

**„Earlier access to medicines“
EAMS in the UK
A comprehensive overview and
comparison to existing accelerated
licensing procedures in the EU and
Germany**

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Jan Horn

aus Berlin

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Erstprüfer/in: **Frau Dr. Rose Schraitle**
Zweitprüfer/in: **Herr Dr. Michael Horn**

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reactions
AHSN	Academic Health Science Networks
AL	Adaptive licensing (renamed Adaptive pathways)
AMG	Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz) German Drug Act
AMHV	Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen (Arzneimittel-Härtefall-Verordnung)
AP	Adaptive pathways (Adaptive licensing renamed)
AP	Adaptive pathways (formerly known as Adaptive licensing (renamed))
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BIA	UK BioIndustry Association
BIS	Department for Business Innovation & Skills
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Federal Office of Consumer Protection and Food Safety
CCG	Clinical Commissioning Groups
CMA	Conditional marketing authorisation
Coh-CUP	Cohorts of patients compassionate use programmes
CP	Centralised procedure
CSR	Clinical study report
CTD	Common technical document
CUP	Compassionate use programmes
DCP	Decentralised procedure
DGSANCO	Directorate General for Health and Consumer Affairs
DH	Department of Health
DHPC	Direct Healthcare Professional Communication
DOH	Department of Health
EAMS	Early Access to Medicines Scheme
EAMSSO	EAMS scientific opinion
EAP	Early Access Programmes

EC	European Commission
EEC	European Economic Community
EMA	European Medicines Agency formerly known as EMEA (also known as The Agency)
EPAR	European assessment report
EU	European Union
EXMA	Exceptional marketing authorisation
FPH	Joint Faculty of the three Royal Colleges of Public Health Physicians of the United Kingdom (London, Edinburgh and Glasgow)
GMC	General Medical Council
GMP	Good Manufacturing Practice
HTA	Health Technology Authorities
LOI	List of outstanding Issues
LOQ	List of outstanding question
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NP	National licensing procedures
NPP	Named patient supply
PAR	Public assessment report
PAS	Patient access schemes
PASS	Post-authorisation safety studies
PEI	Paul Ehrlich Institut
PhV	Pharmacovigilance
PIL	Patient information leaflet
PIM	Promising innovative medicine designation
PPRS	Pharmaceutical Price Regulation Scheme
PSMF	Pharmacovigilance System Master File

PSUR	Periodic safety update report
PVS	Pharmacovigilance system
REA	Relative effectiveness assessment
RMP	Risk management plan
RPSGB/RPS	Royal Pharmaceutical Society of Great Britain
SA	Scientific advice
SAE	Serious adverse event
SEED	Shaping European Early Dialogues for Health Technology
SMEs	Small and Medium Enterprises
SmPC	Summary of Product Characteristics
SO	Scientific Opinion
SPC	Summaries of Product Characteristics
The Agency	EMA

INTRODUCTION

Accelerated or earlier access to medicines mainly has two dimensions; the timing of the drug approval and the number of patients that probably benefit from access to the medicine.

A bunch of schemes already exists in the EU and the UK to support earlier access to new medicines although there is concern that these schemes are not being used as frequently as they could be.

The Early Access to Medicines Scheme (EAMS) in the United Kingdom is a newly introduced UK programme for early access to medicines for patients in need. Identified the shortcomings of existing regulatory regimes the UK Government has introduced the new EAMS to facilitate access to drugs which are not yet authorised in the UK. The intention of the scheme is to give patients with life threatening or seriously debilitation conditions early access to medicines which do not yet have a marketing authorisation when a clear unmet medical need can be identified. As a consequence abreast, it is also the intention in regard to the industry by way of provision of access to medicine early before a full licensure is granted to provide certain incentives for pharmaceutical development activities. That being the case, the scheme lastly also is intended to be rounded up by the introduction of a third step planned, an accelerated Health Technology Authorities (HTA) appraisal procedure facilitating much more quick and consistent reimbursement negotiations.

On EU level existing schemes mainly include conditional marketing authorisation, marketing authorisation granted under exceptional circumstances and accelerated assessment as well as the newly EMA introduced adaptive licensing pilot. In the UK individual patient supply, special exemption and fast track assessment is available.

The thesis provides a review of the new UK EAMS essentials in context to the existing early access schemes and licensing flexibilities for medicine products in Europe. In particular a comparison to the corresponding scheme in Germany in regard to the legal basis, regulatory requirements, applicability, and time lines, advantages for patients and industry, and reimbursement issues will be discussed. Consequently, finally the options for implementation of parts of the new EAMS into existing regular licensing procedures will be regarded.

1 EU Medicines Licensing Flexibilities

Regular licensing procedures for medical products consist of pure national licensing procedures (NP) in one EEC Member State, decentralised marketing authorisation procedures (DCP) where a marketing authorisation in more than one Member State is intended and no marketing authorisation in the EEC already exists, mutual recognition procedure (MRP) in case a marketing authorisation in one or more Member States already exists, and centralised marketing authorisation procedure (CP) used for a community authorisation.

According to Article 6(1) Directive 2001/83/ECⁱ in the EU no medical product may be placed on the Member State market unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with Regulation EC No 726/2004ⁱⁱ read in conjunction with Regulation EC No 1901/2006ⁱⁱⁱ and Regulation EC No 1394/2007^{iv}.

The legal basis for more flexible licensing schemes in the EU is Regulation EC No 726/2004. According Article 3 Regulation EC No 726/2004 in the EU marketing authorisation applications for innovative medicinal products must be made under the EMA centralised procedure. The procedure is mandatory for medicinal products derived from biotechnology, new active substances, treatments for cancer, HIV, immune dysfunctions and viral diseases, neurodegenerative disorders, diabetes, and orphan medicinal products for rare diseases. The minimum time frame for the central assessment is set to 210 days including the option for an accelerated assessment potentially shortening the process to 150 days.

1.1 Existing Flexibilities

The following EU flexibilities for licensing procedures exist.

Full Licensing Schemes

- MRP-DCP
- CP (optional accelerated)

Restricted Licensing Schemes (optional accelerated, orphan designation)

- Conditional Approval Article 14(7) Regulation EC No 726/2004
- Exceptional Circumstances Article 14(8) Regulation EC No 726/2004
- Accelerated Assessment Article 14(9) Regulation EC No 726/2004
- Orphan Designation Article 3 Regulation EC No 141/2000

Opinion Based Non-Licensing Schemes

- Compassionate Use Article 83 Regulation EC No 726/2004
- Named Patient Use Article 5 Directive 2001/83/EC

- Adaptive Licensing – EMA Pilot

On EU national Member State level other licensing flexibilities especially tailored to specific national legislation and reimbursement requirements may exist. Article 5(1) Directive 2001/83/EC provides derogations. An overview on early access programmes (EAP) is presented in Table 1-1 Implemented Early Access Programs and Relevant Legislation.

1.2 Problems Identified with Existing Licensing Schemes

Problems of existing schemes were identified by the MHRA^v through informal consultation of three companies and a trade association as well as in DGSANCO EC reflection paper^{vi}. Accordingly, the most prominent points are gathered here:

- Too little is known by firms about how the schemes work. The existing regulatory flexibilities are not used optimally and proactively as they could.
- The schemes are overly bureaucratic and are often ignored because of the high administrative costs they create.
- Uptake of medicines by the NHS is too uncertain, often commissioners are uncertain about the cost effectiveness of the medicines on offer. Without guidance from the National Institute of Health and Clinical Excellence (NICE), NHS commissioners will be concerned about giving up existing treatments with known benefits.
- The lack of an integral vision from the evaluation of the marketing authorization to the use of the medicinal product and lack of consistent decisions by both regulators and payers has frustrated the conditional approval as a form of stepped access to new treatments for unmet medical needs.
- The current regulatory regime for marketing authorisation is lacking flexibility, possibilities for innovation and has rising costs (pharmacovigilance requirements).
- Currently, we are faced with a complex system of successive evaluations, usually of the same data, without an integrated vision of the evaluation of medicines. The existence of multiple, successive assessments have given different results with the consequent lack of confidence in the system.
- Granting centralised authorisation does not guarantee the availability of a product on all EU markets as Marketing Authorisation Holder (MAH) is not obliged to place the product on every Member States market (especially the ones which are small, but include high costs, especially related to Pharmacovigilance (PhV) obligations).
- As regards conditional marketing authorisation (CMA) the following problems were noted: after authorisation MAHs have presented their products as fully authorised and have demanded access as a full license; MAHs are not fulfilling post-authorisation commitments in timely manner in a way that data lose their

value for regulatory purposes; reluctance of payers due to immaturity of development, lack of data and/or high prices; Low incidence or/and specific characteristics of some illness make on some occasions that clinical data are only obtained from sample estimates that might not represent the targeted population. Therefore, neither clinical nor cost-effectiveness data in real life settings are available, which give rise to clinical and short-term budget impact uncertainties delaying pricing and reimbursement decisions and access to market; patients consider that a new medicine fulfils the same requirements like other (full) authorised medicines and therefore claim for access to medicines independently of their real value and price; doctors feel that a fully prescribable medicine is on the market also for off-label use in other related conditions.

- Reimbursement and commissioning delays and Health Technology Authorities (HTA) high variability across Member States – Market Access.

Table 1. Implemented Early Access Programs, and Relevant Legislation

Country Name	Relevant Legislation		Name of the Program
	Type of Program		
Austria	Federal Medicines Act (Arzneimittelgesetz), 2009. Specific regulation in development	Nominative	<ul style="list-style-type: none"> Compassionate Use. Allows a physician to give a patient with severe condition a medicinal product which has no market approval in Austria
Belgium	Loi Belge 1er Mai 2006 portant révision de la législation pharmaceutique (modifications of the loi du 25 mars 1964 sur les médicaments)	Nominative	<ul style="list-style-type: none"> Compassionate Use. Allows a physician to give a patient with severe condition a medicinal product which has no market approval in Belgium Emergency Medical Program. Intended for the treatment of severe condition and applied to medical product that are under assessment for a market authorization in Belgium
Denmark	Section 29 (1) of the Danish Medicines Act	Nominative	<ul style="list-style-type: none"> Compassionate Use Permit(CUP). Permits the sale or dispensing of limited amounts of medicinal products that are not covered by a marketing authorisation or marketed in Denmark
France	Article 5- Directive 2001/83/CE for the "nominative" ATU Article 83-Regulation no.276/2004/CE for the "cohort" ATU	Cohort or Nominative	<ul style="list-style-type: none"> Temporary Use Authorization(ATU). Allows early access to new drugs or to old drugs not covered by a marketing authorization. <ul style="list-style-type: none"> Cohort ATU. Concern a group of patients and it is issued at the request of the holder of distribution rights. Nominative ATU. Delivered for only one named patient under the responsibility of the prescribing physician. Represent the last option in a situation where the drug has not been requested for a marketing authorization or applied for a cohort ATU
Germany	Section 21 (2) no.6 AMG (German Medicine Act) in conjunction with the article 83 of the European Regulation EG (no.726/2004)	Cohort	<ul style="list-style-type: none"> Hardship Case Program(AMHV). Pharmaceutical without marketing authorization or previous approval in Germany can get distributed among a specific group of patients
Italy	Law no. 326 of 24 November 2003	Cohort or Nominative	<ul style="list-style-type: none"> Compassionate Use. Allows a physician to give a patient with severe condition a medicinal product which has no market approval in Belgium Fondo AIFA 5%. Allows drugs in development for orphan diseases, treating life-threatening conditions to be reimbursed, and medical products awaiting market authorization to be utilized
Norway	Specific regulation is in development	Cohort or Nominative	<ul style="list-style-type: none"> Named Patient Program(NPP). Allows treating physician to prescribe medical products unauthorized in Norway Compassionate Use Program(CUP). Either the treating physician or the manufacturer can apply in order to provide medical product unauthorized in Norway
Poland	n/a	Nominative	<ul style="list-style-type: none"> Named Patient Program. Allows treating physician to prescribe medical products unauthorized in Poland
Portugal	Articles 92-93 of the Decreto Lei no. 176 of 30 th August 2006	Nominative	<ul style="list-style-type: none"> Special Use Authorization(EUA). Allows a physician to give a patient with severe condition a medicinal product which has no market approval in Portugal
Spain	Real Decreto 1015 of 19 th June 2009	Cohort or Nominative	<ul style="list-style-type: none"> Temporary Use Authorization. Allows a treating hospital to give a patient with severe condition a medicinal product which has no market approval in Spain
Sweden	§5 of the Medicine Act no 859 of 1992, recently updated the 28 th August 2012 (LVFS)	Nominative	<ul style="list-style-type: none"> Named Patient Use. The permits are granted as individual licences, in the case when the need for drugs cannot be met by medical products approved in Sweden
Switzerland	Therapeutic Product Act (HMG) of 15 th December 2000	Nominative	<ul style="list-style-type: none"> Named Patient Use Permit(Sonderbewilligung). Allows a physician to give a patient with severe condition a medicinal product which has no market approval in Switzerland
United Kingdom	Schedule 1 of The Medicines for Human Use Regulations 1994 [SI 1994/3144] / The Guidance Note 14 The supply of unlicensed relevant medicinal products for individual patients'	Nominative	<ul style="list-style-type: none"> Special Need. Allows a physician to give a patient with severe condition a medicinal product which has no market approval in UK Earlier Access to Medicine Scheme. Provide access to particularly promising medical products, with a clear positive benefit-risk balance, between the end of phase III trials and licensing. (MHRA has published the public consultation the 17th July 2012 [3] and has received comments the 5th October 2012. A new scheme will follow up by the end of 2012)

Table 1-1 Implemented Early Access Programs and Relevant Legislation^{vii}

2 UK Earlier Access to Medicines Scheme

On 5th December 2011 the Prime Minister announced the ‘New Strategy for UK Life Science’^{viii}, “To increase the speed and efficiency of regulatory and health technology assessment pathways for drug development, we will publish for consultation a new ‘Early Access Scheme’.”^{ix}

On 7th April 2014, after public consultation^{x,xi,xii,xiii}, the MHRA launched the Early Access to Medicines Scheme (EAMS).^{xiv} The scheme is intended to give patients suffering from life threatening or seriously debilitating conditions early access to medicines which are used off-label or do not yet have a Marketing Authorisation in case there is a clear unmet medical need.

The basic idea of the concept for the EAMS was laid down in Sir David Cooksey's 2006 ‘Review of UK health research funding’^{xv} eight years ago.

2.1 Intention of the Scheme

The EAMS is considered enhancing the landscape for developing, licensing, and procuring innovative medicines.^{xvi} In the Government response to UK EAMS consultation - March 2014 - the intention of the scheme is described as to:

- Addresses a public health need to improve access, on an unlicensed or off-label basis, to important innovative medicines for patients with life threatening or seriously debilitating conditions without adequate treatment options.
- Completes the landscape for early access to medicines which reflects the UK Life Sciences Strategy^{xvii} and NHS Innovation Health and Wealth reforms^{xviii}.
- Reflects the profound changes – driven by Genomics, Data, and the rise of Stratified and Personalised Medicines – transforming the drug discovery landscape away from the traditional ‘blockbuster’ model of the post-war years to the world of ‘Translational’ or ‘Experimental’ Medicine in which drugs are designed with and around patients, their data and tissues, in clinical research facilities and hospitals.
- Demonstrates a commitment from the UK to pharmaceutical innovation, through the PIM and earlier patient uptake of new innovative medicines in the health service.
- Encourages start-ups, patient groups and charities to collaborate within the extensive infrastructure via the National Institute for Health Research (NIHR) funded Clinical Research Facilities and Biomedical Research Centres and Units in leading NHS Trust/university partnerships.
- Is clearly distinguished from ideas being developed in relation to “adaptive licensing” which relates to the pro-active use of existing EU licensing flexibilities to gain an early marketing authorisation.

The Scheme will allow the UK to present a coherent landscape for a new model of fast-tracked medicines discovery and development based on an integrated pathway to facil-

itate and accelerate the development of innovative medicines, including stratified medicines, in three key stages.

2.2 Legal Basis

The proposed Early Access to Medicines Scheme is designed to operate within the current UK national and EU legal framework as any other proposals would need to implement changes to the current EU legal basis, which is considered being extensively time consuming due to agreement of the numerous Member States concerned.^{xix}

Directive 2001/83/EC is the legislation laying down the regulatory framework for medicinal products in the EU. The Directive applies to medicinal products for human use intended to be placed on the market in Member States either prepared industrially or manufactured by method involving an industrial process. Under its provisions no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been granted by the competent authorities of that Member State in accordance with Regulation EC No 726/2004.

Article 5(1) Directive 2001/83/EC provides a derogation; “A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.”

The UK respectively has made use of the derogation by implementing national provisions in The Medicines for Use (Marketing Authorisations Etc.) Regulations 1994 No. 3144 as amended^{xx} – Schedule 1. Schedule 1 EXEMPTION AND EXCEPTIONS FROM THE PROVISIONS OF REGULATORY 3 thereof implements the provisions of Article 5(1) Directive 2001/83/EC. Here the conditions are described which permit the manufacture, assembly, importation, and supply of unlicensed medicines to meet the special needs of an individual patient on the direct personal responsibility of the prescriber. The manufacture, assembly, importation and distribution of unlicensed medicinal products may only be carried out by licensed manufacturers and wholesalers, importers are required to notify the Licensing Authority [MHRA] before importing unlicensed medicinal products.^{xxi}

The second basis to be considered is off-label use. Section 10 of the Medicines Act 1968^{xxii} as amended provides the exemptions from licensing which apply to pharmacists whereas Section 9 thereof provides those for a practitioner to order a product without a marketing authorisation. For the use of medicines outside of their authorised indications described in the Summaries of Product Characteristics (SPC) respectively the Patient Information Leaflet (PIL), guidance is given in the UK by the General Medical Council (GMC)^{xxiii} as well the Royal Pharmaceutical Society of Great Britain (RPSGB)^{xxiv}.

2.3 Description of the Scheme

Primarily the scheme is aimed at medicines that have completed phase III trials but might be applied to completed phase II trials in exceptional circumstances.

Under the scheme the MHRA, after a promising innovative medicine designation (PIM) has been issued, will provide a scientific opinion (SO) on the benefit/risk-balance of the medicine on base of the data available at the time of the EAMS submission. The Government recognises that a clear route for earlier access is required following a PIM designation and expects that the applicant will complete clinical development programmes within a reasonable timeframe in order to continue within the scheme.

The opinion could support access by patients to innovative medicines (outside of clinical trials) significantly earlier than the timeframes of the normal drug development process – for instance where compelling evidence exists it is envisaged that the opinion potentially can be given on the basis of phase II studies instead of normally basis of phase III.^{xxv}

The scheme is voluntary and complementary to the normal licensing procedures for medicines and will not replace them. The opinion issued from the MHRA will be valid for one year with the option for renewal.

