effective medicine. The NHS as single payer in the UK would allocate part of a potential cost saving to repay investment into phase II proof of principle trials. www.findacure.org.uk/the-rare-disease-drug-repurposing-social-impact-bond/

[40] The government rejected the bill on the argument of conflict of interest (the government cannot be both applicant and authority (MHRA)). A second argument made was that the government does not want to jeopardize off-label use in all other indications that cannot be converted to an MA. (AMRC 2017)

allow the FDA to require label updates to off-patent medicines under some circumstances, such as when the originator the has withdrawn from the market. The update would include new indications.

The diversity of proposed options underlines that the commercial case for off-patent repurposed drugs to seek license extension possibly fund studies to fill the evidence gaps remains unclear. Charities and foundations already fund clinical research, such as the RECOVERY TRIAL. This may continue to play a vital role in a subset of diseases

6 Conclusions

Closer collaboration of clinical and basic science has contributed to the development of many existing medicines. The growth of predictive technologies that may connect existing drug targets to unresolved disease mechanism will suggest ever more ways in which existing medicines can be used to address unmet medical need.

Such repurposing of existing treatments, often initially by a single academic unit has the potential to treat many diseases for which no option currently exists. However, the use of a drug outside its approved indication may bring a risk to the patient that may not be fully understood. Therefore, clinical trial regulation must balance the safety and potential of drug. It must consider factors such as the safety profile of the drug, the severity of the disease and its treatment options and the evidence for treatment in the new indication.

The examples of propranolol in infant haemangioma (by a single hospital) and the more complex case of treosulfan as a lower-risk conditioning agent in stem cell transplantation (by a research network) shows how academic research and later engagement with industry can lead to the approval new medicinal products.

However, as the search started from the rare examples of such approved medicines, much of the initial work of academic researchers in creating and testing a target hypothesis is not fully reflected in the current work.

The year 2020 has brought drug repurposing into the spotlight as clinicians struggled to treat patients with an emerging infectious disease. As no approved treatment was available, doctors turned to using existing medicines off-label or setting up small investigator-initiated trials of promising repurposing candidates. However, the complexity of the disease and the low efficacy of

most of the treatments meant that these did not produce meaningful evidence. This was also remarked in communications from EMA.
However, based on recent clinical trials infrastructure and with additional government and charitable funding, innovative large-scale trials such as RECOVERY and ACTT were set up that were able to confirm and reject treatment hypothesis and generate data of sufficient quality for approval.
As clinical trials regulation - even though risk-proportionate - places a high burden on individual investigators who would assume the role of a sponsor, trial infrastructure is likely to be a key enabler in quantity and quality of academic research and future approvals. The example of treosulfan is likely to have benefitted from such provisions as part of the research network.
From the *in vitro* and *in vivo* evidence available at the beginning of the COVID-19 IITs, it was clear that academic research contributed much of the laboratory testing of the treatment hypothesis and that clinical researchers were quick to connect the pieces of evidence. The design of clinical trials that met the scientific and regulatory requirements to generate robust evidence remained a challenge to individual researchers.

Drug repurposing is thereby likely to contribute in a significant subset of unmet medical needs. But it will not be able to solve all challenges. In this respect the rapid development of *de novo* biological drug development platforms has shown an equally fast development in COVID-19 treatments.

An open question remains that of industry engagement in cases where there is robust scientific evidence but no commercial incentive. Off-label use creates a dilemma as it often lacks a mechanism of assessment of the available evidence. Thus, risk but also potential benefits go unnoticed. The example of molecular tumour boards shows that if the totality of evidence is assessed by a multidisciplinary expert group, patient outcomes benefit (Kato 2020).

The FDA pilot project renewal and the UKs systematic evaluation of off-label uses by NiCE are likely to clarify many questions about the potential of drug repurposing and the utility of existing and diverse literature data.

In the case of the FDA pilot, and the proposed STAMP EU repurposing framework, regulators seek to recruit academia to collect and prepare current literature evidence in a structured way that is more compatible with the agencies' methods of assessment.

A final enabler of academic repurposing will therefore be a EU Horizon 2020 funded project - STARS (Strengthening Training of Academia in Regulatory Science[41], Starokozhko 2020) coordinated by BfArM, which seeks to provide regulatory training to academia to align academic clinical research with regulatory requirements.

