Compassionate use

Role of EMA and Member States

ŠÚKL
ŠTÁTNY ÚSTAV PRE KONTROLU LIEČIV

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Disclaimer:

I attend this conference as an individual expert, and do not represent the CXMP/WP/SAG.

The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CXMP/WP/SAG or reflecting the position of the CXMP/WP/SAG.

Agenda

- ❑ Regulatory and legal framework of compassionate use in Europe
- ❑ EMA role in compassionate use programme
- ❑ Analysis of EMA experience with CU, case study
- ❑ Conclusion

A frequent situation in life-threatening or severely debilitating diseases

New drug being developed → New drug authorised

Some patients have no more treatment options, their condition deteriorates. Not all are eligible for clinical trials. Some die. All know a product is being developed and may be there soon.

Marketing authorisation

When the drug is authorised, patients can have access.

There is always one patient who will suffer the day before a drug is authorised and who knows the drug will be authorised next day

For all, this is a nightmare

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Regulatory and legal framework

European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 July 2007
Doc. Ref: EMEA/27170/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004

Regulatory and legal framework (1/4)

- Compassionate use (CU) is a mechanism enabling health care professionals in a European Member State (MS) to **provide access** to **investigational products** to **patients** with **serious or life-threatening conditions** who have **no** satisfactory **alternative treatment options** outside clinical trial setting, i.e. investigational products that have not yet been authorised by regulatory authorities.

- European legal framework foresees two situations of exceptional application of a non-licensed medicinal product to patients. Those applicable for a cohort (group) of patients:

  - "Named Patient Use" (also referred to as Named Patient Programme, NPP).
  - CU is intended for a group of patients (i.e. more than one). CU is not a substitute for off-label use or for not conducting clinical trials.

- There is a substantial heterogeneity in EU MSs, with regard to requirements for CU programmes.

Regulatory and legal framework (2/4)

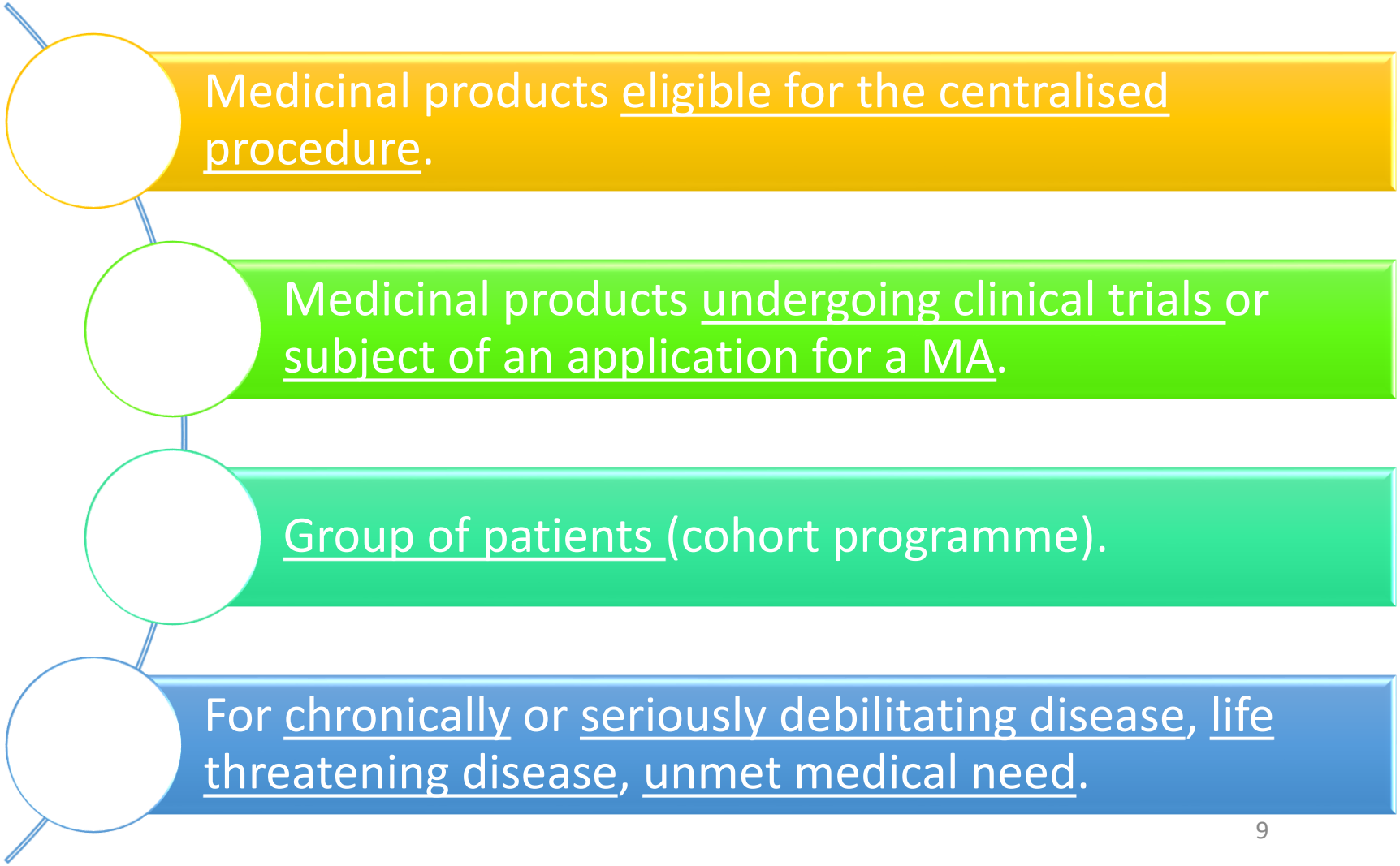
Directive 2001/83/EC provides the legal basis for Member States to implement national programmes:

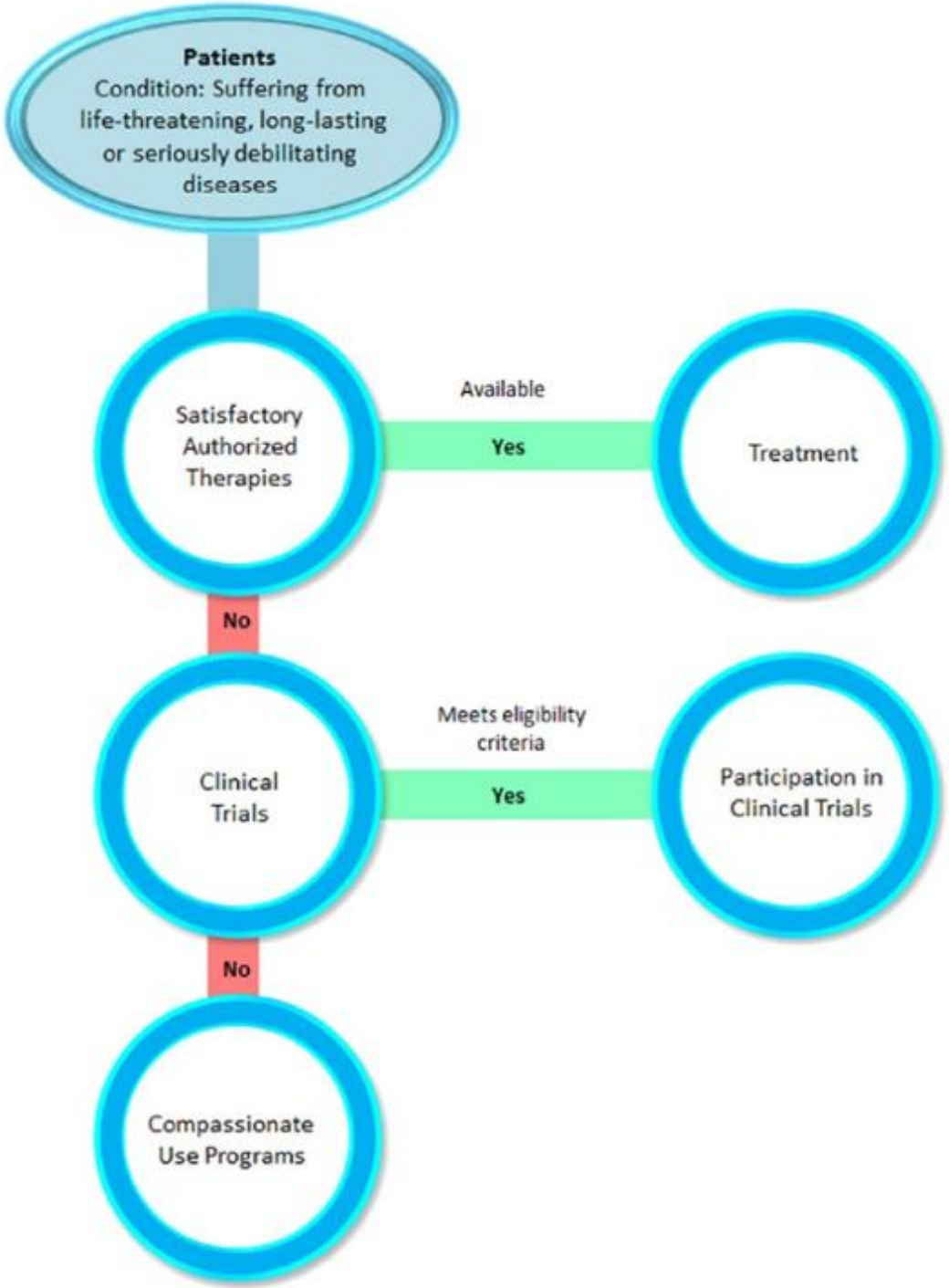
- Article 6 - a medicinal product may not be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State or an authorisation has been granted through a centralized procedure.