The MHRA is responsible for the scientific aspects of the scheme and the scientific opinion will be provided after completion of a *two-step evaluation procedure*. The information upon the opinion will be published on the MHRA website and prescribers and health care professionals could be informed via stakeholder engagement and healthcare organisations. A monthly updated bulletin on drug safety updates for doctors and pharmacists is considered as well as an email alert system for new items. The medicine will be made free of charge by the company until the marketing authorisation is granted after which reimbursement will be subject to an *additional third step*. A new NICE technology (HTA) appraisal scheme is intended.

2.3.1 Step I - Promising Innovative Medicine (PIM) Designation

The Promising innovative medicine (PIM) designation is based on early clinical data and will give an early indication, if positive that a product may be eligible for the scheme. The designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed.^{xxvi}

2.3.1.1 Qualification for PIM Designation

Medicine products which are eligible for a designation application include new biological or chemical entities, also the *re-purposing of established or recently approved drugs* is considered.^{xxvii} The criteria are that the medicine is targeting life threatening or seriously debilitating conditions, which are either conditions for which there is no treatment or conditions for which the available treatment options are not satisfactory, e.g. in

the advanced cancer setting where the tumour is unresponsive to currently authorised medicinal products.

In order to obtain a PIM designation all of the first three criteria below mentioned must be fulfilled, Figure 2.3.1-1 Criteria of an EAMS Application – Step I - Promising Innovative Medicine (PIM) Designation.

Criteria	Criteria of an EAMS application
1	(a) Life threatening or seriously debilitating condition and (b) High unmet need, i.e. there is no methods available or existing methods have serious limitations
2	The medicinal product is likely to offer significant advantage over methods currently used in the UK
3	The potential adverse effects of the medicinal product are considered to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance
4	The Applicant is able to supply the product and to manufacture it to a consistent quality standard (GMP)

Figure 2.3.1-1 Criteria of an EAMS Application – Step I - Promising Innovative Medicine (PIM) Designation^{xxviii}

Explained in more detail according Guidance:

- 1a. The severity of the disease should be justified based on objective and quantifiable medical or epidemiologic information, in terms of mortality and morbidity, with special emphasis on patient quality of life.
- 1b. A critical review of the methods of treatment, diagnosis or prevention currently available in clinical practice in the UK should be provided, including an evaluation of the performance of these methods based on quantifiable data (e.g. data on survival, disease progression/relapses, or patient-reported outcomes). The Applicant should provide a justification for why current methods are not adequate.
2. The Applicant should submit preliminary evidence, based on non-clinical and clinical data, indicating that the advantage and magnitude of effect claimed for the product is predicted to be of significant relevance to the patient and will address their unmet need. A well-argued evaluation of the likelihood of achievement of the product's claims should be provided, based on the totality of information available at the time of designation. Depending on the product, this may include, but not restricted to, direct or indirect comparison to existing therapies/ standard of care in the UK, or evidence of a potential treatment effect in the aetiology of the condition or similar efficacy but better overall tolerability compared to existing therapies.
3. The potential adverse effects of the medicinal product are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit risk balance. A positive benefit risk balance should be based on preliminary scientific evidence, as justified by the applicant, that the safety profile of the medicinal product is likely to be manageable and acceptable in relation to the estimated benefits.

2.3.1.2 Regulatory Requirements for a PIM Designation

The information required for an application is published in a dedicated PIM designation application template^{xxix}. Basically, information on how the medicine product would meet the required qualification criteria 1-3 has to be provided, additionally a brief description of the current pharmaceutical development. After the request for a PIM designation a “Designation Meeting,” for which scientific advice fees apply, will be scheduled within a time frame of 4 weeks. Further additional scientific advice (SA) can be requested at any stage. Neither a positive nor a negative designation result will be published, but the number of designation meetings carried out per year will. An expiry period for the PIM designation has not been foreseen. Figure 2.3.1-2 PIM Designation – Step I of EAMS Schedule schematically visualises the steps and meetings to be followed for preceding the next step, the EAMS opinion application.

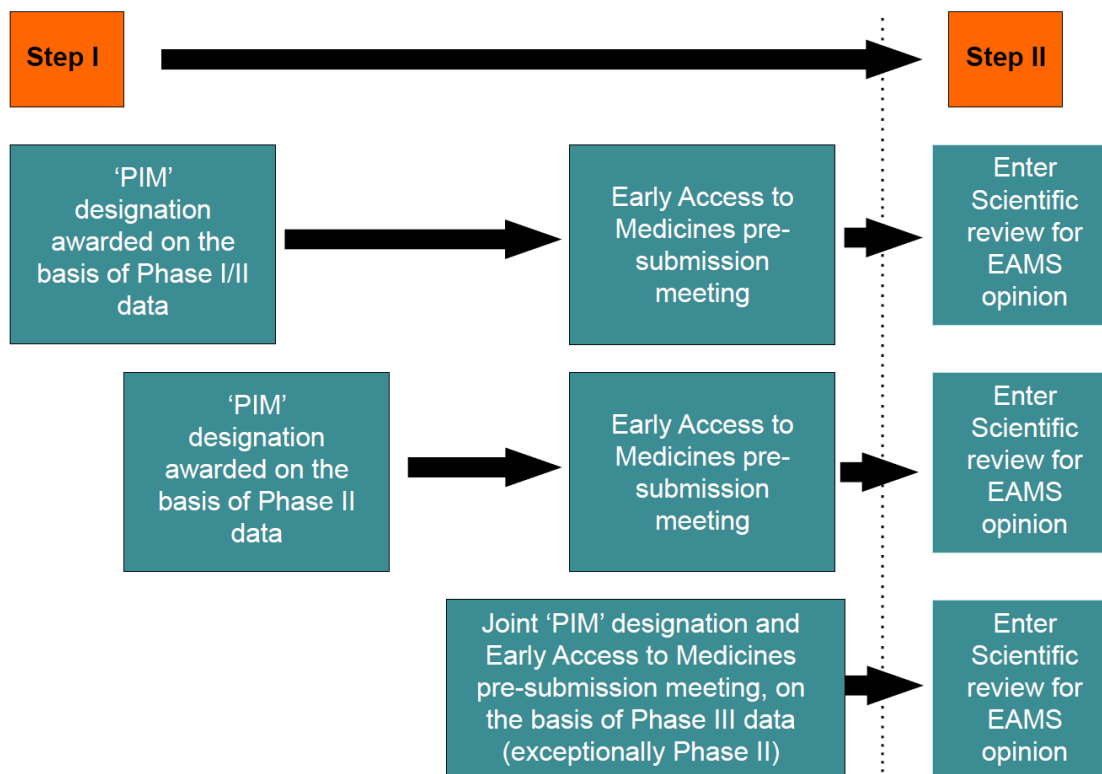


Figure 2.3.1-2 PIM Designation – Step I of EAMS Schedule^{xxx}

2.3.2 Step II - EAMS Scientific Opinion (EAMSSO)

The EAMS Scientific Opinion (EAMSSO) describes the benefits and risks of the medicine based on the information submitted to the MHRA by an applicant after sufficient data has been gathered from the patients who will benefit from the medicine. The opinion will support the prescriber and patient to make an informed decision on whether *to use the medicine before its licence is approved* - still unlicensed or off-label use - but *outside of clinical trials*. Patients participating in clinical trials will not be eligible.

In case the opinion is positive, the medicine is recommended to be *made available free of charge by the company* until a full marketing authorisation is granted. Once a license is obtained, the medicine product is expected to be subject to standard NICE technology appraisal for reimbursement.

2.3.2.1 Qualification for EAMSSO

Prerequisite for obtaining the EAMSSO is a valid *PIM designation and a pre-submission meeting* with the MHRA.

The applicant must be able to supply and manufacture the product to a consistent quality standard under GMP conditions, as criterion 4 stated in Figure 2.3.1-1.

2.3.2.2 Regulatory Requirements for the EAMS Scientific Opinion

The Pre-submission meeting will ensure that the suitability criteria for the scheme are likely to be met and the format of the data required to be submitted to support the benefit/risk opinion can be discussed. In order to ensure that applications for the EAMS are considered as soon as possible following the receipt of the completed joint PIM designation/pre-submission meeting application form a date will be arranged at the earliest opportunity. After the 'free of charge meeting' the MHRA will make 'a recommendation' as to whether the product is considered as a suitable candidate for step II. Nonetheless, it remains within the decision of the applicant to precede further application steps. A template for application is provided.^{xxxi}

The EAMS application submission documentation (EAMS Dossier) is preferred in the CTD format (Module 1-5) exceptionally in case clinical studies are ongoing or a full clinical study report (CSR) is not available yet^{xxxii}. The EAMS dossier consists of a completed EAMS application form^{xxxiii}, a cover letter including the proposed timetable submission slot (MHRA web site) and EAMS number, a summary of the pharmacovigilance system master file (PSMF), and a risk management plan (RMP)^{xxxiv}. The pharmacovigilance arrangements are considered similar to those which would be in place for a licenced medicine product. This involves a monitoring program similar to the RMP and a patient registry, "...this would likely include a drug registry and if required, a full protocol [treatment protocol] will need to be agreed before a positive opinion is issued."^{xxxv} Registry requirements which describe the data relevant to be collected whilst the product is prescribed under the scheme are summed in the Guidance for Applicants for the EAMS Step II. It is highlighted that, "Given the scheme is designed for products where there are no suitable alternative treatment options, it is highly unlikely that comparative data will add value, and thus a drug, rather than a disease registry is likely to be the most appropriate design."

Within a period of 15 days following a positive EAMS scientific opinion the relevant Public Assessment Report (PAR) as well as the EAMS treatment protocol (1.2 Treatment Protocol Earlier Access to Medicines Scheme Application Guidance^{xxxvi}) will be published on the MHRA website including information on:

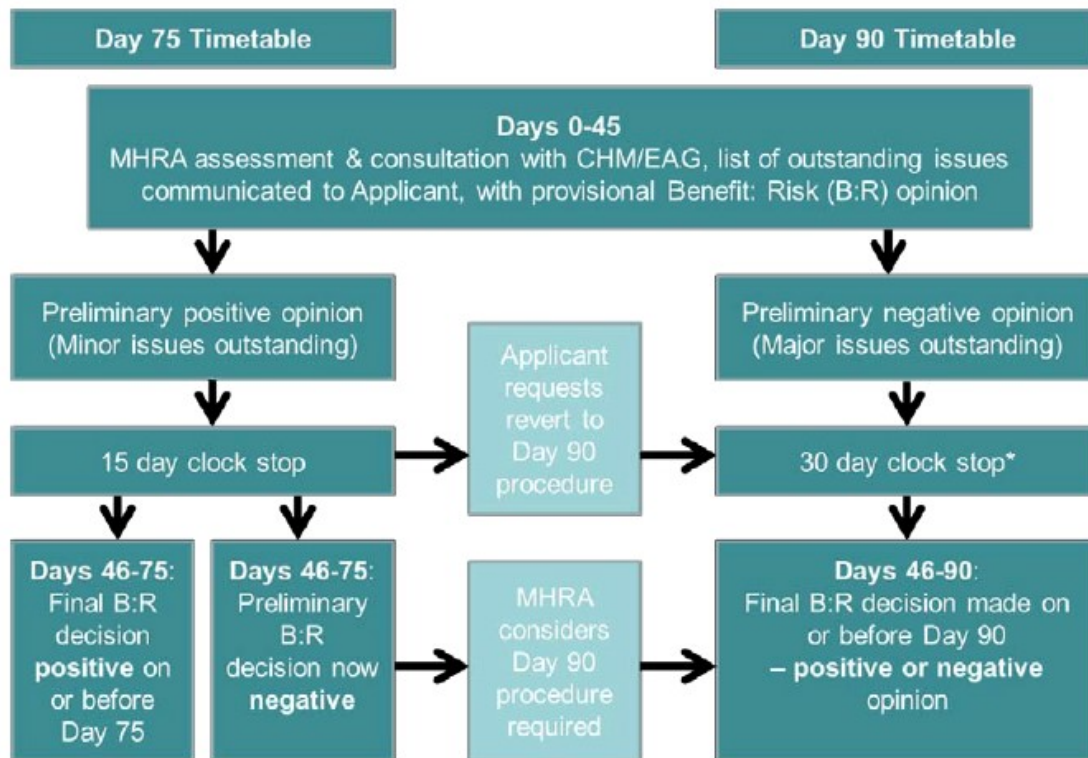
- how the product is used and how it works
- summary of the key clinical studies
- the risks and benefits of the product
- the reason for the positive EAMS scientific opinion
- any uncertainties
- information about ongoing clinical studies

In addition to the first three criteria mentioned in Figure 2.3.1-1 at EAMSSO stage additionally the 4th criterion has to be met. The applicant must be able to supply and manufacture the product to a consistent quality standard under GMP conditions.

Periodic updates and renewals^{xxxvii} will be necessary in case a positive opinion is issued. Regular updates on a 3 month frequent basis are likely but will have to be discussed before opinion emission. Generally, a positive opinion is valid for one year with the option for renewal, but will cease if a regular licence becomes effective.

The MHRA will withdraw an EAMS positive scientific opinion in case further following scientific assessments reveal that the risk-benefit balance considerably is no longer favourable, or a marketing authorisation is granted. Public assessment reports and EAMS treatment protocols then will be removed from the MHRA website. Changes will be communicated adequately. In case a medicine will not get a marketing authorisation the availability under the EAMS will be reviewed.^{xxxviii}

Assessment and decision timetable as by way of illustration in Figure 2.3.2-1 Assessment and Decision Timetable for Early Access to Medicines Scheme Scientific Opinion provides an overview about the different outcomes of the procedure likely. In case the preliminary opinion is issued positive the procedure will take 75 days at least, if not than an extended period of 90 days may apply due to an elongated clock stop of 30 days instead of 15 days expected.



*in exceptional circumstances, the Applicant can request additional 30 days (30+30)

Figure 2.3.2-1 Assessment and Decision Timetable for Early Access to Medicines Scheme Scientific Opinion^{xxxix}

2.3.3 Step III - EAMS Licensing and Rapid Commissioning

For routine patient access to medicines in the UK medicine products once licensed will have to take a 'fourth hurdle' for accessing the (NHS) market - regularly the routine NICE appraisal, normally on basis of evidence collated. In case of EAMS these data upon partly can be collected in earlier stages. To support the accelerated nature of the scheme it is anticipated that a 'Fast Track NICE Appraisal Procedure' would be in place, which presently is not yet. That means, NICE currently cannot issue regular formal guidance on unlicensed medicines unless being directed by the Secretary of State^{xi}, as well as these medicines do not fall within the scope of the Department of Health Pharmaceutical Price Regulation Scheme (PPRS)^{xii}.

The following approach^{xiii} is under discussion; however, the medicines, once licensed, will be subject to the commissioning scheme of the NHS, presumed an allocated fund to pay:

For the EAMS Licensing and rapid commissioning complementing the designation and earlier access a newly co-ordinated NICE technology appraisal and NHS England (NHSE) Commissioning process will be introduced by which:

- medicines once licensed, which have been developed through the EAMS will be appraised by NICE for routine use on the basis of the evidence collected in the earlier stages of the Scheme.

- As part of the appraisal process, manufacturers would be able to make use of PPRS [Pharmaceutical Price Regulation Scheme]^{xliii} provisions for Flexible Pricing or Patient Access Schemes (PAS) to adjust the value proposition for medicines, taking account of the value of the benefits of access and approval to the Sponsor as well as the benefits of the innovative medicine to the patient and healthcare system.
- Medicines in the Early Access Scheme, once licensed, will typically be commissioned by NHS England through its specialised commissioning arrangements, delivering a single national approach to commissioning. NHSE has like (CCGs) [Clinical commissioning groups] a legal duty to fund technologies positively appraised by NICE within three months of publication.
- Academic Health Science Networks (AHSNs) will have significant potential to support this process.

Meanwhile, it should be noticed that the 4 Countries; England, Scotland, Wales, and Northern Ireland are allowed to make separate decisions on HTA and Commissioning. Presently, these questions on reimbursement for the medicines provided under a positive EAMSSOs are managed partly by the recommendation to the applicant company to supply the medicine free of charge, but furthermore, for all medicines weather licensed or unlicensed, it remains that they are subject to commissioning rules of the NHS for treatment cost.

2.4 Discussion

2.4.1 EAMS Position and EU Drug Licensing Pathways

Visualised by Figure 2.4.1-1 EAMS Position and Current Drug Licensing Pathways the scheme covers the time between phase III eventually phase II and marketing approval. Once the 3rd step is introduced the EAMS could be seen extended to licensing and rapid commissioning.

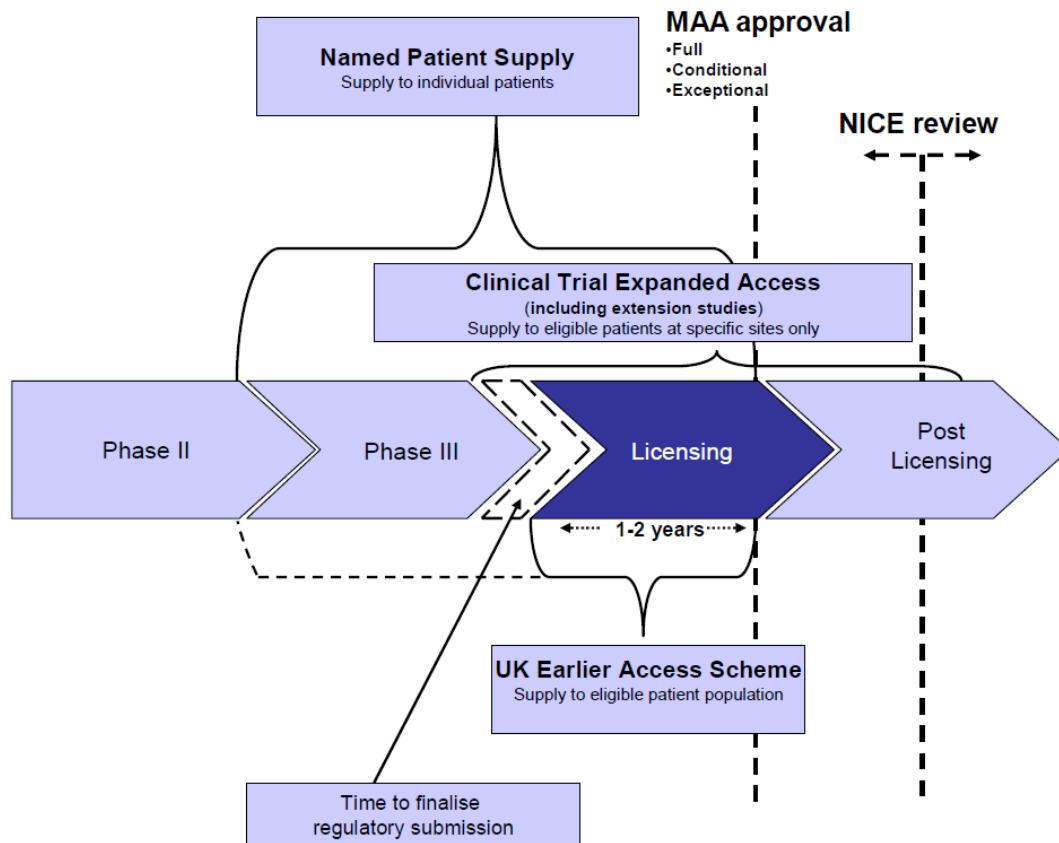


Figure 2.4.1-1 EAMS Position and Current Drug Licensing Pathways^{xiv}

Medicines which have obtained a positive EAMSSO still remain unlicensed in status until fully assessed and authorised according existing EU provisions. Other early access programmes (sometimes referred EAPs) like named patient supply (NPPs) and extension to clinical trials programmes (expanded access programme (EAP))^{xiv}, which also aim to improve the early patient access to new medicines, are in place in the UK. These programmes are based more locally i.e. at Clinical Commissioning Groups (CCGs) and are designed for a more ad-hoc application, whereas the EAMS is intended to reduce these local variations in medicines access to patients by giving a clear regulatory opinion to a nation-wide approach, also in from of free funding of the medicine by the company and an exit-strategy to the scheme in case, which is not specifically defined yet.