[41] Strengthening Training of Academia in Regulatory Science (www.csa-stars.eu)

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8 Annex - Supplementary Tables

8.1 EU orphan designation - approvals according to Art.10a or Art.8(3)(known AS), 2015-2019 and PUMA approvals

Brand name (INN), procedure, year	**MAH**	**EMA Product number**	**Indication**	**Clinical Efficacy trials (EPAR)**	**Clinical Efficacy Literature (EPAR)**	**Comment**
Source: EMA annual reports 2015-2019 Annex 10	EMA list of EPARS	EMA list of EPARS	EMA list of EPARS	EMA public assessment report (EPAR) of initial approval, sponsor from clinicaltrials.gov	EPAR, sponsor information from clinicaltrials.gov,	Clinicaltrials.gov or stated reference **Red: only Industry trials** **Green: at least one IIT or literature** **Yellow: known case of collaboration**
Cufence (**trientine** dihydro-chloride) Art.8(3), known AS 2019	Univar Solutions BV	EMEA/H/C/ 004111	Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults and children aged 5 years or older.	retrospective study based on patient records, UNV-TRI-002 (MAH)	133 literature references dated 1958-2017	
Cystadrops (**mercapt-amine**) Art.8(3), known AS 2017	Recordati Rare Diseases	EMEA/H/C/ 003769	Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.	EudraCT 2009-012564-13 (CHOC) phase III (MAH) EudraCAT 2007-006024-35 (OCT-1) phase II (MAH)	3x small IITs RCT v.s. placebo National Eye Institute & Uni Leeds	New formulation by Academia Tsilou 2003
Jinarc (**tolvaptan**) Art.8(3), known AS 2015	Otsuka Pharmaceutical Netherlands B.V.	EMEA/H/C/ 002788	Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.	156-04-251 phase III (MAH) global trial with 129 centres		
Jorveza (**budesonide**)	Dr. Falk Pharma GmbH	EMEA/H/C/ 004655	Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).	BUU-2/EEA phase II (MAH) BUL-1/EEA phase III (MAH)		

Brand name (INN), procedure, year	MAH	EMA Product number	Indication	Clinical Efficacy trials (EPAR)	Clinical Efficacy Literature (EPAR)	Comment
Art.8(3), known AS 2018						
Namuscla (**mexiletine** hcl) Art.8(3), known AS 2018	Lupin Europe GmbH	EMEA/H/C/ 004584	Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.	MYOMEX phase III (Assistance Publique - Hôpitaux de Paris) NCT02336477		
Natpar (**parathyroid hormone**) Art.8(3), known AS 2017	Shire Pharmaceuticals Ireland Ltd	EMEA/H/C/ 003861	Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.,	REPLACE phase III (MAH) and follow-up RACE		
Onivyde pegylated liposomal (**irinotecan** hydro-chloride) Art.8(3), known AS 2017	Les Laboratoires Servier	EMEA/H/C/ 004125	Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil (5 FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.	NAPOLI phase III (MAH)		NCT00042939 phase II Eastern Cooperative Oncology Group (published 2007) NCT00192712 phase II/III IL in a different formulation in pancreatic cancer (completed 2010)
Spectrila (**asparagin-ase**) Art.8(3), known AS 2016	Medac Gesellschaft fuer klinische Spezialpraeparate mbH	EMEA/H/C/ 002661	Spectrila is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.	MC-ASP.4/ALL phase II (MAH) MC-ASP.5/ALL phase III (MAH)		
Trecondi (**treosulfan**) Art.8(3), known AS 2019	medac Gesellschaft für klinische Spezialpräparate mbH	EMEA/H/C/ 004751	Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non malignant diseases, and in paediatric patients older than one month with malignant diseases.	MC-FludT.8/MDS phase II (MAH) MC-FludT.7/AML phase II (MAH) MC-FludT.17/M phase II(PD) (MAH) MC-FludT.14/L phase III (MAH)		Widely used in IITs since 2004. Caspar2004. MAH and academic collaboration in industry phase II trials.