- Article 5 - defines an exception to this requirement under defined circumstances [*A Member State may, in **accordance with legislation in force and to fulfil special needs**, exclude from the provisions of this Directive [requirement for a marketing authorisation] 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*].

Regulatory and legal framework (3/4)

Regulation (EC) No 726/2004, specifically Article 83, provides **the legal basis for the management of a CU** programme at the EU level. **Directive 2001/83/EC** provides **the legal basis for MS** to implement national programmes.





Pathway to CU program

This figure depicts the pathway to access new medicines through compassionate use program for a patients suffering from severe or enervating diseases.

Regulatory and legal framework (4/4)

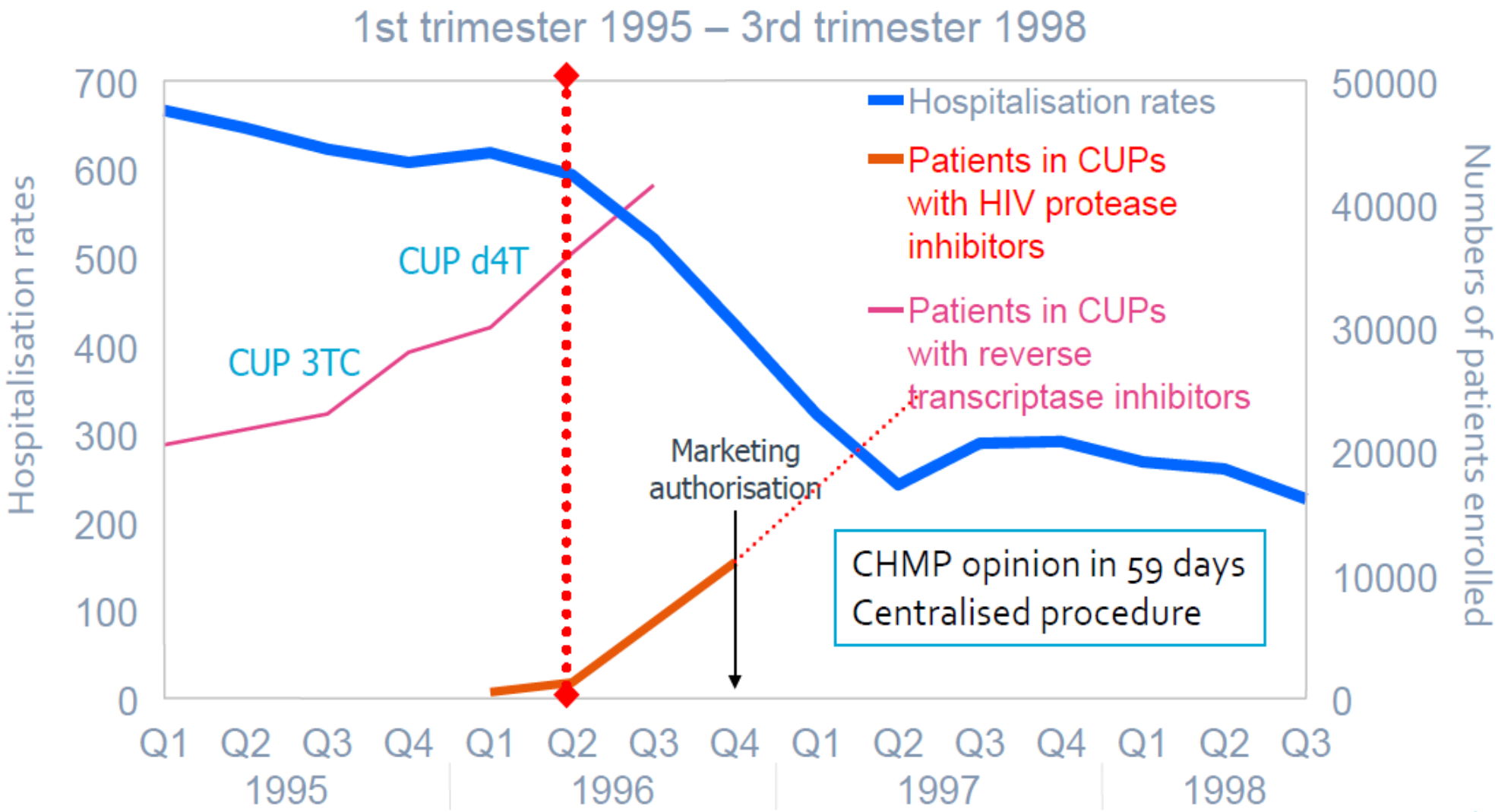
- Article 83 of Regulation (EC) No 726/2004 introduced legal framework for Member State to ask the CHMP when **compassionate use for group of patients** is envisaged to adopt opinions on the conditions for use, conditions for distribution and the patients targeted.

- Article 83 of Regulation (EC) No 726/2004 further states that when a Member State makes use of the possibility for compassionate use for group of patients it shall notify the Agency.

General limitations on knowledge when deciding on CU – **scientific back-ground**

- At this stage in the development of medicine, what is known of the medicine´s safety may be limited. Generally, **toxicological studies should be completed and analysed**, and early PK studies should be conducted.
- There may still be uncertainties about the best way to give medicine to patients, such as **the exact dose to use, the dose frequency** and **the medicine´s safety profile**, which is not yet fully established.