EAMS potentially enables UK patients to get access to innovative medicines much more early than through the existing regular licensing routes. Some expect an acceleration to an extend of 1-2 years, whilst others expect 5 years.^{xvi} Under the presumption that the medicine under the scheme is, in most cases, at a the formal end of its development stage (phase III) the scheme could indeed potentially provide life-saving treatment options about one to two years earlier compared to regular approval procedures by bridging the period for licensing. In case the EAMSSO could be issued at phase II/III the time benefit would be even more pronounced. The data generated from real-life use of experimental therapies will give more insight and understanding of the disease,

the efficacy, safety and quality of the medicines and how they work at the earliest stage. The collection of data on evidence for HTA purposes can start earlier.

The EAMS could be distinguished from existing licensing schemes and compassionate use programmes (CUPs) as it lastly could facilitate licensing by the EMA, i.e. by conditional marketing approval (CMA), exceptional marketing approval (EXMA), or adaptive licensing (AL) under development (AL currently renamed adaptive pathways),^{xlvii} however followed by rapid commissioning after appraisal by NICE in the UK and probably through analogue HTAs elsewhere in EU Member States. In respect, the impact on accelerated access to medicines in other EU Members States will have to be monitored carefully.

EAMS is distinguished from the adaptive licensing concept in so far that adaptive licensing ideas relate to the pro-active use of existing EU licensing concepts to gain an early marketing authorisation while the EAMS provides a scientific based benefit-risk evaluation only - an opinion - and does not lead to any granting of a marketing authorisation. EAMS is a separate scheme that is complement to the EMA adaptive licensing, but clearly it can be seen as that Helen Cline postulates, "The UK's EAMS and the PIM designation may facilitate identification of good candidates for the EMA's adaptive licensing pilot."^{xlviii}

In order to obtain the EAMS scientific opinion applicants need to submit a dossier in the format of the CTD with especial emphasis on key summarising documents in Module 2 – quality, nonclinical and clinical summary, and in addition pharmacovigilance information must be provided, notably the pharmacovigilance system master file (PSMF) and risk management plan (RMP). This implies that *dossier compiling activities must be started much more early than usually planned*, and applicants should be aware of that.

2.4.2 EAMS Flexibilities

A need for submission for marketing authorisation application not necessarily a must be as catalyst for an EAMS entry (designation or scientific opinion), but a sine qua non in case where the data and evidence collected to date sufficiently predict a certain unmet medicinal need is covered.

Flexibilities of the scheme for both, the regulator and the applicant include that an applicant can apply for a number of products, and that regardless to negative outcomes of PIM designation applications (**stage I**) as well as EAMSSOs, as they will not be published, which potentially provides enhanced options for interaction with the regulator apart from business requirements. However, companies not considering for the EAMS process as a whole still can apply for a PIM designation, costing a relative small price of about 4.027 £, which if it attracts potential acquirers or strengthen negotiation procedures when early entry into licensing or development arguments. The fee for assessment of the scientific opinion for new chemical or biological medicinal products is £29,000 and the renewal fee, if applicable, is £14,500. The fee for the assessment of

the scientific opinion for new indications is £9,232 and the renewal fee, if applicable, is £4,616. For example in comparison an EMA Marketing-authorisation application, single strength, one pharmaceutical form, one presentation costs from €278 500.^{xlix} Especially smaller companies depending on external investments may use this system to substantiate to their prospective investors or shareholders that the drug they are developing is considered by the UK authority as an innovative drug. For example, the promising innovative medicine designation (PIM) can be obtained as early as after Phase I data are available which are able to give an indication of the products benefits very early in product development. With the EAMSSO (stage II) the regulator will be given an opportunity to assess the clinical and non-clinical data much more early. Therefore, the applicant, by receiving a decision whether “yes”, “no”, or “under the condition,” will have much more clarity about his projects much more early and the advantage to adjust and strengthen his forward strategies appropriately. Companies may also use the EAMSSO to secure investment and increase the creditability of the medicines in the scheme probably in other countries.

Repurposes of old drugs for new indications are permitted under the scheme. Medicines currently licensed for other indications, but intended for off-label use, are considered eligible to be included in the scheme theoretically allowing generic drug products being repurposed also.^l

Conditions for exit pathways for patients under treatment in terms of an EAMSSO has to be revoked or the final licensing will not take place are not explicitly defined and might need to be made more clear and specific. With the Governments response on consultations to the question it has been stated that, “...the clinician will be responsible for deciding when a patient starts and stops treatment. Even if a medicine does not gain a licence it can still be prescribed, provided that supplies are made available by the company. If safety issues about a drug in the scheme were to arise, MHRA would reconsider its opinion and if necessary publish updated information on the risk:benefit profile, amend or withdraw the scientific opinion and provide further guidance as appropriate through safety updates to health professionals.”^{li} A transfer to other existing treatments was suggested as an option also. Another question is sustained supply and the handling thereof in such situations where the company business ceases for various reasons.

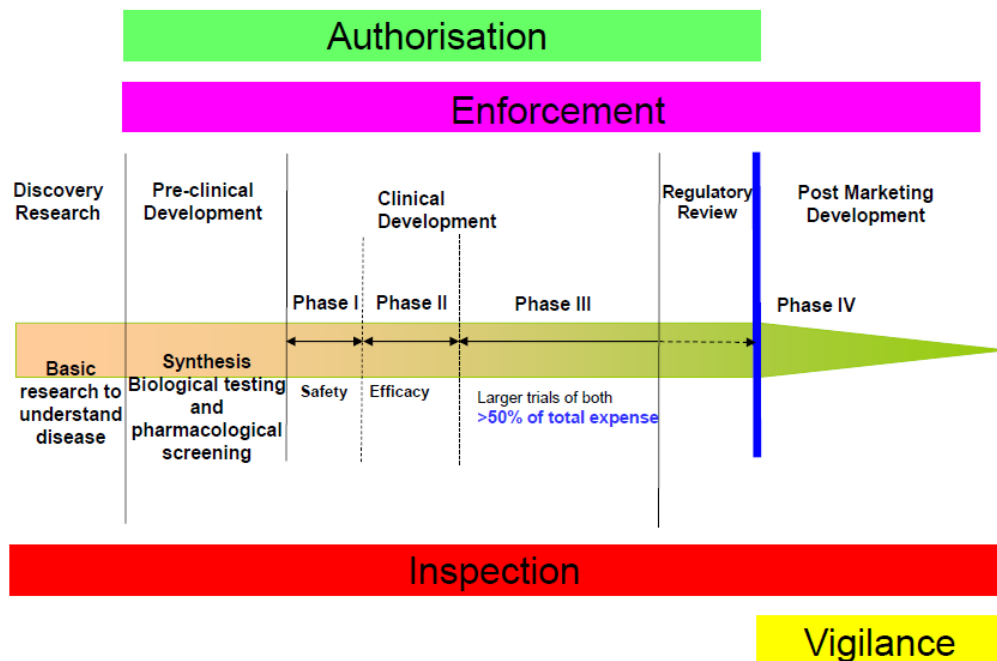
2.4.3 EAMS Development Opportunities

Concerns related to funding of the scheme lead to the question if the obligation to supply the medicine product free of charge before licensing will deter small companies like biopharmaceutical companies with high investment burden and probably high expenditure on manufacturing. It has been taken into account by the Government that some biotech firms (companies with an annual turnover of less than \$ 1 billion)^{lii} may be unable to precede from stage I to stage II due to incapability to capitalise for the entry of more expensive phase III studies. On the other hand, a certain benefit can be derived for the industry form free commissioning of the therapy much more quick; faster access

to patients, real-life data generation, closer collaboration with clinical experts and real clinical value exploration outside of controlled clinical trials, faster diffusion before licensing and "Often, patients with critical or life-threatening illnesses don't qualify for clinical trials. Some are just too sick. Or perhaps their previous medical treatment disqualifies them from the study."^{liii} Another point to be considered is that firms would be able to recycle the EAMS documentation and information once gained for their full application submission later on.

Figure 2.4.3-1 Proportion of Cost of Drug Development Process in phase III: Authorisation, Enforcement, Inspection, and Vigilance, illustrates that in regular licensing approaches >50% of the total expenditure are sought to be spend on larger clinical trials in phase III. Of course, it might be questionable, if earlier access to medicines would have a significant impact on the overall expenditure necessary, as the medicine probably has to be made available before phase II/III studies are stated, ongoing or finalised.

Drug development process



By courtesy of Sir Kent Woods at MHRA

Figure 2.4.3-1 Proportion of Cost of Drug Development Process in phase III: Authorisation, Enforcement, Inspection, and Vigilance^{liv}

It is possible that some biotech firms are unable to make the jump from phase II to phase III trials, because they cannot raise the capital required to enter the much more expensive phase III trials. Smaller companies depending on external investments could use this system to prove to their prospective investors or shareholders that the drug they are developing is considered by the UK authority as an innovative drug as such its benefit-risk ratio would be considered as positive. For example, the Promising Innovative Medicine Designation (PIM) can be obtained as early as after phase I data are

available, which can give an indication of products benefits very early in product development.

Adjusted mechanisms for HTA are to be developed. The data available to support evidence on risk-benefit are generated from much earlier stages than under regular licensing conditions and currently it is unclear at what stage of the scheme the NICE will be involved in the appraisal and commissioning process (expected is stage III). Theoretically this would allow for an easier post-approval Health Technology Assessment (HTA) and pricing negotiations. Good data and early engagement with HTA and Commissioning Bodies is and will remain critical.

Reputational risk with not being made public a negative EAMSSO it might cost doubt on the effectiveness and safety profile of the medicine product. However, more clarity of the MHRA as the regulatory body on how to respond in regard to the freedom of information act requirements would be required. The release of each clinical data as part of the approved process and its impact of a withdrawn EAMMSO needs to be considered as to risks accommodated.

Uncertainties in regard to data protection concerning 8 years intellectual property rights, and market exclusivity 10/11 years may remain as the period for protection, which starts being commonly defined at the time point where the full licence for the product is granted (Article 14(11) DIRECTIVE 2001/83/EC)^{lv} - which in terms of an EAMSSO is not the case, Figure 2.4.3-2 Data and Marketing Exclusivity for Medicinal Products - 8+2+1 Formula. In terms of maintenance of registry data questions on the required information, the gathering, holding, and access to the relevant data for third parties such as access pathways for health care professionals and patients may need to be made much clearer. Advertisement and information on medicines is restricted by law.^{lvi,lvii,lviii,lix,lx} The information pathways on the availability of medicine products under the scheme might made be more transparent.

Data and marketing exclusivity for medicinal products - 8+2+1 formula

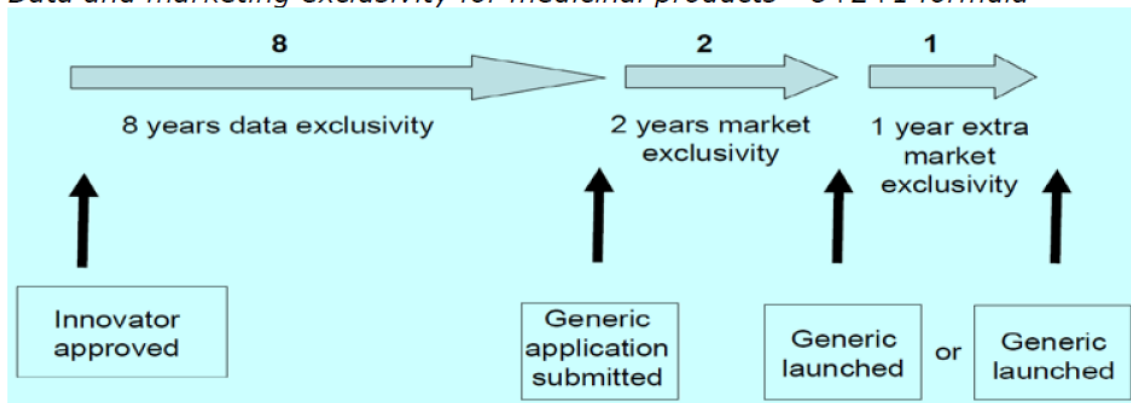


Figure 2.4.3-2 Data and Marketing Exclusivity for Medicinal Products - 8+2+1 Formula^{lxi}

In order to properly use this scheme, companies must carefully plan ahead and need to know how many resources and activities need to be invested.

The liability for clinicians prescribing and pharmacists dispensing and preparing the medicine still unlicensed also remains to be defined most clearly. Lastly the final decision for a prescription rests with the prescriber of the medicine. Clinicians have to have a pivotal role in medicines access to patients. Since pharmacists are involved responsible for supply and manufacture of the unlicensed medicine, sharing liability to a certain extent, both, the prescriber and pharmacist might be reluctant in taking the risk for being sued for negligence, as they take the full responsibility in case of unlicensed medicine^{lxii}. To a certain extent the issued EAMSSO might give justification, probably in conjunction with the proposed new (draft) Medical Innovation Bill (Saatchi Bill),^{lxiii} allowing doctors to “depart from the existing range of accepted medical treatments for conditions”. This is also brought to public consultation by the Department of Health with the issue ‘Legislation to encourage medical innovation: A consultation’. “Currently, there is no Act of Parliament that indicates the meaning of responsible medical innovation or that sets out a test of clinical negligence. Instead, the existing law governing negligence is to be found in case law (decisions by the courts).” “The main case law is in the case of *Bolam v Friern Hospital Management Committee* [[1957] 1 WLR 582], which was later refined in *Bolitho v City and Hackney Health Authority* [[1998] A. C. 232]. These cases establish that to avoid a successful claim in negligence a doctor should be able to demonstrate support for a decision from a responsible body of medical opinion (*Bolam*) and that the opinion is capable of withstanding logical analysis by the courts (*Bolitho*).^{lxiv}

In respect, the EAMSSO and inherently the treatment protocol issued by the MHRA could be held as a reference for justification.

Criticism, the scheme is controversial for stakeholders including the UK Faculty of Public Health at the Royal College of Physicians (FPH)^{lxv} who has more prominent questions about the value the scheme will provide to patients given its current scope. Mainly it is questioned that; “The program undermines the current centralised (EMA) system to review clinical trial data to ensure they meet the standard for efficacy and safety prior to approving drugs for public use” and that “The program will not improve public health given its small scale (potentially 2 drugs a year are estimated to be eligible for the scheme by the MHRA) and the fact that it provides access to individual patients while the majority will have to await the usual EMA timelines for approval.” The Association of the British Pharmaceutical Industry (ABPI) and UK BioIndustry Association (BIA) welcomed the initiative. However, they are concerned by the lack of central funding and requested the scheme to be reviewed after the first year.^{lxvi}

2.4.4 EAMS Current Application

3 PIMs have been issued since the scheme has been launched on 7th April 2014. On 16th September 2014 the first PIM designation was issued for DCVax-L developed by the US-based pharmaceutical company Northwest Biotherapeutics Inc. (NW Bio).^{lxvii} The designation for DCVax-L covers all malignant gliomas, which would include both Glioblastoma multiform (the most severe grade) as well as less malignant grades, and

would include both, newly diagnosed and recurrent gliomas. The information has been made public by the company.

2.5 Conclusion

For an accelerated implementation of the new EAMS, the scheme is established on the basis of existing EU and UK national legislation making use of the derogation provided in Article 5(1) Directive 2001/83/EC, no changes are necessary. The scheme is applicable to new drugs for treatment, diagnose or prevention of life-threatening or serious debilitation conditions without adequate treatment options present. New medicine products subject to national and centralised authorisation procedures are eligible as well as the repurpose of existing drug products providing a wider range of applicability. There are no restrictions on therapeutic areas, but the medicine product must promise an advance in treatment in a particular therapeutic field at phase III clinical trials to avoid conflicts with clinical trials. Exceptionally the option for application is extended to include medicines in phase II, if evidence of benefit is significantly demonstrated. With exemption of patients in clinical trials all patients of all ages can be included in England, Scotland Wales and Northern Ireland; children are eligible also to be treated under the scheme.

For an EAMSSO application a subset of data collected like for a full application for marketing authorisation is required in the format of the CTD, but exceptional in cases of very early medicine development stages and ongoing clinical trials. The regular regulatory assessment period for an EAMSSO, after a promising designation (PIM) issued consists of 75 days, in extended cases 90 days. An annually renewal process as well as frequent updates concerning the data gained holds the EAMSSO up to date. All relevant information on the EAMSSO including updates and treatment protocols are publicised in a public assessment report (PAR) on the MHRA website. Safety monitoring is established via patient registry and the UK yellow card system. Additional safety monitoring is considered on a case by case decision.

An EAMSSO issued can be used as an official reference for justification to use a medicine product concerned 'off-label' or 'unlicensed', which can significantly provide earlier access to medicines for a cohort of patients (treatment protocol) in need several years before a full license is granted.

A prepared EAMS dossier (CTD) eminently suited can be used further for a full marketing authorisation application at later stages. The data gained between an issued EAMSSO and a full licence is granted theoretically can accelerate the HTA appraisal procedures due to early availability of real-life data. Cost free supply of the medicine within the scheme is likely to provide incentives for an uptake of treatment with the medicines at Clinical Commissioning Groups (CCGs) and can enhance a more nationwide harmonised access to medicines concerned. On the other hand, this circumstance may deter potential investments in the scheme by companies mitigating the effect originally intended to provide incentives for pharmaceutical development.

Good data and early engagement with HTA and commissioning bodies is and will remain critical. The lack of funding under the UK new EAMS could make it unattractive compared to other earlier access routes available. It will be important to get clarity around the proposed rapid HTA and commissioning at stage 3 of the EAMS, so that it is much clearer at the outset what commercial advantages and risks are to be considered by the companies and investors and the that route is expected successful.

Given the small scale of potentially 2 drugs per year are estimated to be eligible for the scheme (granted opinions estimated by MHRA)^{lxviii}, and with regard to the intended provision of access to a narrow subset of patients while the majority will have to await regular EMA timelines for approval, it is questionable if the program provides a significant impact on public health. The scheme only allows UK based patient earlier access to unmet medical need medicines but not EU citizens. The impact on the latter will have to be monitored.