Brand name (INN), procedure, year	MAH	EMA Product number	Indication	Clinical Efficacy trials (EPAR)	Clinical Efficacy Literature (EPAR)	Comment
Verkazia (**ciclosporin**) Art.8(3), known AS 2018	Santen Oy	EMEA/H/C/ 004411	Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.	NOVATIVE phase II/III (MAH) VEKTIS phase III (MAH)		
Vyxeos liposomal Daunorubicin +Cytarabin Art.8(3), known AS 2018	Jazz Pharmaceuticals Ireland Limited	EMEA/H/C/ 004282	Vyxeos liposomal is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	CLTR0310-301 phase III (MAH) plus supporting study 201		
Well-established use (Art.10a)						
Elmiron (**pentosan polysulfate** sodium) Art. 10a 2017	bene-Arzneimittel GmbH	EMEA/H/C/ 004246	Elmiron is indicated for the treatment of bladder pain syndrome characterized by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.	NCT00086684 Phase IV RCT (other company) and Queens University, Ca	Four 75-148 patient trials from US Universities incl. Interstitial Cystitis Clinical Trials Group	
Diagnostic: SomaKit TOC (**edotreotide**) Art.10a 2016	Advanced Accelerator Applications	EMEA/H/C/ 004140	This medicinal product is for diagnostic use only.After radiolabelling with gallium (68Ga) chloride solution, the solution of gallium (68Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.		30 publications on clinical efficacy (diagnostic)	diagnostic (radionucleotide)
Paediatric-use marketing authorisations						
Buccolam (**midazolam**)	Shire Services BVBA	EMEA/H/C/ 002267	Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents	*(PK only)*	Literature only 10(3) 5 comparator-controlled studies	

Brand name (INN), procedure, year	MAH	EMA Product number	Indication	Clinical Efficacy trials (EPAR)	Clinical Efficacy Literature (EPAR)	Comment
Art.10(3) **PUMA** 2011			(from three months to less than 18 years)., , Buccolam must only be used by parents / carers where the patient has been diagnosed to have epilepsy., , For infants between three and six months of age, treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.,			
Hemangiol (**propranolol**) Art.8(3) known AS **PUMA** 2014	Pierre Fabre Dermatologie	EMEA/H/C/002621	Hemangiol is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy:, , Life- or function-threatening haemangioma,, Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,, Haemangioma with a risk of permanent scars or disfigurement., It is to be initiated in infants aged 5 weeks to 5 months.,	V00400 SB201 phase II/III RCT (MAH)	additional 71 supporting academic publications since initial study on 11 children Leauté-Labrèze in 2008, data from compassionate use program	*Safety: Literature review of 60 scientific publications (involving 1367 patients with IH treated with propranolol* The publication of the pivotal trial has the same authors as the initial study. The initial publication states that the authors had applied for a use patent.
Sialanar (**glyco-pyrronium**) Art. 10a **PUMA** 2016	Proveca Pharma Limited	EMEA/H/C/003883	Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.,	referred to 3rd party published study by Shionogi (sponsor) and Texas Children's Hospital NCT00425087 phase III (Zeller 2012). Mier2000 dose finding study		

8.2 EU orphan designation – extensions of indication 2002-2019

Brand	INN	MAH	Indication	Appro-val	OD until	EPAR (procedure No.)	Main and supporting clinical trials in the clinical efficacy section of the EPAR	Ind. phase II/III for AS	Acad. phase II/III for AS	Comment
Source: The grey section of the table is taken from the EURODIS Rare Diseases Europe, marketing authorizations with orphan designation (OD) since 2000 and reduced to those cases where another indication was added subsequently. www.eurordis.org/orphan-drug-designations-marketing-authorisations. **Blue = cancer indications, dark blue = solid tumors**						Source: EMA website	Source: EPAR shown on left, clinicaltrials.gov **Yellow: Initial indication** **Red: only Industry trials** **Green: at least one IIT**	Number of all interventional phase II/III studies found in Clinicaltrials.gov		
Glivec	*imatinib*	*Novartis Europharm Limited*	*Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcrabl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. The effect of Glivec on the outcome of bone marrow transplantation has not been determined.*	*2001*	*expired*		Not followed			
Glivec	*imatinib*	*Novartis Europharm Limited*	*Glivec is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).*	*2002*	*withdrawn*		Not followed			
Glivec	*imatinib*	*Novartis Europharm Limited*	*Treatment of adult patients with unresectable recurrent and/or metastatic dermafibrosarcoma protuberans*	*2006*	*withdrawn*		Not followed			
Glivec	*imatinib*	*Novartis Europharm Limited*	*Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) as monotherapy*	*2006*	*withdrawn*		Not followed			
Glivec	*imatinib*	*Novartis Europharm Limited*	*Treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR gene re- arrangement*	*2006*	*withdrawn*		Not followed			
Glivec	*imatinib*	*Novartis Europharm Limited*	*Treatment of adult patients with hypereosinophilic syndrome (HES) and chronic eosinophilic leukaemia (CEL)*	*2006*	*withdrawn*		Not followed			
Tracleer	*bosentan*	*Actelion Registration Limited*	*hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III.Efficacy has been shown in: - Primary (idiopathic and familial) PAH. - PAH secondary to scleroderma without significant interstitial pulmonary disease. - PAH associated with congenital systemic- to-pulmonary*	*2002*	*expired*	EMEA/H/C/ 000401	Not followed			