CU impact on public health – the case of HAART / AIDS: when it all began?



Hospitalisation rates for 1000 AIDS patients, France 1995-1998.

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EMA role in CU opinions:

Application of compassionate to EMA/CHMP

- National competent authorities send requests for CHMP scientific opinion on compassionate use for investigational product to EMA:
  - Rapporteur and Co-Rapporteur appointment and timetable for assessment
  - CHMP/EMA will request applicant to provide data and submit dossier
- CHMP opinion on how to administer, distribute and use certain medicines for compassionate use; Member States should take note of these recommendations when making decisions.
- Pharmacovigilance rules and responsibilities (as per Article 28(1) of Regulation 726/2004) are applicable to medicinal products used as part of compassionate use. The Member State(s) ensure that these pharmacovigilance obligations are fulfilled.
- Manufacturers and marketing-authorisation applicants should not contact EMA to request an opinion, but they may wish to inform the Agency of applications at national level.

Analysis of EMA experience (2005-2019)

- Since the introduction of Article 83 of Regulation EC No 726/2004 in 2005, **the CHMP adopted 5 scientific opinions for Compassionate Use** for two conditions (hepatitis C and influenza).
- An analysis of the experience to date for **Compassionate Use intended for group of patients** at EU level demonstrates that few member states appear to follow the requirements to notify the EMA about nationally implemented CU programmes.
- Of the MS that notify the EMA of CUP, few have made use of the option to request a CHMP Opinion on conditions for use, the conditions for distribution and the patients targeted for CU.