EAMS is to be distinguished from existing licensing schemes and adaptive licensing in so far that these schemes lead to a marketing authorisation, in case of adaptive licensing in a proactive use of the existing schemes whereas EAMS only provides an opinion on the risk-benefit of the product and does not lead to any granting but can support AL.

The new EAMS and subsequent possibilities for marketing authorisation approval pathways are new, untested. Certain uncertainties in terms of strategy planning remain. From the patient and regulatory perspective the scheme is very complex, also expert advice is recommended at various stages. It could be expected that the experience will help to optimise the scheme and certainly will have an impact on decisions in other European countries or Europe as a whole to discuss and adopt similar ideas.

A certain impact can be estimated for medicine products under the scheme which enter regular licensing routes. Existing clinical data, real-life clinical data, a precompiled dossier (CTD) as required, as well as several scientific advices and assessments theoretically can be used to accelerate regular approval procedures, at least for accelerated procedures.

Uncertainties in regard to data protection concerning 8 years intellectual property rights, and market exclusivity 10/11 years are not identifiable.

3 Marketing Authorisations under Conditional Circumstances

3.1 Intention of the Scheme

With the motivation “In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid process of science and therapies,^{lxi} Recital 33 and Art 14(7) of Regulation EC No 726/2004 the ‘Conditional Marketing Authorisation’ (CMA) has been adopted by 31st of March 2004.

The aim of the scheme is to provide medicinal access to patients with unmet medicinal need in treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to public health threats recognised either by the WHO or Community framework,^{lxx,lxxi} or designated orphan medicinal products^{lxxii} by granting a marketing authorisation on the basis of less complete clinical data than it is normally necessary subject to specific obligations ‘conditional marketing authorisations’.

The benefits to public health of making the medicinal product available on the market immediately should outweigh the risk inherent in the data still required. The risk-benefit balance should be positive as per Directive definitions of Article 1(28a) Directive 2001/83/EC.

Inherently the scheme will allow obtaining a marketing authorisation at the earliest stages of the clinical development phase which present evidence for an agreed positive risk-benefit balance than at later development phases under conditions for regular marketing approvals - therefore earlier medicines access to patients in need.

3.2 Legal Basis

The particularities for conditional approval are set out in Commission Regulation EC No507/2006^{lxxiii} on the conditional marketing authorisation (CMA) for medicinal products for human use within the scope of Article 14(7) Regulation EC No 726/2004 ‘conditional marketing approval’ (specific obligations). Medicinal products for human use which fall under Article 3(1) and (2) of Regulation EC NO 726/2004 and belong to *one [at least]* of the following *categories* of Article 2 Regulation EC No 507/2006:

1. medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;

3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000,

and which *meet all of the requirements* according Article 4 of Regulation (EC) No 507/2006;

A CMA may be granted, if the CHMP finds that *all* of the following requirements are met, although comprehensive clinical data referring to the safety and efficacy of the medical product *have not been* provided:

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

According Article 11 Regulation EC No 507/2006 a Guideline on the practical arrangements for application for conditional marketing authorisations has been published in 2006.^{lxxiv}

3.3 Qualification for Conditional Marketing Authorisation Approval - Categories and Requirements

A conditional marketing authorisation is applicable to medicinal products eligible to be licensed via the centralised procedure only. According Recital 8 Regulation EC No 726/2004 the procedure for evaluating is considered to be the normal procedure laid down in Regulation EC No 726/2004 with the option for request of an Article 14(9) accelerated assessment procedure, Recital 7 Regulation EC No 507/2006.

Conditional marketing applications apply to situations where *the clinical part of the application dossier is not as complete as required in normal procedures only*, according Recital 4 Regulation EC No 507/2006 and Article 4(1). Exemptions in regard to the non-clinical or pharmaceutical parts have to be carefully justified, i.e. in emergency situations, Article 2(2) Regulation EC No 507/2006. Categories and requirements for medicine products further specified in the Guideline^{lxxv} apply.

3.3.1 Categories for Medicine Products under Conditional Marketing Authorisation Application

Generally *one* of the categories needs to be justified:

Seriously debilitating diseases or life-threatening disease has to be justified on objective and quantifiable medical or epidemiologic data. Life-threatening disease can be described by figures of mortality; the seriously debilitating disease is to be described on

quantifiable mortality and consequences on the patient daily life functions. Serious debilitation or fatal outcome should be the prominent reason for the indication in question. *Medicinal products to be used in emergency situations* are to be described by reference to WHO Resolution, Decision, or Decision 2119/98/EC.

Medicinal products designated as orphan according Regulation EC No 141/2000 criteria;

- (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, *or*

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community *and* that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; *and*

- (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community *or*, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

3.3.2 Requirements for Medicine Products under Conditional Marketing Authorisation Application

Generally *all* of the following requirements need to be fulfilled:

The risk benefit balance of the product is positive defined according Article 1(28a) of Directive 2001/83/EC. For the demonstration the requirements laid down in Annex 1 of the Directive are applicable as far as for any other regular marketing authorisation application. “For the demonstration of a positive benefit-risk balance, the data requirements laid down in Annex 1 of Directive 2001/83 (ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PRO-TOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS), are also applicable for products granted conditional marketing authorisation.”^{lxvii} Hence, under conditional circumstances, it should be possible and required to obtain comprehensive data once ongoing or new studies have been completed. Apart from, incomplete non-clinical and pharmaceutical data should only be accepted in emergency situations to keep uncertainties for clinical data derived from these to a minimum. The following points are to be addressed:

- Positive risk-benefit balance of the product.
- The robustness and degree of external validity of the results
- A discussion of any aspects of the positive benefit risk balance that require confirmation from further studies (e.g., confirmation of effect on other end-points, long-term effects, effect in special populations or identification of responders)

It should be likely that the applicant will be able to provide comprehensive data. A clear rationale and explanation on how and what the remaining questions on safety and efficacy are and how the provision of the comprehensive data for the proposed indication will be obtained in an agreed time frame should be presented. The development should be completed in so far that, as soon as possible, any uncertainties due to the lack of comprehensive data do not persist indefinitely. The feasibility and quality of the studies required as specific obligation should be reassured; hence, it should be mentioned that “an authorisation early in the development may lead to potential difficulties in the recruitment, breaking of blinding in ongoing or planned studies, or compromise the statistical analyses, in particular for trials with patients from the same population as covered by the authorisation.”^{lxxvii} For an annually informed judgement on the risk-benefit balance specific obligations on the collection of pharmacovigilance data should be introduced. Special requirements for ongoing or new studies as part of the obligations are described in the Guideline according Article 11 Regulation EC 507/2006. *Unmet medical need* is defined in Article 4(2) Regulation EC 507/2006. It means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community, or even if such a method exists in relation to which the medicinal product is concerned will be of major therapeutic advantage to those affected. The need has to be justified on a case-by-case basis on quantifiable medical and epidemiologic data.

The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. The positive as well as negative impact of immediate availability of the product on public health has to be justified on objective quantifiable epidemiological data in respect to the product availability under regular marketing application conditions. The following points need to be addressed:

- Benefits to public health of the immediate availability on the market
- Risks inherent in the fact that additional data are still required
- How the benefits to public health in the context of immediate availability outweigh the risks (also taking into account the remaining questions)

On the ground of incomplete data, the conditional marketing authorisation is subject to specific obligations like initiation of studies in regard to confirmation of the positive risk-benefit balance and quality, the safety and efficacy of the product and pharmacovigilance measures. These obligations clearly specified will be made public by the EMA as part of the European assessment report (EPAR) on the Agency website. Table 4-1 EU Medicines under Conditional and Exceptional Circumstances Marketing Authorisation and Orphan Drug Designations, source EMA EPAR^{lxxviii}, presents an overview about the current situation.

3.4 Regulatory Requirements for Conditional Marketing Authorisation Application Approvals

3.4.1 Proposal for Conditional Marketing Authorisation / Scientific Advice

In order to facilitate a seamless procedure the applicant in terms of a conditional marketing authorisation application intended should notify the European Medicines Agency by statement of intent of a conditional marketing authorisation at least 7 month before submission of application, or later at the time of application by 'letter of intent'.^{lxxix} Also, the CHMP can propose a conditional marketing authorisation application in case of need identified, according Article 3(2) Regulation EC No 507/2006 in accordance to Article 6 Regulation EC No 726/2004. The latter might be done at the earliest time point the relevant details may let identify a fulfilment of the necessity for, usually likely at day 120 LOQ, D150 JAR, or D180 LOI (List of Outstanding Issues).

Additionally, the application for a potential marketing application under conditional circumstances is eligible for scientific advice. According Article 10 of Regulation EC 507/2006 the applicant is addressed to seek advice prior to the application submission to discuss the applicability of the categories and requirements to the product at development stage.

3.4.2 Validity, Renewal, Labelling Obligations, Pharmacovigilance and Authorisation Transition/Transformation Probabilities

The conditional marketing authorisation is valid only for one year on a renewable basis at least six month prior to expiry. Furthermore, a conditional marketing authorisation is not intended to remain as conditional infinitely, but should be replaced with a regular marketing authorisation once sufficient data collated as part of the specific obligations imposed to the Conditional Marketing Authorisation Holder. Currently for a renewal of a conditional marketing authorisation no fee is payable to the European Medicines Agency.

In reflection to the conditional status the product information Summary of Product Characteristics/Patient information leaflet (SmPC/PIL) should clearly mention the fact and the nature of the license status including the date the renewal is due. Periodic safety update reports (PSUAR) according Article 24(3) Regulation EC No 726/2004 are to be submitted up on request of the European Medicines Agency or at least every six months following the granting, or at renewal. In 2010 the new pharmacovigilance legislation has been adopted, Regulation EC No 1235/2010^{lxxx} and Directive EC 2010/14 amending Regulation EC No 726/2004 and Directive EC 2001/83 in conjunct to Regulation EC No 520/2012. This legislation has an immense impact on marketing authorisation applications and marketing application holders. According Recital 16 Regulation EC No 1235/2010 "...to complement the data available at the time of authorisation with additional data about the safety and, in certain cases, also about the efficacy of medicinal products for human use authorised in

accordance with Regulation (EC) No 726/2004. The Commission should therefore be empowered to impose on the marketing authorisation holder the obligation to conduct *post-authorisation studies on safety and on efficacy*. It should be possible to impose that obligation at the time of granting the marketing authorisation or later, and it should be a condition of the marketing authorisation...^{108xxi} Furthermore, according to Recital 17 "...Competent authorities may also require *additional monitoring* for specific medicinal products for human use that are subject to the obligation to conduct a post-authorisation safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product that will be specified in the *risk management plan*..." These conditions are reflected in Article 21a of Directive EC 2001/83, "...a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

- (a) to take certain measures for ensuring the safe use of the medicinal product to be included in the *risk management system*; [RMP]
- (b) to conduct *post-authorisation safety studies*; [PASS]
- (c) to comply with obligations on the recording or reporting of suspected adverse reactions which are *stricter* than those referred to in Title IX; [SAE]
- (d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;
- (e) the existence of an adequate *pharmacovigilance system*; [PVS]
- (f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down *deadlines for the fulfilment of these conditions* where necessary...

Conditional marketing authorisations are distinct from those in exceptional circumstances according to Article 14(8) Regulation EC 726/2004 as they are granted before all data are available. In contrast, marketing authorisations under exceptional circumstances and in respect to regular marketing authorisations the marketing authorisations under exceptional circumstances formally never will be able to gather a complete dossier. Although, it will not be possible for marketing authorisations granted not within the scope or under exceptional circumstances to change into a conditional marketing authorisation and; the conditional marketing authorisation does not apply to new indications submitted as part of variation or extensions to marketing authorisations already existing.

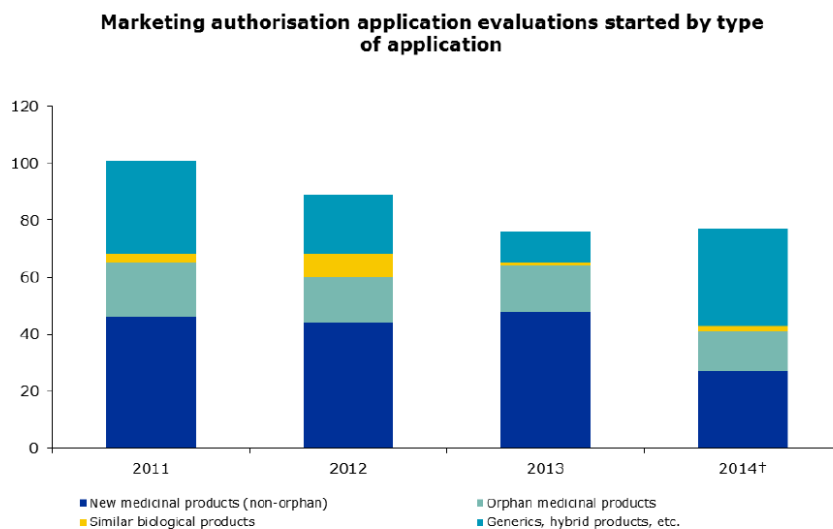
The validity of conditional marketing authorisation is expressed in Commission Deci-

sions by reference of date of notification to the Marketing Authorisation Holder in the OJ, although in case of renewal.

3.5 Discussion

3.5.1 Limitations of Applicability

The Conditional marketing authorisation concept is applicable only to a narrow subset of medicine products described under the categories and requirements; new drug products, new indication, centrally licensing procedures, orphan drug products. The narrowed pathway is mirrored by a low number of applications, Figure 3.5.1-1 Marketing Authorisation Application Evaluation Started by Type of Application (Monthly statistics report: October 2014, EMA/696699/2014). Generally a constant decline in centralised applications can be seen since 2011; also, the ratio of applications potentially falling into the conceptual scope for conditional circumstances is in decline whereas the procedures for generic applications have increased. Additionally, it has to be remarked that the concept also does not apply to new indications submitted in the frame of an extension or variation procedure.



† Figures for the current year are cumulative, year to date. Figures for preceding years are totals for the year.

Figure 3.5.1-1 Marketing Authorisation Application Evaluation Started by Type of Application (Monthly statistics report: October 2014, EMA/696699/2014)^{lxxxii}

3.5.2 Acceleration, Transition Period to Regular Marketing Authorisation, Individual Patient Access

Figure 3.5.2-1 Time from Conditional Marketing Authorisation to Normal Marketing Authorisation (source: Conditional Marketing Authorisations in the European Union, Hilde Boone European Medicines Agency Liaison Official) exemplarily shows the transition times of conditional marketing authorisations for oncology products into “normal” regu-

lar marketing authorisations. A theoretical (including the not yet converted) calculated average transition period of 1.7 years elapses for transformation. Therefore if possible - probably exceptional with regard to national HTA assessment for reimbursement issues - it can be postulated that these drug products are likely to be available on the market, and so far theoretically accessible to the patient, round about 2 years earlier than under regular marketing authorisation approval conditions. Let alone a valid single conditional or central marketing authorisation does not imply that the product in question would be available to the patients on the individual patients Member State national market, the decision-making processes for reimbursement and pricing of medicine products is laid within the merits of the relevant national bodies. National regulatory, especially national reimbursement requirements in the EU could form certain inequalities to the individual EU patient in terms of access to medicines. For example, the analyses by Roll, K. et. al. on 'Authorization and Reimbursement of Orphan Drugs in an International Comparison' reveals that; "Die Verwendung von Bewertungskriterien zur besonderen Berücksichtigung von Orphan Drugs für die Erstattung variiert gemäß unserer Analyse stark zwischen den Ländern [According our analyses the application of evaluation criteria for the reimbursement dedicated to Orphan Drugs starkly varies between the States]."^{lxxxiii}

Nonetheless, in 2010 the EMA introduced a pilot project for parallel scientific advice with HTA authorities in order to meet the issue. "HTA is a multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value"^{lxxxiv} M. Berntgen cites.^{lxxxv} "Criteria for HTA vary between countries, but generally HTA bodies in Europe use relative effectiveness assessment (REA), a European equivalent to comparative effectiveness research in the United States, as part of the HTA process"^{lxxxvi} M. Berntgen cites.^{lxxxvii} Within this scheme around 25 procedures had been finalised or were ongoing as of November 2013.^{lxxxviii} Another project designed to resolve the lack of harmonisation across Europe is the Shaping European Early Dialogues for Health Technology (SEED) consortium.^{lxxxix}

Despite the results of the scientific advices will not imply any legal binding status to the authorities or to the applicant to future marketing authorisation activities, it has been approved to contribute to the success of the procedures to a certain level. For example in terms of scientific advice for marketing authorisation, Spiros Vamvakas, Head of Scientific Advice at the Agency, explains, "... 90% success rate at the stage of marketing-authorisation application compared with a 30% success rate for companies that do not comply* with scientific advice."^{xc}

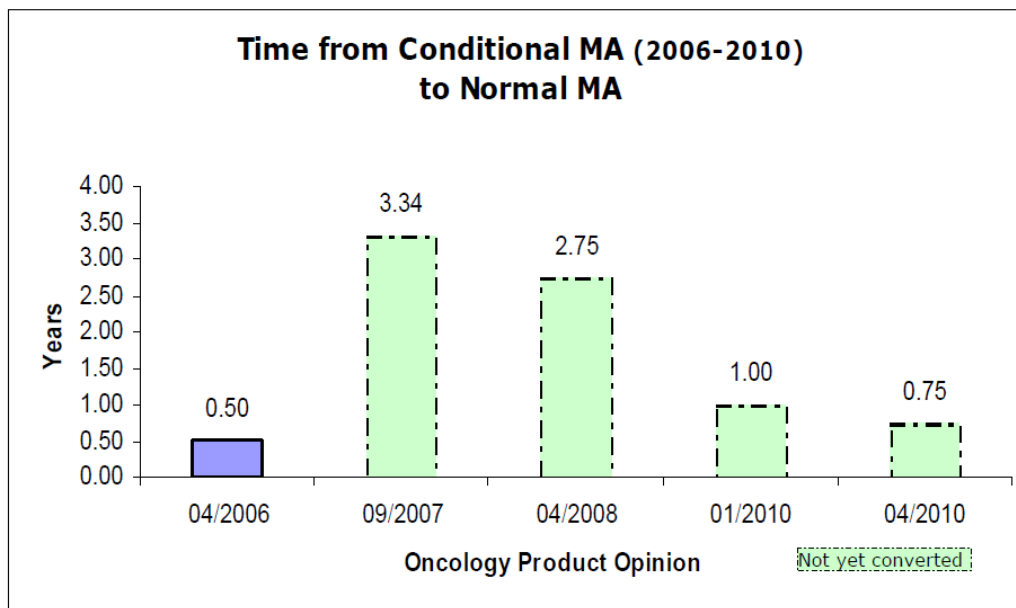


Figure 3.5.2-1 Time from Conditional Marketing Authorisation to Normal Marketing Authorisation (source: Conditional Marketing Authorisations in the European Union, Hilde Boone European Medicines Agency Liaison Official)

3.5.3 Consequences on Clinical Trial Concepts

As per Guideline, a marketing authorisation early in the development may for instance lead to potential difficulties in recruitment, breaking of blinding in ongoing or future studies, or otherwise compromise the statistical analyses, particularly for trials with patients from the same population as covered by the authorisation.^{xci} In regard to H.G. Eichler constitutes, “Conditional Approval may have unintended consequences: It challenges the concept of equipoise. It may raise ethical implications, reduce the availability of patients for randomised clinical trials, and close the window of opportunity for certain randomised clinical trials.”^{xcii} In the light that clinical trials were planned to be conducted have to pass the ethical measures which vary between the individual EU Member States the approval of additional clinical trials could be somewhat challenging.