Brand	INN	MAH	Indication	Appro-val	OD until	EPAR (procedure No.)	Main and supporting clinical trials in the clinical efficacy section of the EPAR	Ind. phase II/III for AS	Acad. phase II/III for AS	Comment
			shunts and Eisenmenger's physiology. *- Some improvements have also been shown in patients with PAH WHO functional class II."*							
Tracleer	*bosentan*	*Actelion Registration Limited*	*Indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. [new therapeutic area]*	*2006*	*withdrawn*		Not followed			
Zavesca	*miglustat*	*Actelion Registration Limited*	*Zavesca is indicated for the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.*	*2002*	*expired*	EMEA/H/C /000435	OGT 918-004 (study not found)	13	4	
Zavesca	*miglustat*	*Actelion Registration Limited*	*Extension of Indication – to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.*	*2009*	*expired*	EMEA/H/C/ 000435/II/0 029	**OGT 918-006 National Institute of Neurological Disorders and Stroke (NINDS) phase I/II** **+ National Eye Institute (NEI)** **OGT 918-007 phase II (MAH)**			**Parallel phase III IIT in Taiwan NCT 01760564**
Carbaglu	*carglumic acid*	*Orphan Europe Sarl*	*Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.*	*2003*	*expired*	EMEA/H/C/ 000461	**retrospective series of 20 patients including 6 case study publications**	0	5	
Carbaglu	*carglumic acid*	*Orphan Europe Sarl*	*This variation concerns an extension of indication of Carbaglu to add the treatment of hyperammoniemia due to isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia.* *[similar therapeutic area]*	*2010*	*Jun 21*	EMEA/H/C/ 000461/P4 6/033	**retrospective series submitted according to Art.46 EC/1901/2006 MAH (MAH)**			**4 phase II/III IITs in US/SA**
Nexavar	*sorafenib tosylate*	*Bayer Healthcare AG*	*For the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy*	*2006*	*expired*	EMEA/H/C/ 000690	100391 phase II (MAH) 11213 phase III (MAH)	238	290	most industry studies standard of care, 40 MAH
Nexavar	*sorafenib tosylate*	*Bayer Healthcare AG*	*Extension of Indication to include treatment of hepatocellular carcinoma.*	*2007*	*expired*	EMEA/H/C/ 690/II/05	10874 phase II (MAH) 100554 phase III (MAH)			
Nexavar	*sorafenib tosylate*	*Bayer Healthcare AG*	*Extension of indication for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.*	*2014*	*May 24*	EMEA/H/C/ 000690/II/0 035	**5x phase II IITs (12791, 12636, 12192, 100369, unknown)** 14295 phase III (MAH)			
Revlimid	*Lenali-domide*	*Celgene Europe Ltd*	*Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.* *Revlimid in combination with dexamethasone is indicated*	*2007*	*expired*	EMEA/H/C/ 000717	CC-5013-MM-009 phase III (MAH)	382 (257 MAH)	303	