What is the role of the EMA regarding CU?

- The EMA's CHMP can provide recommendations to all EU Member States (MS) on **how to administer**, **distribute** and **use certain medicines** for compassionate use. It does also **identify which patients may benefit** from compassionate use programmes.
- The CHMP can provide these recommendations at the request of a MS. It can also do so when it becomes aware that compassionate use programmes with a given medicine are being set up in a number of MS.
- **The recommendations complement national legislation**, and do not replace it. They also do not create any legal framework in the EU Member States. **The recommendations are optional**, and are only implemented by the MS that wish to use them for their patients.
- **The EMA's recommendations aim to standardise CU programmes across the EU**. They may also help to make the conditions of existing compassionate use programmes clearer.

Article 83 vs. MS Authority

- The CHMP may adopt an opinion on the conditions for use, distribution and patients targeted
- CHMP opinions are not binding on MS; however, ”MS shall take account of any available opinions”
- The recommendation complements national legislation, which it does not replace
- The recommendations are optional, and are only implemented by the MS that wish to use them for their patients

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Analysis of EMA experience (2005-2019):

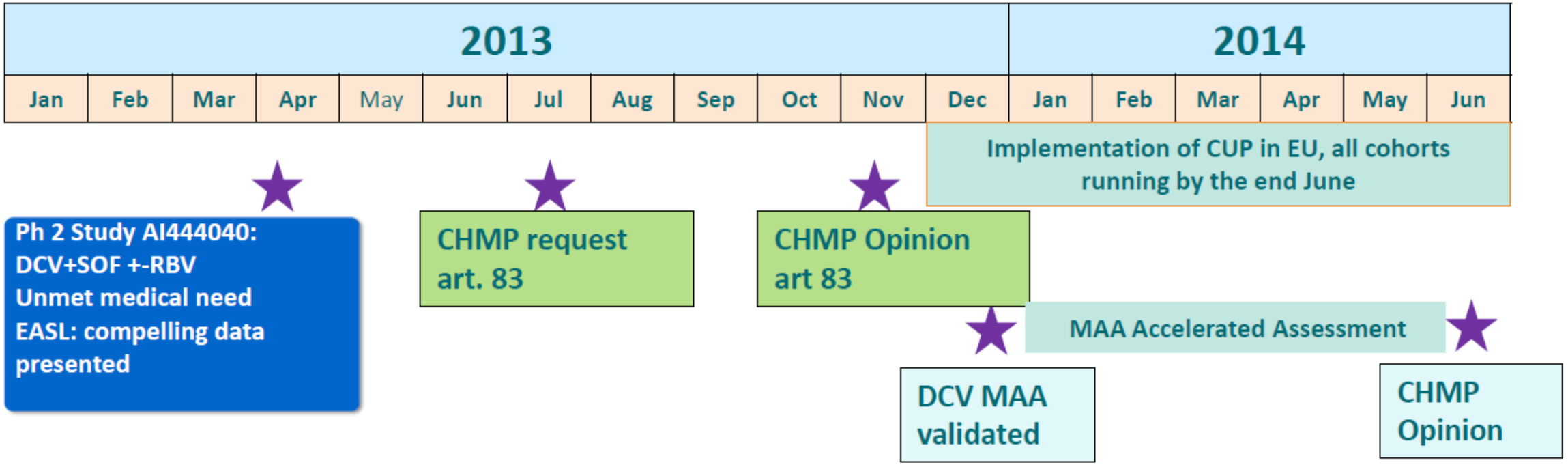
CHMP Scientific Opinions on CU to Date

	Product	Requesting Country	Year	Procedure No.
1.	**Ledipasvir/Sofosbuvir**	IE	2014	EMEA/H/K/003892/CU
2.	**Daclatasvir**	SE	2013	EMEA/H/K/003867/CU
3.	**Sofosbuvir Gilead**	SE	2013	EMEA/H/K/003891/CU
4.	**IV Zanamivir**	SE	2010	EMEA/H/K/002287/CU
5.	**Tamiflu IV**	FI	2010	EMEA/H/K/002287/CU

- ❑ Publication of compassionate use opinions includes the CHMP's recommendations on how a medicine should be used, and the type of patient who should be eligible.
- ❑ Not transparent in which countries the CHMP Opinion led to the availability of the product under CU.