3.5.4 Staggered Approach and Flexibilities

The more staggered approach than the binary regular licensing approach with several repeated steps of reassessment, scientific advices, not at least HTA negotiations on national and/or EU level imply the necessity of an increased amount of manpower and human resources both sides - the applicant and the authority, and therefore probably a significant increase of personnel expenditure could be expected. The relative fixed stepwise approach for the narrow subset of medicine products not only will enable to adapt the range of the marketing authorisation in question in analogue to the growth of the scientific knowledge gained stepwise at time point of administration of the drug product on an increased number of patients “real life”, but also could accelerate a decision in terms the data gained probably present results being not

as comfortable to justify further investigation activities towards granting a marketing authorisation – i.e. negative opinion at time of renewal.

Albeit the flexibilities the conditional marketing authorisation scheme can provide, the most common route for authorisation of new medicines remains to be the traditional route, Figure 4.5.2-5 *CHMP Opinions; Art 8(3) applications only; excluding duplicates.^{xciii}

4 Marketing Authorisation under Exceptional Circumstances

4.1 Intention of the Scheme

The scheme is available in the EEC since it has been introduced by Council Directive 75/318/EEC^{xciiv} in May 1975 and later included by Regulation EC No 726/2004 confirming the centralised procedures (CP). It is intended to be used in case the applicant would not be able to provide comprehensive clinical data under normal circumstances (full dossier), due to the rarity of the nature of the disease, the scientific knowledge not sufficient at present time of submission and ethical constraints for the clinical trials recommended. In addition, with the introduced accelerated procedure available on request by the applicant or CHMP, the scheme may foster a faster market entry of the drug product in question inherently providing a potentially faster access to medicine for patients in need which gathered - may be expected to be seen as an incentive for the pharmaceutical companies on development activities.

4.2 Legal Basis

The basis for a marketing approval under exceptional circumstances is Article 22 Directive 2001/83/EC and Article 14(8) of Regulation EC No 726/2004. In Article 22 it is stated that in exceptional circumstances, and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions; in particular relating to the safety of the medicinal product, the notification to the national competent authorities of any incident relating to its use and action to be taken. Furthermore, that the marketing authorisation may be granted only when the applicant can indicate that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective verifiable reasons, which must be based on one of the grounds laid down in Annex I [Annex I [Part II] to Directive 2001/83/EC]. Finally, the continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.

The procedure is applicable to marketing authorisation applications for medicinal products for human use falling within the scope of Articles 3(1) and 3(2) of Regulation EC No 726/2004. A dedicated Guideline on the procedure has been issued by the (CHMP).^{xcv}

4.3 Qualification for Approval under Exceptional Circumstances

The legal basis provide the grounds on which an approval under exceptional circumstances may be granted, namely: comprehensive efficacy and safety data cannot be generated, because the indication the product is intended for is so rare that comprehensive evidence is most unlikely to be generated, or that the scientific knowledge at the present state cannot provide comprehensive information, or that the collection of such data would be considered unethical.

In sum - these qualifications need to be justified based on current epidemiological and scientific data presently available.

4.3.1 Objective Verifiable Reasons for Approval under Exceptional Circumstances

Objective and verifiable reasons for granting a MA in exceptional circumstances described in Annex I Part II of Directive 2991/83/EC are; the *indications for which the product in question is intended are encountered so rarely* that the applicant cannot reasonably be expected to provide comprehensive evidence, or *at present state of scientific knowledge* comprehensive information cannot be provided, or it would be *contrary to generally accepted principles of medical ethics* to collect such information. The obligations provisional for a granting are; the applicant shall complete an *identified programme of studies* within a time period specified by the competent authority, the results of which shall form the basis of a re-assessment of the benefit-risk profile, the medicinal product in question may be *supplied on medical prescription only* and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person, *the package leaflet and any medical information shall draw the attention* of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

In conjunct, the Guidelines on Pharmacovigilance for Medicinal Products for Human Use provide the activities on pharmacovigilance and interventions proactively designed to identify, characterise, and prevent, or minimise risks relating to medicinal products.^{xvii}

The inability to provide comprehensive data on efficacy and safety in regard to the rarity of the disease is expected to be demonstrated on hand of the discussion of the feasibility of such studies with respect to epidemiological evidence to quantify the rarity of the conditions worldwide, the quantity of the population available for such studies, and previous studies available in fields similar. Also, the probability to conduct studies that would not yield to comprehensive data material but would provide more information towards efficacy and safety should be considered. The evaluation of study designs, error probabilities, hypothesis, statistical considerations and recruitment assumptions,

the sample size calculation, methodology, and follow-up probabilities should be part of the justification.

For the justification of the lack of scientific knowledge required present and probably present in future. The knowledge which would be required should be identified and the justification why reasonable knowledge will not be available in an adequate period of time should be provided, i.e. diagnostic tools.

In regard to the ethics of information collection it should be demonstrated that international accepted standards and principles are contrary to the study requirements by provision of statements and decisions of ethic committees or relevant authorities. Also, the probability to conduct other studies not necessarily comprehensive, but enhancing information should be taken into account.

Nevertheless, specific obligations may be imposed with such an approval; the completion of certain clinical trials within a defined time period and milestones, the distribution of the product on prescription only, detailed conditions for use and restrictions on special supervision (i.e. hospital, prescriber qualification), and explicitly - the highlighting in the SmPC and patient information leaflet (PIL) that the data available on the product is limited so far.

4.4 Regulatory Requirements for Conditional Marketing Approvals

4.4.1 Proposal for Exceptional Marketing Authorisation / Scientific Advice

The applicant is requested to seek scientific advice from the EMA on the applicability of the application for marketing authorisation under exceptional circumstances to discuss the justification for application under exceptional circumstances, the inability to provide comprehensive data, the limitations imposed by the rarity of the disease, the knowledge on information on safety and efficacy as early in the development phase. Advice on ethical aspects of the collection of data required will not be subject. Conjoint to the pre-submission meeting further discussions may take place at least 4-6 month before submission. The request for the pre-submission meeting should include the 'justifications on the grounds for approval under exceptional circumstances'.

Based on the legal criteria the CHMP can propose the possibility of adoption of an opinion under exceptional circumstances, even if not raised by the applicant. The time point for such proposal including any specific obligations may occur is considered usually to be close to the adoption of the opinion, e.g. at Day 120 List of Questions (LOQ), List of outstanding issues (LOI), CHMP assessment report.

4.4.2 Validity, Renewal, Labelling Obligations, Pharmacovigilance and Authorisation Transition / Transformation Probabilities

The continuation of the exceptional status will be reviewed annually, namely by *re-assessment* of the appropriateness of the risk-benefit balance by the CHMP. No fee is payable for the annual re-assessment. The CHMP conclusions in relation to the annual re-assessment procedure will be published on the EMA website (EPAR).

Principally, the *renewal* of the marketing authorisation under exceptional circumstances remains same as for regular marketing authorisations, Article 14(1-3) Regulation EC No 726/2004; valid for five years once renewed it is valid for an infinite period, otherwise, relating to pharmacovigilance reasons only, justified for another five year renewal period whereas the Article 14(8) Regulation EC No 726/2001, the recommendation that the “Continuation of the authorisation shall be linked to an annually reassessment of these conditions [Annex 1 [Part II] to Directive 2001/83/EC]” remains. In regard to pharmacovigilance measures Regulation EC No 1235/2010 and Directive EC 2010/14 amending Regulation EC 726/2004 and Directive EC 2001/83 in conjunct to Regulation EC 520/2012 is applicable (for further details see 3.4.2.)

According to the applicable Guideline on the processing of renewals in the centralised procedure EMA/140721/2012^{xcvii} an opinion on products authorised under exceptional circumstances in accordance with Article 14(8) of Regulation EC No 726/2004 and Part II.6 of the Annex to Directive 2001/83/EC as amended, the CHMP will have to consider whether any specific obligations have been fulfilled.

As both, the reassessment and the renewal are in a separate scope, the reassessment cannot be combined with a renewal.^{xcviii}

Since in case of a marketing authorisation under exceptional conditions it is considered unlikely that comprehensive data on efficacy and safety will be available, it is theoretically expected that a marketing authorisation under exceptional circumstances will remain *exceptional and neither can be transformed* into a regular marketing authorisation nor into a conditional marketing authorisation either – even in case of fulfilment of the specific obligations set – the completion of a full dossier is expected impossible.

Otherwise, according to the Guideline EMEA/357981/2005, “In the rare case where the applicant has finally been able to provide comprehensive data on the efficacy and safety under normal conditions of use (“full dossier”) and specific procedures/obligations do not remain, a “normal” marketing authorisation could be granted.”^{xcix}

Although, for a marketing authorisation under exceptional circumstances it is possible to add new indications or introduce variations thereof which will not have an impact on the exceptional status at all.

In general, a distinction between a conditional and an exceptional marketing authorisation should be made, “A marketing authorisation under exceptional circumstances

should not be granted when a conditional marketing authorisation is more appropriate.”
c

Theoretically, but not explicitly mentioned by legislation, the marketing application under exceptional circumstances would be eligible for an accelerated procedure according to recital 33 and Article 14(9) of Regulation EC 726/2004 so far, ...for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutically innovation the applicant may request an accelerated procedure... In fact, the assessment can be accelerated, so shortened from a normally 210 day procedure to a 150 day procedure.

4.4.3 Orphan Drug Status and Exceptional circumstances

The marketing authorisation under exceptional circumstances procedure also is applicable to medical products which have already received the designated orphan product status and fulfil the criteria set as described above. Otherwise, within the Guideline it is clarified that the Orphan status solely does not sufficiently justify the inability of the provision of comprehensive data in terms of safety and efficacy required per se. Both the criteria for exceptional circumstances as well as for Orphan designation remain independent from each other. Annex I Part III (5) of Directive EC 2001/83, “In case of an orphan medical product in the meaning of Regulation EC 141/2000, general provisions of Part II (6) exceptional circumstances can be applied. The applicant shall than justify in the non-clinical and clinical summary that the reason for which it is not possible to provide the complete information and provide justification of the benefit/risk balance for the orphan medicinal product concerned.”

In practise the case could occur where the Marketing authorisation under exceptional circumstances procedure as well as the conditional marketing authorisation procedure might be applicable. For the adequate choice of the procedure it is advisable to seek scientific advice from the EMA at the earliest time, also in regard to planning the early phase in product development. Scientific advice for orphan medicinal products is free of charge.

4.5 Discussion

4.5.1 Limitations of Applicability

Applicable only in case of indications for which comprehensive clinical data cannot be expected and scientific knowledge is not available as well as ethical constraints hinder the collection of the needed information. These premises narrow the subset of medicine products eligible for application under the scheme dramatically to about 10% of centralised applications, Figure 4.5.2-5 *CHMP Opinions; Art 8(3) applications only; excluding duplicates. The figure changes in regard to specific medicine products, i.e. for indications in oncology to 16%.

4.5.2 Acceleration, Transition Period to Regular Marketing Authorisation, Individual Patient Access

Theoretically but not explicitly mentioned by legislation the marketing application under exceptional circumstances would be eligible for an accelerated procedure according recital 33 and Article 14(9) of Regulation EC 726/2004 so far ... for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutically innovation the applicant may request an accelerated procedure ... In fact, the assessment can be accelerated, so shortened from a normally 210 day procedure to a 150 day procedure.

In general a distinction between a conditional and an exceptional marketing authorisation should be made, "A marketing authorisation under exceptional circumstances should not be granted when a conditional marketing authorisation is more appropriate."^{ci} (also see 4.4.2, 4.4.3). In the absence of a clear descriptive Guidance in terms of classification on whether neither the exceptional nor the conditional path for approval is more appropriate for application the decision after assessment is in the merit of the CHMP, but the applicant is encouraged to seek early advice via scientific advice procedure or request at the time of pre-submission application.^{cii} "It also is unclear what the conditions and arguments are to apply this policy and whether they are justified," it has been remarked by Annette van der Vossen.^{ciii} Consequently, Anne Louise Kirkegaard posits: "Since the conditional MA as possibility of obtaining an MA early in the development phase has only recently [2005 SIC!] been introduced in the EU pharmaceutical legislation, it is likely to assume that several of those medicinal products which have in the past gained an MA under exceptional circumstances, if they would be assessed today they might be granted a conditional MA instead of an MA under exceptional circumstances."^{civ}

Figure 4.5.2-1 exemplarily shows the transition times of Exceptional marketing authorisations (EXMA) for oncology products into "normal" regular marketing authorisations. For oncologic drug products a theoretical (including the not yet converted) calculated average transition period of 6 years elapses for the transformation from an EXMA into a regular marketing authorisation. Therefore, if possible - probably exceptional with regard to national HTA assessment for reimbursement issues - it can be postulated that these drug products are likely to be available on the market and so far accessible to the patients round about 6 years earlier than under normal marketing authorisation approval conditions.

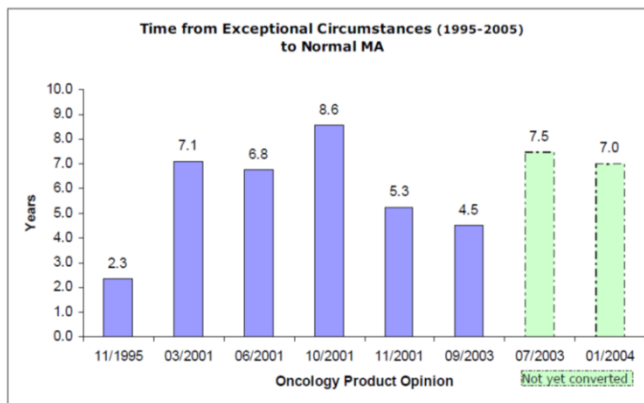


Figure 4.5.2-1 Transition Time from Exceptional Circumstances MA into Normal MA for Oncologic Drug Products^{CV}

In the EU currently (13-12-2014 EPAR) 109 medicines are listed, whether conditional, exceptional or orphan labelled, see Table 4-1. 29 medicine products including 4 withdrawn, Onselal, Daronix, Riloncept Regeneron previously Arcalyst, and Xigris are listed under the exceptional circumstances pathway, whereas 16 thereof are designated orphan status (14 authorised), but 24 products are currently authorised exceptional (since 02/2005). 17 (including 3 withdrawn) products are listed under the conditional pathway. Since 12/2007 14 of them are authorised, whereas 8 of them are designated orphan also. Altogether 87 products of the 109 products are listed designated orphan. Figures are presented graphically with Figure 4.5.2-2, Figure 4.5.2-3, Figure 4.5.2-4.