Brand	INN	MAH	Indication	Appro-val	OD until	EPAR (procedure No.)	Main and supporting clinical trials in the clinical efficacy section of the EPAR	Ind. phase II/III for AS	Acad. phase II/III for AS	Comment
			for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.				CC-5013-MM-010 phase III (MAH)			
Revlimid	*Lenali-domide*	*Celgene Europe Ltd*	*Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.*	*2013*	*Jun 23*	EMEA/H/C/ 000717/II/0 056	MDS-003 phase II (MAH) MDS-004 phase III (MAH)			**supplemen tary safety from IITs**
Revlimid	*Lenali-domide*	*Celgene Europe Ltd*	*Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma*	*2016*	*Jul 26*	EMEA/H/C/ 000717/II/0 079	MCL-002 phase II (MAH) + 3x supporting (MAH)			
Soliris	*eculizumab*	*Alexion Europe*	*Indicated in adults and children for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history*	*2007*	*expired*	EMEA/H/C/ 000791	**C04-001 phase II Jonsson Comprehensive Cancer Center** C04-002 phase III (MAH)	53	15	
Soliris	*eculizumab*	*Alexion Europe*	*Extension Of Indication for atypical haemolytic uremic syndrome (aHUS) [new indication]*	*2011*	*Nov 23*	EMEA/H/C/ 000791/II/0 027	C08-002/3 phase III (MAH)			
Soliris	*eculizumab*	*Alexion Europe*	*Extension Of Indication for Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive [new indication]*	*2017*	*Aug 27*	EMEA/H/C/ 000791/II/0 090	ECU-MG-301/2 phase III (MAH) C08-001 phase II (MAH)			
Yondelis	*trabectedin*	*PharmaMar SA*	*Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients*	*2007*	*expired*	EMEA/H/C/ 000773	ET743-STS-201 phase II (MAH) + **phase II studies MAH/NIH**	34	28	*unable to connect studies*
Yondelis	*trabectedin*	*PharmaMar SA*	*Indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. [different stage]* *In combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer. [different cancer]*	*2009*	*expired*	EMEA/H/C/ 000773/II/0 008	ET743-OVA-301 phase III (MAH) + **other phase II studies MAH/NIH**			*unable to connect studies*
Torisel	*Tem-sirolimus*	*Pfizer Limited*	*First-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors.*	*2007*	*expired*	EMEA/H/C/ 000799	3066K1-200 phase II (presumed MAH) 3066K1-304 phase III (MAH)	166	327	
Torisel	*Tem-sirolimus*	*Pfizer Limited*	*EXTENSION OF INDICATION to include treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.*	*2009*	*expired*	EMEA/H/C/ 000799/II/0 001	3066K1-305 phase III (MAH) 3066K1-139 phase II (MAH) 3066K1-402 phase II (MAH)			

Brand	INN	MAH	Indication	Appro-val	OD until	EPAR (procedure No.)	Main and supporting clinical trials in the clinical efficacy section of the EPAR	Ind. phase II/III for AS	Acad. phase II/III for AS	Comment
Arzerra	*Ofatumu-mab*	*Glaxo Group Limited - UK*	*Refractory chronic lymphocytic leukaemia (CLL): Arzerra is indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab*	*2010*	*With-drawn*		*Not followed*			
Arzerra	*Ofatumu-mab*	*Glaxo Group Limited - UK*	*Previously untreated chronic lymphocytic leukaemia (CLL): Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.*	*2014*	*With-drawn*		*Not followed*			
Signifor	*Pasireo-tide*	*Novartis Europharm Limited UK*	*Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed*	*2012*	*Apr 22*	EMEA/H/C/ 002052	B2305 phase III (MAH) B2208 phase II (MAH)	33	18	
Signifor	*Pasireo-tide*	*Novartis Europharm Limited UK*	*Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue [new indication]*	*2014*	*Nov 24*	EMEA/H/C/ 002052/X/0 010	C2305 phase III (MAH) C2304 phase III (MAH)			
Adcetris	*Brentuxi-mab vedotin*	*Takeda Pharma A/S, Danmark*	*Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ H83 (Hodgkin's lymphoma): 1.following autologous stem-cell transplant (ASCT) or; 2.following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option*	*2012*	*Oct 22*	EMEA/H/C/ 002455	SG035-0003 phase II (other company) SG035-0004 phase II (other company)	60	56	
Adcetris	*Brentuxi-mab vedotin*	*Takeda Pharma A/S, Danmark*	*Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)*	*2012*	*Oct 22*	no variation	*Not followed*			
Adcetris	*Brentuxi-mab vedotin*	*Takeda Pharma A/S, Danmark*	*ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy*	*2017*	*Dec 27*	EMEA/H/C/ 002455/II/0 048	C25001 phase III (MAH)			
Iclusig	*ponatinib*	*ARIAD Pharma Ltd - UK*	*Iclusig is indicated in adult patients with: 1) chronic-phase, accelerated-phase or blast- phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation*	*2013*	*Jul 23*		*Not followed*			
Iclusig	*ponatinib*	*ARIAD Pharma Ltd - UK*	*2) Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation*	*2013*	*Jul 23*	no variation	*Not followed*			
Kolbam	*cholic acid*	*FGK Representativ e Service*	*Inborn errors in primary bile-acid synthesis*	*2014*	*With-drawn*		*Not followed*			