Medicine Name	Active Substance	Marketing Authorisation Holder	Status	Revision number	Authorisation date	Condition Approval	Exceptional Circumstance	Is Orphan
Ellelyso	taliglucerase alfa	Pfizer Ltd.	R	0	-	no	no	yes
Folotyn	pralatrexate	Allos Therapeutics Ltd	R	0	-	no	no	yes
Istodax	romidepsin	Celgene Europe Ltd.	R	0	-	no	no	yes
Masican	masitinib	-	R	0	-	no	no	yes
Mycograb	recombinant human monoclonal antibody to hsp	NeuTec Europa plc	R	0	-	no	no	yes
Mylotarg	gemtuzumab ozogamicin	Wyeth Europa Ltd	R	0	-	no	no	yes
Rhucin	recombinant human C1 inhibitor	Pharming Group N.V.	R	0	-	no	no	yes
Sovrima	idebenone	Centocor B.V.	R	0	-	no	no	yes
Imbruvica	ibrutinib	Janssen-Cilag International NV	A	0	21/10/2014	no	no	yes
Translama	ataluren	PTC Therapeutics International Limited	A	0	31/07/2014	yes	no	yes
Gazyvaro	obinituzumab	Roche Registration Ltd	A	0	23/07/2014	no	no	yes
Sylvant	siltuximab	Janssen-Cilag International NV	A	0	22/05/2014	no	no	yes
Deltyba	delamanid	Otsuka Novel Products GmbH	A	0	28/04/2014	yes	no	yes
Vimzim	recombinant human n-acetylgalactosamine-6-sulfatase (rhgalns)	BioMarin Europe Ltd	A	0	28/04/2014	no	no	yes
Granupas (previously Para-aminosalicylic acid Lucane)	para-aminosalicylic acid	Lucane Pharma	A	0	07/04/2014	no	no	yes
Kolbam (previously Cholic Acid FCG)	cholic acid	FGK Representative Service GmbH	A	0	04/04/2014	no	yes	yes
Adempas	riociguat	Bayer Pharma AG	A	0	27/03/2014	no	no	yes
Cometriq	cabozantinib	TMC Pharma Services Ltd	A	0	21/03/2014	yes	no	yes
Sirturo	bedaquiline fumarate	Janssen-Cilag International N.V.	A	0	05/03/2014	yes	no	yes
Opsumit	macitentan	Actelion Registration Ltd	A	0	20/12/2013	no	no	yes
Defitelio	defibrotide	Gentium SpA	A	0	18/10/2013	no	yes	yes
Orphacol	cholic acid	Laboratoires CTRS	A	0	12/09/2013	no	yes	yes
Procysbi	mercaptopurine bitartrate	Raptor Pharmaceuticals Europe BV	A	0	06/09/2013	no	no	yes
Imnovid (previously Pomalidomide Celgene)	pomalidomide	Celgene Europe Ltd	A	0	05/08/2013	no	no	yes
Imvanex	modified vaccinia Ankara - Bavarian Nordic (MVA-BN) virus	Bavarian Nordic A/S	A	0	31/07/2013	no	yes	no
Lojuxta	lomitapide	Aegeron Pharmaceuticals	A	0	31/07/2013	no	yes	no
Eriverde	vismodegib	Roche Registration Ltd	A	0	12/07/2013	yes	no	no
Iclusig	ponatinib	Ariad Pharma Ltd	A	0	01/07/2013	no	no	yes
Bosulfif	bosutinib (as monohydrate)	Pfizer Ltd.	A	0	27/03/2013	yes	no	yes
NexoBrid	concentrate of proteolytic enzymes enriched in bromelain	MediWound Germany GmbH	A	0	18/12/2012	no	no	yes
Adcetris	brentuximab vedotin	Takeda Pharma A/S	A	0	25/10/2012	yes	no	yes
Glybera	alipogene tiparovec	uniQure Biopharma B.V.	A	0	25/10/2012	no	yes	yes
Xalkori	crizotinib	Pfizer Ltd.	A	0	23/10/2012	yes	no	no
Dacogen	decatibine	Janssen-Cilag International N V	A	0	20/09/2012	no	no	yes
Revestive	teduglutide	NPS Pharma Holdings Limited	A	0	30/08/2012	no	no	yes
Jakavi	ruxitinib (as phosphate)	Novartis Europharm Ltd.	A	0	25/08/2012	no	no	yes
Kalyydeco	ivacaftor	Vertex Pharmaceuticals (U.K.) Ltd.	A	0	23/07/2012	no	no	yes
Pisuvri	pikantone dimaleate	CTI Life Sciences Limited	A	0	10/05/2012	yes	no	yes
Signifor	pasireotide diaspertate	Novartis Europharm Ltd.	A	0	24/04/2012	no	no	yes
Bronchitol	mannitol	Pharmaxis Pharmaceuticals Ltd.	A	0	13/04/2012	no	no	yes
Xaluprine (previously Mercaptopurine Nova Laboratories)	6-mercaptopurine monohydrate	Nova Laboratories Ltd	A	0	09/03/2012	no	no	yes
Caprelsa	vandetanib	AstraZeneca AB	A	0	17/02/2012	yes	no	no
Vynndaqel	tafamidis	Pfizer Ltd.	A	0	16/11/2011	no	yes	yes
Plenadren	hydrocortisone	ViroPharma SPRL	A	0	03/11/2011	no	no	yes
Votubia	everolimus	Novartis Europharm Ltd.	A	0	02/09/2011	yes	no	yes
Tobi Podhaler	tobramycin	Novartis Europharm Ltd.	A	0	20/07/2011	no	no	yes
Fampyra	fampidine	Biggen Idtec Ltd	A	0	20/07/2011	yes	no	no
Pumark	pandemic influenza vaccine (H5N1)	GlaxoSmithKline Biologicals S.A.	A	0	04/03/2011	no	yes	no
Esbriet	pirfenidone	InterMune UK Ltd	A	0	28/02/2011	no	no	yes
Vpriv	velaglucerase alfa	Shire Pharmaceuticals Ireland Ltd.	A	0	26.08.2010	no	no	yes
Humenza	split influenza virus, inactivated	Sanofi Pasteur S.A.	W	0	08/06/2010	yes	no	no
Azerna	ofatumumab	Glaxo Group Ltd	A	0	19/04/2010	yes	no	yes
Arepanrix	split influenza virus, inactivated	GlaxoSmithKline Biologicals S.A.	W	0	23/03/2010	yes	no	yes
Tepadina	thiotepa	ADIENNE S.r.l.	A	0	15/03/2010	no	no	yes
Firdapse (previously Zenas)	amifampridine	BioMarin Europe Ltd	A	0	23/12/2009	no	yes	yes
Rioncept Regeneron (previously Arcalyst)	ronacept	Regeneron UK Limited	W	0	23/10/2009	no	yes	yes
Ilaris	canakinumab	Novartis Europharm Ltd	A	0	23/10/2009	no	yes	no
Foclivia	influenza virus surface antigens, inactivated	Novartis Vaccines and Diagnostics S.r.l.	A	0	19/10/2009	no	yes	no
Pandemic Influenza Vaccine H5N1	influenza vaccine (whole virion, inactivated)	Baxter AG	A	0	16/10/2009	no	yes	no
Adjupanrix	split influenza virus, inactivated	GlaxoSmithKline Biologicals S.A.	A	0	10/10/2009	no	yes	no
Cayston	aztreonam lysine	Gilead Sciences International Limited	A	0	21/09/2009	no	no	yes
Mozobil	plerixafor	Genzyme Europe B.V.	A	0	31/07/2009	no	no	yes
Vedrop	tociferosolan	Orphan Europe S.A.R.L.	A	0	24/07/2009	no	no	yes
Peyona (previously Nymusa)	caffeine citrate	Chiesi Farmaceutici SpA	A	0	02/07/2009	no	no	yes
Mepact	mifamurtide	Takeda France SAS	A	0	06/03/2009	no	no	yes
Nplate	romiplostim	Amgen Europe B.V.	A	0	04/02/2009	no	no	yes
Vidaza	azacitidine	Celgene Europe Ltd.	A	0	17/12/2008	no	no	yes
Kuvan	sapropterin dihydrochloride	Merck Serono Europe Ltd.	A	0	02/12/2008	no	no	yes
Ceplene	histamine dihydrochloride	Meda AB	A	0	07/10/2008	no	yes	yes
Firazyr	icatibant	Shire Orphan Therapies GmbH	A	0	11/07/2008	no	no	yes
Tyverb	lapatinib	Glaxo Group Limited	A	0	10/06/2008	yes	no	no
Volbris	ambrisentan	Glaxo Group Ltd.	A	0	21/04/2008	no	no	yes
Thalidomide Celgene	thalidomide	Celgene Europe Limited	A	0	16/04/2008	no	no	yes
Vectibix	panitumumab	Amgen Europe B.V.	A	0	03/12/2007	yes	no	no
Tasigna	nilotinib	Novartis Europharm Ltd.	A	0	19/11/2007	no	yes	yes
Torisel	temsirolimus	Pfizer Limited	A	0	19/11/2007	no	no	yes
Yondelis	trabectedin	Pharma Mar S.A.	A	0	17/09/2007	no	yes	yes
Gilolan	5-aminolevulinic acid hydrochloride	Medac GmbH	A	0	07/09/2007	no	no	yes
Atriane	nelarabine	Glaxo Group Limited	A	0	23/08/2007	no	no	yes
Increlex	mecasermin	Ipson Pharma	A	0	03/08/2007	no	yes	yes
Siklos	hydroxycarbamide	Addmedica	A	0	29/06/2007	no	no	yes
Soliris	eculizumab	Alexion Europe SAS	A	0	20/06/2007	no	no	yes
Revlimid	lenalidomide	Celgene Europe Ltd	A	0	14/06/2007	no	no	yes
Daronrix	Whole virion, inactivated	GlaxoSmithKline Biologicals S.A.	W	0	21/03/2007	no	yes	no
Cystadane	betaine anhydrous	Orphan Europe S.A.R.L.	A	0	15/02/2007	no	no	yes
Inovelon	rufinamide	Eisai Ltd	A	0	16/01/2007	no	no	yes
Elaprase	idursulfase	Shire Human Genetic Therapies AB	A	0	08/01/2007	no	yes	yes
Diacomit	stripentol	Biocodex	A	0	04/01/2007	no	no	yes
Sprycel	dasatinib	Bristol-Myers Squibb Pharma EEIG	A	0	20/11/2006	no	no	yes
Exjade	deferasirox	Novartis Europharm Limited	A	0	28/08/2006	no	no	yes
Savene	dexrazoxane hydrochloride	Clinigen Healthcare Ltd	A	0	28/07/2006	no	no	yes
ATryn	antithrombin alfa	GTC Biotherapeutics UK Limited	A	0	28/07/2006	no	yes	no
Nexavar	sorafenib	Bayer Pharma AG	A	0	19/07/2006	no	no	yes
Evotra	clofarabine	Genzyme Europe B.V.	A	0	29/05/2006	no	yes	yes
Myozyme	alglucosidase alfa	Genzyme Europe B.V.	A	0	29/03/2006	no	no	yes
Naglazyme	galsulfase	BioMarin Europe Ltd.	A	0	24/01/2006	no	yes	yes
Revatio	sildenafil	Pfizer Limited	A	0	28/10/2005	no	no	yes
Orfadin	nitisinoine	Swedish Orphan Biovitrum International AB	A	0	21/02/2005	no	no	yes
Prialt	ziconotide	Eisai Ltd.	A	0	21/02/2005	no	no	yes
Xagrid	anagrelide	Shire Pharmaceutical Contracts Limited	A	0	16/11/2004	no	yes	yes
Wiltin	zinc	Orphan Europe S.A.R.L.	A	0	13/10/2004	no	no	yes
Pedea	ibuprofen	Orphan Europe S.A.R.L.	A	0	29/07/2004	no	no	yes
Litak	cladribine	Lipomed GmbH	A	0	14/04/2004	no	no	yes
Onsenal	celecoxib	Pfizer Limited	W	0	17/10/2003	no	yes	yes
Aldurazyme	laronidase	Genzyme Europe B.V.	A	0	10/06/2003	no	yes	no
Carbaglu	carlumic acid	Orphan Europe S.A.R.L.	A	0	24/01/2003	no	no	yes
Zavesca	miglustat	Actelion Registration Ltd.	A	0	20/11/2002	no	no	yes
Xigris	drotrecogin alfa (activated)	Eli Lilly Nederland B.V.	W	0	22/08/2002	no	yes	no
Replagal	agalsidase alfa	Shire Human Genetic Therapies AB	A	0	03/08/2002	no	yes	no

Table 4-1 EU Medicines under Conditional and Exceptional Circumstances Marketing Authorisation and Orphan Drug Designations, source EMA EPAR^{CVI}

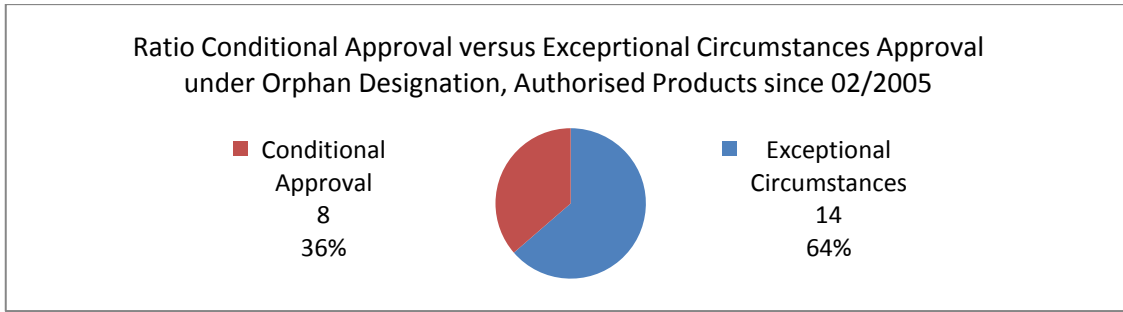


Figure 4.5.2-2 Ratio Orphan Drug Designation under Conditional Approval versus Exceptional circumstances Under Orphan Designation, Authorised Products since 02/2005

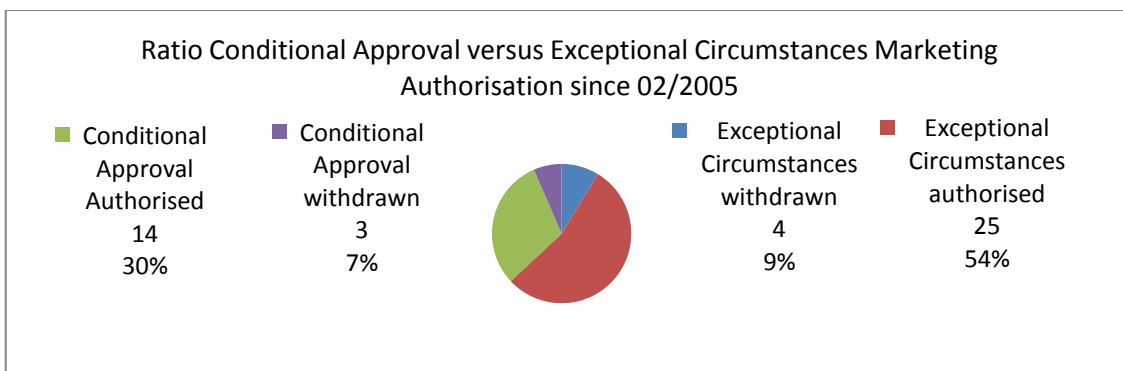


Figure 4.5.2-3 Ratio Conditional Approval versus Exceptional Circumstances Marketing Authorisation since 02/2005



Figure 4.5.2-4 Ratio Conditional Approval versus Exceptional circumstances Marketing Authorisation since 02/2005

The graphics visualises, since introduction of the conditional approval in 2005, the ratio exceptional/conditional approval under which orphan designated products have been authorised is 36% to 64%. The rate of withdrawal is about 4% for each procedure.

New Marketing Authorisation Applications Outcome 2006-2010*

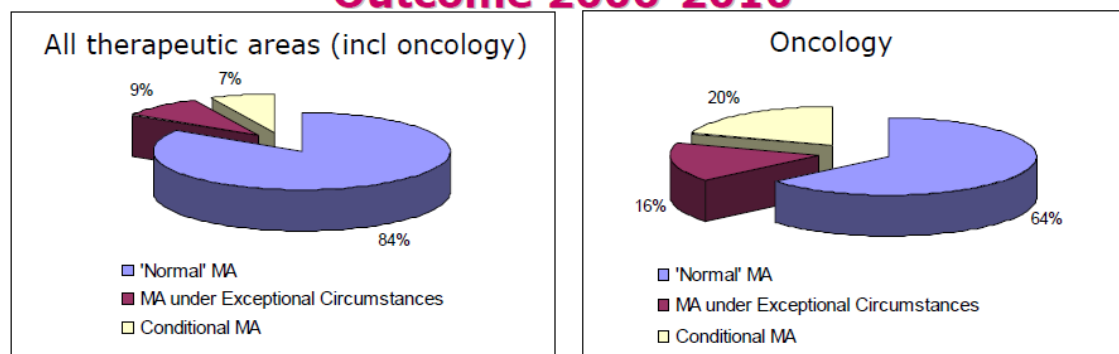


Figure 4.5.2-5 *CHMP Opinions; Art 8(3) applications only; excluding duplicates^{cvii}

4.5.3 Staggered Approach and Flexibilities

Despite the inflexibility of the marketing authorisation scheme under exceptional circumstances originally is intended for and the limitation to forward the accelerated accessibility to medicines to patients with rare diseases in need and in case the data being presently and probably in future will never be available sufficiently comprehensive to grant a regular marketing authorisation provides, some flexibilities remain. The 'not so clear defined classification' of applicability of conditional versus exceptional, the exemptions for transformation into other, conditional or regular marketing authorisations, possible after assessment by the CHMP, as well as the possibility of extensions and variations, theoretically widens the port of entry for a regular marketing authorisation after granting an exceptional marketing approval.

The scheme primarily might not be seen as a staggered approach; hence the definition originally recommends that a development of comprehensive scientific data is not foreseeable, but in regard to the outcome presented with Figure 4.5.2-1 Transition Time from Exceptional Circumstances MA into Normal MA for Oncologic Drug Products, the scheme demonstrate to perform acceptable in the light of a staggered approach in sense of non-binary authorisation schemes.

4.5.4 Probability of Serious Safety Issues of Conditional and Exceptional Marketing Authorisation Post-Approval

As it is inherent to the approval procedures intended to meet an unmet medical need, conditional approval, approval under exceptional circumstances and explicit orphan drugs limited clinical and less safety data is required for approval pre-marketing. In regard to, the question if they are less safe post-approval than products authorised via the regular path remains. Or otherwise questioned - is there an additional safety risk? Arna H. Arnardottir has investigated, "Additional safety risk to exceptionally approved drugs in Europe?"^{cviii} The conclusion reads as; "The EC/CA procedure is not associated with a higher probability of Direct Healthcare Professional Communication (DHPCs) despite limited clinical development data. These data do not support the view that early

drug approval increases the risk of serious safety issues emerging after market approval.” The study has some limitations such as, “The acceptability of serious safety issues in the overall benefit/risk balance may be higher [for CMA/EXMA, SIC!] and could have a higher threshold for issuing a DHPC resulting in less strong safety-related regulatory action, such as a change in the Summary of Product Characteristics.” On the other hand, the DHPC measure is a thoroughly approved EU evaluation procedure. In contrast to regular authorised drug products the population using drug products authorised under CMA/EXMA is relative small with the effect that finding rare adverse events will be reduced, it has been remarked. Biosimilars were excluded also.

4.5.5 Intellectual Property Rights - Conditional and Exceptional Marketing Authorisation Probably Eroding Regulatory Data Protection

In the EU medicine products new authorised are eligible to benefit from an 8 year period of data protection and overall a 10/11 year period of marketing protection (see also below 2.4.3. Uncertainties in regard to data protection and also Figure 2.4.3-2 Data and Marketing Exclusivity for Medicinal Products - 8+2+1 Formula). The protection period starts from the date of the granting the marketing authorisation extended in certain limited circumstances. Actually, no specific guidance is given on when the period of data and market exclusivity starts for authorisations granted under EU procedures for earlier approval. With a response to a commission consultation it has been remarked by industry that, “Conditional Marketing Authorizations can have a seriously negative impact on intellectual property as Regulatory Data Protection (10y) starts from the first approval. As an incentive the 10-year period for RDP should only begin with the first Non-Conditional Approval.”^{cix} Christian Hill and Professor Sarah Garner postulates, “There is no specific guidance as far as we are aware on when the period of data and market exclusivity starts for authorisations granted under EU procedures for earlier approval but it is arguable that it commences on the grant of the earlier conditional approval and not on full approval. Earlier approvals, such as conditional authorisations, commonly focus on a narrowly defined indication with few patients. For commercial viability research generally continues into broader and less urgent indications. During that period of further research the regulatory data protection period is gradually being eroded.”^{cx}

5 Adaptive Licensing

5.1 Intention of the Scheme

On 19 March 2014 the EMA started the adaptive licensing pilot project.^{cxii} The project is designed to explore the adaptive licensing approach with real medicines in development. Adaptive licensing is seen as an extension to existing marketing authorisation procedures. “An important concept in this debate is a so-called, ‘adaptive’ approach to marketing authorization, which can be seen as an extension of developments such as Conditional Approval.”^{cxiii} H.G. Eichler describes the scheme as following, “Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made”.^{cxiii} To a wider extent the scheme, as like the EAMS is intended, covers the period after licensing when the reimbursement is negotiated. “While the concept was entitled “adaptive licensing,” it has been argued that clinical drug development, licensing, reimbursement/coverage, utilisation in clinical practice, and monitoring of treatment outcome should be viewed as a continuum and, to the extent possible, should be planned in a prospective and integrated way, with cooperation and input from all stakeholders.”^{cxiv} “cxv

5.2 Description of the Scheme

Adaptive licensing uses the existing EU legal framework and the regulatory processes established with. Therefore, only existing regulatory tools are to be used including extensive scientific advice with participation of HTA bodies, payers and other stakeholders. Centralised compassionate use programmes assessment, the regular marketing authorisations, conditional marketing authorisations, marketing authorisations under exceptional circumstances, and other provisions for pharmacovigilance legislation, including risk management plans, patient registries etc., but however, data protection and other relevant legal provisions remain unchanged. At current stage, the pilot aims to give assistance to applicants to explore the feasibility of their proposals to optimise development pathways with the target on an optimal balance of time for patient access and increasing knowledge on benefits and risks.

5.2.1 Adaptive Licensing in Practise

Applicants are requested to consider the pilot at the time of submission of their application. Within two weeks after application a confirmation will be issued providing the dis-

cussion date of the application. A limit of ten applications per month is considered suitable to be processed by the Adaptive Licensing Discussion Group (ALDG) in the project. Exceeding applications will be postponed.

Products of interest for the adaptive licensing concept based on the selection criteria will be selected for a 'brainstorming telephone conference' with the applicant at the next following ALDG meeting. The conference dependent on the complexity will take one hour and will focus on the elements essential for adaptive licensing identified in the development plan according initial experiences of the pilot, i.e. Adaptive Licensing Pilot project EMA/417706/2014. Also a discussion on other authorisation and development pathways possible and the obstacles associated will take place including the applicability of paediatric and orphan medicine product regulatory aspects. The telephone conference is not considered as a formal scientific advice. In-depth discussions of scientific issues remain in the field of competence of the scientific advice working group. It is an early dialogue led by the scientific advice working party (SAWP) chair and assessors assigned for reviewing the plausibility of the development plan and regulatory steps possible. The result of the conference is a list of comments similar to those issued after regular scientific advices, but including the minutes of the HTA and other stakeholder discussion comments as an attachment. It remains in the remits of the applicant to implement the recommendations into forward development plans. Further discussions with the applicant and experts, also under confidential conditions, are possible. The HTA/SA parallel advice based on the results of the discussion will follow. The process is possible to be repeated several times before follow-up scientific/regulatory advice or submission of the marketing authorisation application. In regard to the project nature all participants are requested for feedback by questionnaires.

6 Compassionate Use

6.1 Compassionate Use in the EU

6.1.1 Intention of the Scheme

Introduced in the EU in 2004 the programme is designed to overcome the ethical dilemma to facilitate the availability to patients of new treatments options under development where efficacy has been proven to a certain extent. It is a treatment option for patients who are suffering from a disease for which no satisfactory licensed alternative therapy exist, or who cannot enter a clinical trial subject to certain reasons. The EU-framework does not include any binding elements for the individual Member State on the implementation of their own compassionate use procedures. Furthermore, the scheme provides an option for the individual Member State to ask the EMA, respectively the CHMP, for an opinion about the administration, distribution and use for compassionate medicines. The programme also is intended to improve the access to compassionate use programmes for EU patients, to facilitate a common approach in regard to conditions of use and distribution and patients targeted by these programmes in the EU as well as to improve transparency between the Member States.

Other “Compassionate use programmes” (CUP), making medicine products available on a named patient basis (Named patient programmes (NPPs)) or to cohorts of patients (Coh-CUP), are governed by individual national Member State legislation.

6.1.2 Legal Basis

The implementation of compassionate use remains within the competence of the Member States, Recital 33 of Regulation EC No 726/2004, “...a common approach should be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under MS’ legislation...”^{CXVI}

The legal framework for the provision of compassionate use for medicinal products, which are eligible to be authorised via the Centralised Procedure, is described by Article 83(1) of this Regulation, “By way of exemption from Article 6 of Directive 2001/83/EC, Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation EC No 726/2004 available for compassionate use.” Article 83(2) specifies the group of patients eligible, “... a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be *life-threatening*, and who cannot be treated satisfactorily by an authorised medicinal product...,” and specifies that the concerned medical product, “...must either be the *subject of an application* for a marketing authorisation in accord-

ance with Article 6 of this Regulation *or must be undergoing clinical trials...*,” the latter in the EU or elsewhere.

Therefore, Article 83 neither is applicable to products not eligible for centralised procedures, nor to products on a named patient basis (individuals according Article 5 Directive 2001/83/EC) and products already licensed via centralised marketing authorisation procedure. For the latter, even if the conditions of the target population is different from those enclosed in its marketing authorisation.

In contrast, an existing community authorisation (central marketing authorisation) is without prejudice to national legislation in relation to compassionate use. Furthermore, compassionate use cannot replace clinical trials, “...Article 83(9) shall be without prejudice to Directive 2001/20/EC and Article 5 Directive 2001/83/EC...” The opinion [CHMP] referred to does not affect civil or criminal liability of the manufacturer or applicant for marketing authorisation, Article 83(7) EC No 726/2004.

6.1.3 Regulatory Requirements

The Member State competent body anticipating making a medicinal product available under Article 83 EC No 726/2004 shall notify the EMA. In case products of categories according Article 3(2) EC No 726/2004 are subject, only when the CHMP confirmed their eligibility to the centralised procedure previously^{cxvii}, the CHMP after consultation of the manufacturer or applicant may adopt opinions on the conditions for use, distribution, and the target patient group intended for the medicinal product therapeutic indication. These opinions updated on a regular basis will not be binding to the Member States, but should be taken in account *as per intention of common approach according* Recital 33 EC No 726/2004. The opinions are applicable to any subsequent notification from another Member State.

Direct company contact to the EMA for a request on an opinion is not foreseen, but on their initiative they should inform the EMA of applications or ongoing schemes at national level, so that the EMA than can contact the relevant Member State for information. The EMA keeps an up-to date list of the opinions adopted on their website^{cxviii}

The scientific data upon which the CHMP provides the opinion in terms of efficacy, in case of parallel assessment for marketing authorisation application could be based on mature randomised phase III trials, or promising early data observed in explanatory trials (uncontrolled phase II trials). In terms of safety all data available contributing to the refinement of the conditions for use is accepted.

Once an opinion has been adopted, the provisions on pharmacovigilance, defined in Articles 24(1) and 25 of the Regulation referring to centrally authorised products, apply (Article 83(6) Regulation EC No 726/2004).

Updates of the opinion are initiated by Member States request or if considered appropriate by the CHMP until the medicinal product is fully licensed (commercial available).

In the meantime, the company shall warrant that patients enrolled to the scheme have access to the medicine product in question.

Once licensed, fees for the opinion on compassionate use shall be deductible from those for the marketing authorisation application of the medicinal product. Small and medium enterprises (SME) are eligible for a 90% reduction on scientific service fees, Article 7.1(c) Regulation EC No 2049/2005. For transparency reasons and information purpose, in accordance to Article 83(6) Regulation EC No 726/2004, the EMA keeps a record published on their website.

6.1.4 Compassionate Use versus Off Label Use and Clinical Trial

Compassionate use is to be *distinguished from off-label-use^{cxix}, named-patient schemes, and individual importation of authorised drug products* abroad. Off-label use is the use of the product outside of its authorised indication, whereas compassionate use is the use of a product which still has not already received an authorisation. In contrast to named-patient schemes the product is addressed to a *group of patients*. The difference to individual importation of products authorised in the state of origin, but not in the state of importation is that it targets a patient group and not an individual patient and additionally, it does not to be authorised in the country of origin.

Compassionate use is to be *distinguished from clinical trials*. Clinical trials by measure are the only appropriate source to generate creditable and substantial evidence on efficacy and safety data for a medicine product. However, compassionate use programmes also generate “real-life” clinical data, but these data cannot replace proper planned clinical trials for an investigational medicine product according the standards of good clinical practice (GCP). Regardless of where conducted, in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC all clinical trials included in applications for marketing authorisation for human medicines in the European Economic Area (EEA) must comply. Clinical trials conducted in the EEA have to comply with European Union clinical-trial legislation Directive 2001/20/EC, yet replaced by Regulation EC No 536/2014 on clinical trials on medicinal products for human use, in force on 16th June 2014 and applicable no earlier than on 28th May 2016. Whereas clinical trials conducted outside the EEA have to comply with the ethical principles equivalent to those set out in the EEA conforming to international good clinical practice and the Declaration of Helsinki. Derived from these premises, it is acknowledged that compassionate use should not compromise or decelerate the implementation or continuation of clinical trials intended to provide essential information to the risk-benefit balance of a medicine product.

6.1.5 Discussion

The EU Regulation has established a framework eligible for central marketing authorisation which in parallel is used as a reference for national legislation for medicine products being intended licensed nationally. National authorities may take divergent

views on compassionate use programs due to specific national requirements, nationally different unavailability of treatment options, national medical practise, available resources, funding, and probably different points of view in regard to assessment.

Compassionate use programs are set up in major EU states such as in Germany, France, Spain and others, see Table 1-1 Implemented Early Access Programs and Relevant Legislation. In the majority of the Member States an authorisation from the competent body is necessary whilst others only recommend a notification and specific certifications. However, in regard to the picture the table provides a company planning a compassionate use scheme in the EU is faced with a patchwork of national regulations. The CHMP in such case can resolve issues by provision of an opinion.

On the other hand, compassionate use programs used provide the opportunity to meet ethical obligations towards patient need and offer the possibility for companies to gain early access to patients and clinical data outside of controlled clinical trials prior to marketing authorisations.

Furthermore, the scheme does not exempt products which are not eligible for central marketing authorisation procedures and can only be authorised via national authorisation procedures. For such scenarios Member States have established specific national legislation.

A variety of reimbursement policies for medicine product available under compassionate use schemes exist between Member States due to different insurance systems. The majority recommends that the compassionate use product is made available free of charge. In case not, it has to be considered that the price set can be used for benchmarking in health technology appraisal later on or for reimbursement negotiations.

Differing liability risks for treatments between Member States have an impact on the use of compassionate use schemes. In Germany the liability under a compassionate use scheme resides with the company providing the medicine product, whereas in the UK it has to be distinguished between the responsibility of the company for quality aspects and the prescriber for clinical negligence. Adverse event reporting is mandatory in all Member States, but different reporting schemes apply.

Compassionate use programmes cannot be employed by generic manufactures for early entry if the protection of the originator has not expired.

The EU legislation restricts advertising on medicines which have not obtained an authorisation, so that information on compassionate use medicine is limited to EMA or national competent authority publication or concerned health care professional networks.

In all of these scenarios managed access programmes provide an effective route to innovative drugs prior to approval or launch, potentially providing medicines to patients who have run into need.

6.2 Compassionate Use Germany Härtefallprogramm 'Hardship Case Programme'

6.2.1 Introduction

In regard to the Regulation EU 726/2004 the 'Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen' by amendment of the German Drug Act (Gesetz über den Verkehr mit Arzneimitteln - Arzneimittelgesetz (AMG)) has been introduced in Germany in 2005. Initially the legislation only covered products eligible for central marketing authorisation but later was expanded to cover products eligible for national marketing authorisation as well. With the amendment in 2009 the condition that the product must be supplied free of charge has been implemented additionally. In 2010 the Regulation on Administrative Procedures for Compassionate-Use Programms, the Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen 'Arzneimittel-Härtefall-Verordnung (AMHV)' ('Hardship Case Programme') has been introduced. The Regulation came into force on 22nd July 2010 and is applicable [only] to compassionate-use programs for products that have not yet obtained a marketing authorization anywhere in the EEC.

6.2.2 Legal Basis

According § 21 Abs. 2 (6) AMG a marketing authorisation (Zulassung) shall not be required for medicinal products which; *"...are made available free of charge under the conditions specified to in Article 83 of Regulation (EC) No. 726/2004 for administration to patients with a seriously debilitating disease or whose disease is life-threatening, and who cannot be treated satisfactorily with an authorised medicinal product; this applies equally to medicinal products which do not fall under the categories stipulated in Article 3 first or second paragraph of Council Regulation (EC) No. 726/2004; rules of procedure shall be specified in an ordinance pursuant to Section 80 [§ 80 AMG]...."*^{cxx}
^{cxxi}

The provisions pursuant to § 80 S. 1 Nr. 3a AMG are provided in the Arzneimittelhärtefallverordnung (AMHV)^{cxxii} in force by 22nd July 2010. § 77 AMG designates the responsible Competent Federal Authority. According to the nature of the medicine product the BfArM or PEI will be in charge. In regard to § 1 AMHV the scheme is applicable only to finished medicine products for human use which do not have obtained a marketing authorisation anywhere in the EU/EEC yet but are subject to Article 3(1)(2) Regulation EC 726/2004 or § 21 Abs.1 AMG. To distinguish the program from individual treatment § 1 Abs. 2 AMHV explicitly clarifies that the AMHV is not applicable to an individual approach of non-licensed medicine products for an individual patient or, to the administration under a direct prescriber responsibility. Furthermore, § 2 Abs. 2 AMHV defines that the Härtefallprogramm is a "compassionate-use" according Regulation EC 726/2004.

For distinction to individual patient schemes it is further explained in the Guideline 'Leitfaden zur Anzeige eines Arzneimittel-Härtefallprogramms nach Arzneimittel-Härtefall-Verordnung (AMHV)' that in case of an individual administration of a medical product to a patient on an individual basis the restrictions set by § 21 Abs. 6 AMG and AMHV, the restrictions on importation and marketing of a non-licensed, non-authorised medical products are not waived. In such case it remains questionable if the administration could be justified as an act of necessity according the criminal code and § 96 Abs. 5 AMG may apply. The case is to be judged individually and remains out of the competence of the authorities concerned; it has been noted by the Guideline.

In case of a non-licensed/non-authorised medicine product has been administered before the introduction of the scheme came into force and also the medicine product remains non-licensed/non-authorised and is intended to be administered to the patient within the same indication in repeat, it should be considered as a Härtefallprogramm in accordance to the AMHV (§ 9 AMHV)^{cxiii}.

Principally, a planned application of the same medical product to more than one patient within the same indication, even at different time points, should be considered as a Härtefallprogramm in sense of the AMH and therefore has to be 'acknowledged' before start.

6.2.3 Regulatory Requirements

The AMHV is applicable only to Arzneimittelhärteprogramme (compassionate use) intended to treat a group of patients and not for the treatment of individual cases. The competent Federal Authorities are in charge to decide whether the proposed programme is eligible or not. Both the BfArM and PEI have published a decision tree^{cxiv} (Annex B) on the recommendations for eligibility. For medicine products in the scope of the Paul Ehrlich Institute (PEI) the application steps can be found visualised in Annex C. The application for the Härtefallprogramm (Compassionate Use Programme) is free of charge. To facilitate a Härtefallprogramm according § 3 AMHV the applicant must denote a responsible person resident in the EU/EEC responsible for the application, conduct, organisation, and finance. The person will have to be notified by the Competent Federal Authority. The program is allowed to be started only when the authority has given consent by 'Acknowledged Application' (Bestätigte Anzeige).

6.2.4 Assessment and Decision Timetable

After two weeks of the receipt of sufficient application data as required to § 3(2) AMHV the Authority acknowledges the receipt of application (Bestätigte Anzeige). The format of data to be presented, which is different from the CTD-format, is described in the AMHV, i.e.; justification that alternative treatments are insufficient, data on quality and efficacy, the SmPC or investigators brochure alternative, PIL and patient consent protocols, the justification that patients would not be eligible to be included in clinical trials, the medicine product is manufactured under GMP, declaration of consent to publicise

basic data and information of the programme. In case deficiencies in the data will be identified the applicant will be allowed to recover these within a time frame of two weeks.

If not, again, the authorities will acknowledge the receipt provided successful data presented. The normal period for scientific assessment will take two weeks. In case of advanced medicine products or in case the product has not been subject to clinical approval within the same indication before max. 60 days will be allowed for the assessment by the authority. If gene-technological material is concerned additionally the Federal Office of Consumer Protection and Food Safety (BVL) will have to evaluate a risk analysis. Its acknowledgement would be necessary in addition, so the period for assessment is allowed to cover an 'appropriate time'.

Option for Reapplication, Periodic Updates, and Pharmacovigilance

Normally, the Härtefallprogramm will cease one year after receipt of acknowledgment, on decision for discontinuation by the applicant, or revocation of the acknowledged application by the authority, and finally in case the product is available on the market full licensed. The option to submit a new application on basis of the data already presented potentially is given. A one year period is introduced in the view that the scheme shall not enrol as a function for replacement to regular medicine product licensing procedures as it is sole intended for earlier access to patients under the conditions described. A reason for renewal could be a licensing procedure currently maintained.^{cxxv} In regard to secure the continuity of the patient supply a renewal is deemed necessary to be planned adequately in advance.

In terms of pharmacovigilance § 6 Abs. 1 AMHV states, that any adverse event should be reported to the Federal Authority immediately, at least within a period of 15 days. Furthermore according Abs. 4a AMHV a safety report must be submitted after the program finishes. Results obtained with similar compassionate use programmes conducted according Article 83 (4) EC 726/2004 must be submitted to the Federal Authority immediately.

The Federal Authority will inform the EMA about the compassionate use programmes as well as all on received adverse events within a period of 15 days of receipt of information. A list of all programmes will be made public on the Authority website^{cxxvi, cxxvii}

6.3 Discussion

In respect to EU Regulation 726/2004 the scheme was introduced in Germany in 2005 by amendment of the German Drug Act (14th AMG Novelle). Initially, only covering products eligible for central marketing authorisation, but later expanded to products eligible for national marketing authorisation as well. The amendment in 2009 (15th AMG Novelle) introduced that the products eligible must be made free of charge for patient access and that drug products eligible for national marketing authorisations are applicable also. The regulation on administrative procedures for compassionate-use pro-

grams (Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen), in force since 22nd July 2010, is applicable (only) to compassionate-use programs on products that have not yet obtained a marketing authorization anywhere in the EEC. It remains questionable why drug products which possess an authorisation outside of Germany but in the EU/EEC, will not qualify for the scheme.

The free of charge provision of the drug product under the scheme could be seen as a disincentive for setting up a compassionate-use program, especially Small and Medium Enterprises (SMB) and Start-ups who develop bio-technological products with high costs. The scheme is purely national and it will remain questionable if such a programme is adequate in regard to the European landscape. In regard to that the reimbursement of the therapeutic costs is subject to specific social legislation which will imply a higher burden of administration the applicability of the scheme could be challenging.

7 Conclusion

7.1 The new EAMS

The three step UK Early Medicines Access to Medicines Scheme based on current EU and national legislation recognises the need for a faster access to innovative medicines for patients with life threatening or seriously debilitating conditions without adequate treatment options reflecting the changes driven by genomics, data, and the rise of stratified and personalised medicines on an ‘unlicensed or off-label basis’ through acceleration of early application data assessment, advice procedures, and provision of official reliable opinion. It provides incentives to start-ups, prescribers, patients, and charities to collaborate within the infrastructure. EAMS complements the European licensing landscape and can support adaptive licencing pathways by generation of real-life data on safety and efficacy.

7.1.1 Different Legal Approaches

The legal base for regular marketing authorisation procedures in the EU is described in 3.2 and 4.2. The legal basis for EAMS described in 2.2 is Article 5(1) Directive 2001/83/EC, whereas compassionate-use described in 6.1.2, as the German Härtefallverordnung is defined to, is based on Article 6 of Directive 2001/83/EC. Both cover the use of unlicensed medicines under individual national legislation, and both are intended to provide access to unlicensed medicines to a group of patients, whereas the Härtefallverordnung explicitly excludes medicines approach to individual patients, which is still covered by the legislation on importation or named patient access programmes. Albeit the EAMS does so, but it provides only a good ‘reference for justification’ for the administration of the medicine to a group of patients described in the EAMSSO under the direct personal responsibility of the prescriber for the individual patient (treatment protocol of the public assessment report in question). So far, it is used as an enhanced tool for the individual prescriber’s justification. In contrast to the Härtefallverordnung the EAMS additionally takes into account ‘off-label use’; un-licensed and off-label use is covered, whereas the Härtefallprogramm does not (6.2.2). Both schemes exclude patients in clinical trials. The ground for the different legal approach to a certain extent might be explained with different liability legislation for prescribers and pharmacists defined in UK national legislation (6.1.5).