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		GmbH, Germany								
Kolbam	*cholic acid*	*Retrophin Europe Ltd*	*Inborn errors in primary bile-acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults 11/2025*	*2015*	*Nov 25*	no variation found	*Not followed*			
Gazyvaro	*obinutuzumab*	*Roche Registration Ltd*	*Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy*	*2014*	*Jul 24*	EMEA/H/C/002799/0000	BO21004/CLL11 phase III (MAH) BO21003 phase II (MAH) BO20999 phase II (MAH)	82	35	
Gazyvaro	*obinutuzumab*	*Roche Registration Ltd*	*Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced Follicular lymphoma FL*	*2016*	*Jun 26*	EMEA/H/C/002799/II/0007	GAO4753g phase III (MAH)			
Imbru-vica	*ibrutinib*	*Janssen-Cilag International NV*	*Imbruvica is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma*	*2014*	*Oct 24*	EMEA/H/C/003791/0000	PCYC-1102-CA phase I/II (MAH) PCYC-1104-CA phase II (MAH)	154	94	
Imbru-vica	*ibrutinib*	*Janssen-Cilag International NV*	*Imbruvica is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo immunotherapy*	*2014*	*Oct 24*	no variation	*Not followed*			
Imbru-vica	*ibrutinib*	*Janssen-Cilag International NV*	*Imbruvica is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy*	*2015*	*Jul 25*	EMEA/H/C/003791/II/0001	PCYC-1118E (not found, presumed MAH)			
Lenvima	*lenvatinib mesylate)*	*Eisai Europe Ltd*	*Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)*	*2015*	*With-drawn*		*Not followed*			
Lenvima	*lenvatinib mesylate)*	*Eisai Europe Ltd*	*Lenvima is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC)*	*2015*	*With-drawn*		*Not followed*			
Cre-semba	*Isavu-conazole*	*Basilea Medical Ltd*	*Cresemba is indicated for the treatment of adults with invasive aspergillosis*	*2015*	*Oct 25*		*Not followed*			
Cre-semba	*Isavu-conazole*	*Basilea Medical Ltd*	*Treatment of mucormycosis in patients for whom amphotericin B is inappropriate*	*2015*	*Oct 25*	no variation	*Not followed*			

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Rydapt	*Midos-taurin*	*Novartis Europharm Ltd*	*Adult patients with acute myeloid leukemia (AML)*	*2017*	*Sep 27*		*Not followed*			
Rydapt	*Midos-taurin*	*Novartis Europharm Ltd*	*Adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL)*	*2017*	*Sep 27*	no variation	*Not followed*			
Myalepta	*Metre-leptin*	*Aegerion Pharmaceutic als B.V.*	*Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control*	*2018*	*Aug 18*		*Not followed*			
Myalepta	*Metre-leptin*	*Aegerion Pharmaceutic als B.V.*	*Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with confirmed congenital generalised LD (Berardinelli-Seip syndrome)*	*2018*	*Aug 18*	no variation	*Not followed*			
Myalepta	*metreleptin*	*Aegerion Pharmaceutic als B.V.*	*Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above*	*2018*	*Aug 18*	no variation	*Not followed*			
Myalepta	*Metre-leptin*	*Aegerion Pharmaceutic als B.V.*	*Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients with confirmed familial partial LD*	*2018*	*Aug 18*	no variation	*Not followed*			
Kymriah	*Tisagen-lecleuce*	*Novartis Europharm Limited*	*Kymriah is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL)*	*2018*	*Aug 28*		*Not followed*			
Kymriah	*Tisagen-lecleuce*	*Novartis Europharm Limited*	*Adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL)*	*2018*	*Aug 28*	no variation EPAR	*Not followed*			
Yescarta	*Axicab-tagene ciloleucel*	*Kite Pharma EU B.V.*	*Treatment of adult primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.lymphoma (PMBCL)*	*2018*	*Aug 28*		*Not followed*			
Yescarta	*Axicab-tagene ciloleucel*	*Kite Pharma EU B.V.*	*Treatment of adult patients with relapsed or refractory diffuse large B- cell lymphoma (DLBCL)*	*2018*	*Aug 28*	no variation EPAR	*Not followed*			