7.1.2 EAMS Position in the Licensing Landscape

In the current drug licensing landscape the EAMS is positioned between phase III, eventually phase II and final marketing approval. Once introduced the 3rd step, health technology appraisal and reimbursement, it can be seen extended to licensing and

rapid commissioning, reducing local variations in medicines access to patients and providing a clear regulatory opinion to a nation-wide approach. Presumed medicines are at their formal end of development stage (phase III) the EAMS potentially can provide life-saving treatment options one to two years, some expect 5 years earlier compared to regular approval procedures by bridging the period for licensing. Real-life data of experimental therapies out of clinical trials can give more insight and understanding of the disease, the efficacy, safety and quality of the medicines, and how they work at the earliest stage. Evidence collection for HTA purposes can start earlier. Respectively the impact on accelerated access to medicines in other EU Members States will have to be monitored carefully.

7.2 Regulatory Requirements

Medicines that qualify for the EAMS include new biological or chemical entities. Also the re-purposing of established or recently approved drugs is considered. Medicines are eligible if the 3 target criteria could be met; life threatening or seriously debilitating conditions, a high unmet need (no treatment method exists or methods have serious limitations), and significant advantages over methods currently used in the UK must be identified, adverse effects considerably must be outweighed by benefits (reasonable expectation of positive risk-benefit ratio), and lastly sufficient quality must be guaranteed for a positive opinion. In contrast the German 'compassionate use' specifies that medicines qualify if they are indicated for treatment of a seriously debilitating disease, or a disease which is life-threatening, and which cannot be treated satisfactorily with an authorised medicinal product expected (6.2.2). Compared to compassionate use and EU licensing schemes described in 3.3 and 4.3 EAMS provides more flexibility in regard to the medicines spectrum accepted for qualification as well as with the wider acceptance criteria. The scientific data required for decision making on the EAMSSO under the scheme is considered based on phase III, exceptional phase II data, as well as the data recommended on which the decision for an 'acknowledged application' in terms of the Härtefallprogramm is considered. The EAMS application submission is required in CTD format, which fortunately can be re-used later for regular applications. The data format required for application submissions according the Härtefallverordnung is slightly different.

7.3 Time Lines

The assessment period for an EAMSSO application after a promising designation (PIM) has been issued consists of 75 days, in extended cases 90 days. The annually renewal process and a 3 month frequent data update holds the EAMSSO actual. Relevant information is publicised via public assessment report (PAR) on the MHRA website. The data assessment for an 'acknowledged application' is determined to minimal 2 up to 60 weeks, for exceptional cases a period is not specified. EU marketing authorisation procedures can be processed in 150 days when accelerated, otherwise 210 days, or ex-

tended, due to the required data provided and implemented. The advantage of the EAMS clearly is the possibility to start the assessment early in phase II, the short assessment period and the scientific advice implemented.

7.4 Reporting and Pharmacovigilance

In terms of pharmacovigilance EU requirements as described for exceptional and conditional marketing authorisations (3.4.2, 4.4.2) apply. In case of EAMS periodic updates of the EAMSSO on a 3 month frequency and a renewal on an annually basis is implemented. The reporting of adverse events according the UK yellow card scheme is mandatory. Recommendations necessary will be communicated by the MHRA. The Härtefallprogramm respectively the 'acknowledged application' is valid for one year with an option for re-application. Adverse events and adverse events suspected must be reported to the competent body within 15 days. Further handling is defined according the provisions on pharmacovigilance in Articles 25(1) and 25 of the Regulation referring to centrally authorised products Article 83(6) Regulation EC No 726/2004. Therefore they are to be communicated on EU level. Reporting of adverse events under EAMS is based more nationally organised, using the well-established yellow cards system. In terms of EU pharmacovigilance and information distribution on EU level, the compassionate use schemes provide the advantage of central gathering and evaluation of information, also providing central access for Member States

7.5 Limitation of Applicability

The conditional and exceptional marketing authorisation concept is applicable only to a narrow subset of medicine products described under the categories and requirements (3.3.1, 3.3.2, 4.3); (CMA) new drug products, new indication, central licensing procedures, orphan drug products. Applicable (EXMA) only in case for indications for which comprehensive clinical data cannot be expected and scientific knowledge is not available as well as ethical constraints hinder the collection of the needed information. This is mirrored by a low number of applications (Figure 3.5.1-1). Also, the ratio of applications potentially falling in the conceptual scope for conditional circumstances is in decline, whereas the procedures for generic applications have increased. The concept of conditional marketing approval also does not apply to new indications submitted in the frame of an extension or variation procedure. Premises for exceptional marketing authorisation applications narrow the subset of medicine products eligible dramatically to about 10% of centralised applications (Figure 4.5.2-5), changing in regard to indications i.e. for in oncology to 16%. The flexibilities provided with the EAMS potentially can overcome these limitations for patient access to medicines by making available the medicines before granting (full) license.

7.6 Staggered Approach and Flexibilities

Generally the more staggered approach than the binary regular licensing approach with several repeated steps of reassessment, scientific advices, not at least HTA negotiations on national and/or EU level imply an increased amount of manpower and human resources both sides at the applicant and the authority. Therefore, probably a significant increase of personnel expenditure is expected. The relative fixed stepwise approach for a narrow subset of medicine products not only will enable to adapt the range of the marketing authorisation in question in analogue to the growth of the scientific knowledge gained stepwise at time of administration of the drug product on an increased number of patients “real-life”, but also could accelerate a decision in terms the data gained probably present results being not as comfortable to justify further investigation activities towards granting a marketing authorisation, i.e. negative opinion at time of renewal.

Despite the inflexibilities in the marketing authorisation scheme under exceptional circumstances originally intended, and the limitation to forward the accelerated accessibility to medicines to patients with rare diseases in need, and in case the data being presently and probably in future available will never be sufficiently comprehensive to grant a regular marketing authorisation, some flexibilities remain. The ‘not so clear defined classification’ of applicability of conditional versus exceptional (4.5.2), the exemptions for transformation into other, conditional or regular marketing authorisations, possible after assessment by the CHMP, as well as the possibility of extensions and variations, theoretically widens the port of entry towards a regular marketing authorisation after obtaining an exceptional marketing approval. Transition times from conditional and exceptional marketing authorisation to regular marketing authorisations between 1.7 years and 6 years can be expected (3.5.2, 4.5.2). EAMS as well as compassionate use schemes open the gate much more flexible to gain real-life data before marketing authorisation and therefore are a vital step towards an adaptive pathway model in drug licensing by using established legal framework.

7.7 Safety Issues Post-Approval

Inherent to the approval procedures intended, limited clinical and less safety data is required for approval or pre-marketing authorisation. The question if they are less safe post-approval than products authorised via the regular path remains vital. Otherwise questioned - is there an additional safety risk? Results of studies investigating this for exceptional approved drugs present that CMA/EXMA procedures are not associated with a higher level of Direct Healthcare Professional Communications as an indicator for higher safety concern (4.5.4). But in contrast to regular authorised drug products the population using these drug products is relative small with the effect that finding rare adverse events will be reduced.

7.8 Erosion of Intellectual Property Rights - Regulatory Data Protection

In the EU medicine products new authorised are eligible to benefit from an 8 year period of data protection and overall a 10/11 year period of marketing protection starting from the date of the granting of the marketing authorisation and extended in certain limited circumstances. No specific guidance on when the period of data and market exclusivity starts for authorisations granted under EU procedures for earlier approval (CMA/EXMA) is given yet. In regard to EAMS and compassionate use these concerns do not apply.

Advertisement and information on unlicensed medicines is restricted by law. The information pathways on the availability of medicine products under the scheme might be made more transparent to enable patients and healthcare professionals are kept informed more adequately to provide an equal access to the medicine.

7.9 Flexibilities of the Scheme for Both, the Regulator and the Applicant

As the PIM designation will not be published enhancing the options for interaction with the regulator apart from business requirements. This include that an applicant can apply for a number of products regardless of negative outcomes giving concern for negative reputation. A PIM designation can be obtained as early as after phase I data are available which are able to give an indication of the products benefits very early in product development. Especially smaller companies depending on external investments may use this system to substantiate to their prospective investors or shareholders that the drug they are developing is considered by the UK authority as an innovative drug. With the EAMSSO (stage II) the regulator will be given an opportunity to assess the clinical and non-clinical data much more early. Therefore, the applicant, by receiving a decision whether “yes”, “no”, or “under the condition,” will have much more clarity about his projects much more early and the advantage to adjust and strengthen his forward strategies appropriately. The official promising designation can be seen as an advantage compared to compassionate use programmes lacking this dedicated incentive for development.

A certain benefit can be derived for the industry form free commissioning of the therapy much more quick; faster access to patients, real-life data generation, closer collaboration with clinical experts and real clinical value exploration outside of controlled clinical trials, faster market diffusion. Also patients may benefit before licensing because patients with critical or life-threatening illnesses often don't qualify for clinical trials.

Repurposing of old drugs for new indications is permitted under the scheme. Medicines currently licensed for other indications, but intended for off-label use, are considered eligible allowing generic drug products being repurposed also.

7.10 The Liability for Clinicians Prescribing and Pharmacists

The liability for clinicians prescribing and pharmacists dispensing and preparing the medicine still unlicensed lastly rests with the prescriber of the medicine. In respect, the EAMSSO and inherently the treatment protocol issued by the MHRA could be held as a reference for justification.

7.11 Questions from Stakeholders

The EAMS is seen controversial for stakeholders. Prominent are questions about the value the scheme will provide to patients given its current scope. Some expect that the program undermines the current centralised EMA system to review clinical trial data to ensure that medicines meet the standard for efficacy and safety prior to drug approval for public use and that given its small scale the program will not improve public health to the extent expected, and that the majority will have to await the usual EMA timelines for approval. The scheme only allows UK based patient earlier access to unmet medical need medicines but not EU citizens. The impact on the latter will have to be monitored. The industry expressed concern about the lack of central funding and requested the scheme to be reviewed after the first year. The lack of funding could make EAMS unattractive compared to other earlier access routes available. It will be important to get clarity around the proposed rapid HTA and commissioning at stage 3 of the EAMS, so that it is much clearer at the outset what commercial advantages and risks are to be considered by the companies and investors and that that route is expected successful.

From the patient and regulatory perspective the scheme is very complex, also expert advice is recommended at various stages. It could be expected that the experience will help to optimise the scheme and certainly will have an impact on decisions in other European countries or Europe as to discuss and adopt similar ideas.

A certain impact can be estimated for medicine products under the scheme which enter regular licensing routes. Existing clinical data, real-life clinical data, a precompiled dossier (CTD) as required, as well as several scientific advices and assessments theoretically can be used to accelerate regular approval procedures in Europe, at least for accelerated procedures.

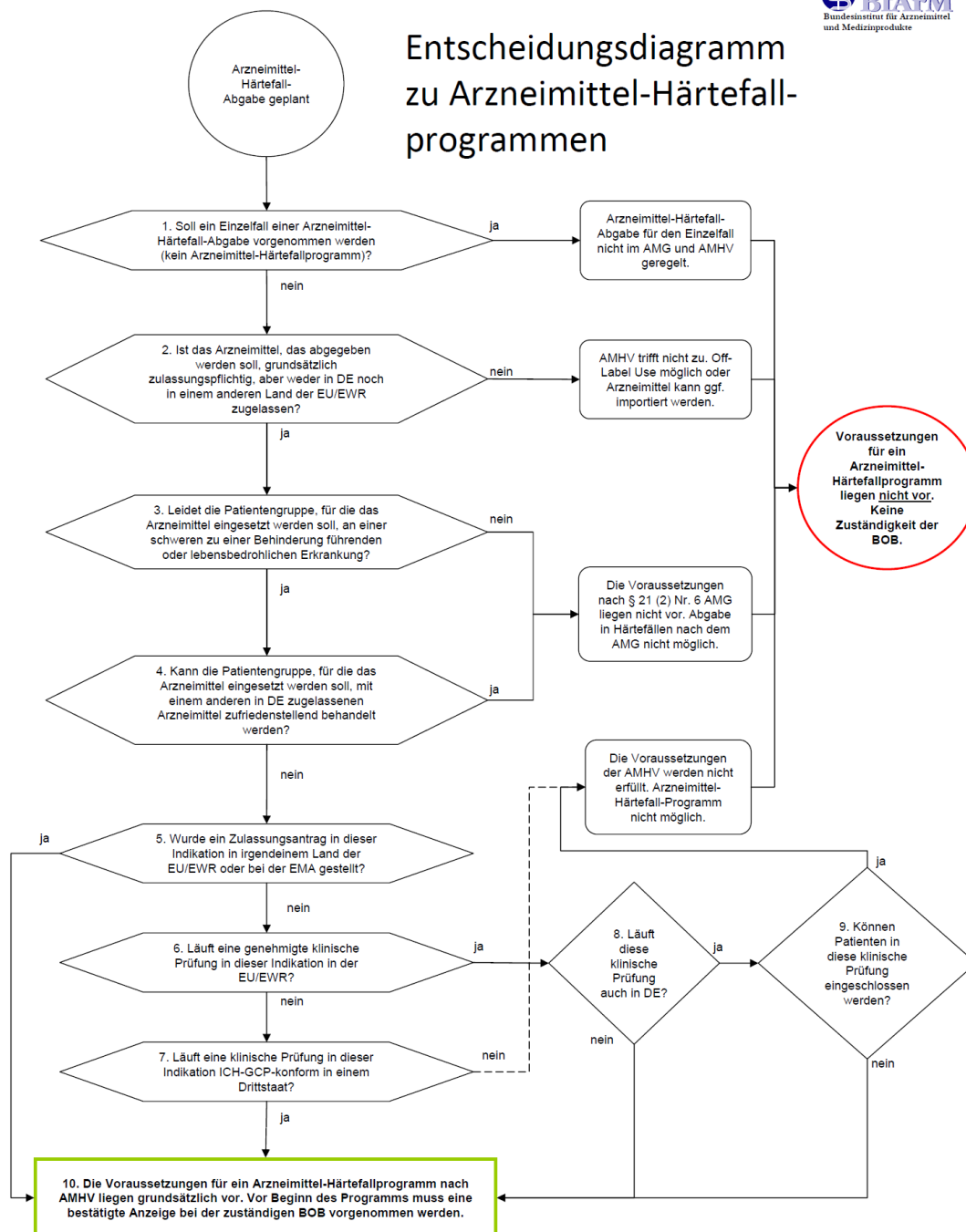
EAMS is a new proactive scheme specifically designed for its application. It provides interesting options to facilitate earlier access to medicines; new flexibilities based on existing legislation and could have an impact in the view on European medicines licensing approaches.

Annex B

Decision Tree AMHV



Entscheidungsdiagramm zu Arzneimittel-Härtefallprogrammen



AMHV: Arzneimittel-Härtefall-Verordnung; AMG: Arzneimittelgesetz; BOB: Bundesoberbehörde (hier BfArM oder PEI); DE: Deutschland; EMA: Europäische Arzneimittel-Agentur; EU: Europäische Gemeinschaft; EWR: Europäischer Wirtschaftsraum; ICH-GCP: Gute Klinische Praxis (GCP) gemäß der Internationalen Konferenz für Harmonisierung (ICH)

Annex C

Bearbeitungsfristen für Anzeigen von Härtefallprogrammen für die verschiedenen Arzneimittelkategorien im Zuständigkeitsbereich des Paul-Ehrlich Instituts

Kategorie 1 – Frist 1

Das Arzneimittel ist dem PEI durch klinische Prüfung oder Zulassungsantrag bekannt (inkl. genetisch veränderter Organismen, sofern keine Änderungen vorgenommen wurden, die die Bewertung des Risikos für Dritte oder die Umwelt verändern; exkl. Arzneimittel für neuartige Therapien).



* bei unvollständigen Unterlagen siehe Frist 4 Quelle: PEI

Kategorie 2 – Frist 2

- Das Arzneimittel ist dem PEI weder durch einen Antrag auf Genehmigung klinischer Prüfungen noch durch einen Zulassungsantrag bekannt
- **oder**
- Das Arzneimittel ist ein Arzneimittel für neuartige Therapien (dem PEI bekannt oder unbekannt)



* bei unvollständigen Unterlagen siehe Frist 4 Quelle: PEI

Kategorie 3 – Frist 3

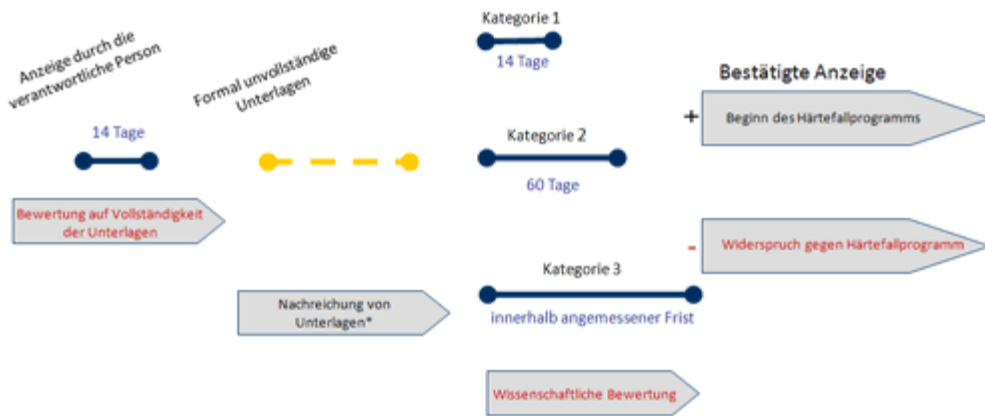
- Genetisch veränderte Organismen, die dem PEI weder durch eine klinische Prüfung noch durch einen Zulassungsantrag bekannt ist
- Bekannte genetisch veränderte Organismen, bei denen Änderungen vorgenommen wurden, die die Bewertung des Risikos für Dritte oder die Umwelt verändern



* bei unvollständigen Unterlagen siehe Frist 4 Quelle: PEI

Kategorie 1,2,3 – Frist 4

Formal unvollständige Unterlagen



* die Nachreichung von Unterlagen unterliegt keiner Frist Quelle: PEI

Eidesstattliche Versicherung

Name: Horn Vorname: Jan
Matrikel-Nr.: 2417657 Studiengang: Drug Regulatory Affairs

Hiermit versichere ich, Jan Horn an Eides statt, dass ich die vorliegende Masterarbeit mit dem Titel „Earlier access to medicines“ EAMS in the UK - A comprehensive overview and comparison to existing accelerated licensing procedures in the EU and Germany selbständig und ohne fremde Hilfe verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe. Die Stellen der Arbeit, die dem Wortlaut oder dem Sinne nach anderen Werken entnommen wurden, sind in jedem Fall unter Angabe der Quelle kenntlich gemacht. Die Arbeit ist noch nicht veröffentlicht oder in anderer Form als Prüfungsleistung vorgelegt worden.

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Wer von einer zur Abnahme einer Versicherung an Eides Statt zuständigen Behörde eine solche Versicherung falsch abgibt oder unter Berufung auf eine solche Versicherung falsch aussagt, wird mit Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft.

Ort, Datum

Unterschrift

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