Daclatasvir (Case Study)

- Art. 83 CHMP Opinion: November 2013



- **27 June 2014, EMA site:**

***"EMA recommends approval of Daklinza in chronic hepatitis C. First-in-class medicine to offer new treatment option for patients"*. Authorised by European Commission on 22 Aug. 2014**

Overall CUP Experience with Daclatasvir

Regulatory & Medical Implementation

- Article 83 dossier: collaboration with EMA excellent in all steps.
- Regulatory environment highly varied across MSs (2013/2014).
- Not a ‘clinical trial’ but interest to maximise data collection via treatment protocol (incl. efficacy).
- “Real life” safety & efficacy data collected.
- Interim data published & presented in international congresses (dissemination of knowledge).
- Opportunity for thousands of patients with no other treatment options and highest medical need.

CUP Daclatasvir and Real World Data

Some key efficacy data collected from the cohort program

- Situation mimicked the “real world setting” for the sickest patient population, for which clinical studies were not available in EU.
- Collection & reporting of safety data followed national & EU laws: varied.
- Patient population included patients with common co-morbidities - highest medical need. Welcomed by treating physicians.

CHMP opinion document for Daclatasvir

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2013
EMA/24463/2014
Evaluation of Medicines for Human Use

Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring adressed to member states for Daclatasvir available for compassionate use

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use: daclatasvir**
- **Active substance(s): daclatasvir**
- **Pharmaceutical form: film coated tablet**
- **Route of administration: oral use**
- **Strengths: 30 and 60 mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom
Tel: +44 1895 52 3740
Fax: + 44 1895 52 3677
Email: medical.information@bms.com

3. TARGET POPULATION

Daclatasvir for the use in combination with sofosbuvir +/- ribavirin, for genotype 1 patients that are above 18 years of age and at a high risk of decompensation or death within 12 months if left untreated.

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE
2. NAME AND CONTACT DETAILS OF THE COMPANY
3. TARGET POPULATION
4. CONDITIONS FOR DISTRIBUTION
5. CONDITIONS OF USE
5.1 Posology
5.2 Contraindications
5.3 Special warnings and precautions for use
5.4 Interaction with other medicinal products and other forms of interaction
5.5 Pregnancy and lactation
5.6 Incompatibilities
5.7 Overdose
5.8 Shelf life
5.9 Storage conditions
5.10 Special precautions for disposal
6. OTHER INFORMATION (Summary of relevant pharmacological properties, Summary of relevant clinical properties, Pharmacokinetics).
7. CONDITIONS FOR SAFETY MONITORING
8. DATE OF CHMP OPINION

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Daklinza

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daclatasvir

WITHDRAWN
This medicine is now withdrawn from use in the European Union.

Table of contents

Analysis of EMA experience (2020):

CHMP Scientific Opinion on Compassionate Use to Remdesivir Gileade

	Product	Requesting Country	Year	Procedure No.
1.	Remdesivir Gilead	Estonia, Romania, The Netherlands and Greece	2020	EMEA/H/K/005622/CU

- SK indirect participation on scientific opinion at CHMP and and direct finalisation of „CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED ADRESSED TO MEMBER STATES “.

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Compassionate use is a response for patients with the most urgent need for a new option

New drug being developed

New drug authorised

Compassionate Use

But whenever a compassionate use programme starts, there will always be patients for whom it will be too late.

Summary - Improve Current System

Within the existing framework

- **Application:** MSs to make more use of Art 83 and leverage the CHMP expertise.
- **Request:** Possibilities for patient groups and industry to request Art. 83 via MSs. (Co-) Rapporteur identified early in PRIME to allow for early request of Art. 83 opinions after consultation with applicant (optional).
- **Real world data:** Utilise CUPs to allow for critical real world data gathering and establish guidelines for collection and more structured assessment of this first real world data.
- **Alignment:** MSs to drive for stronger alignment between different national compassionate use systems in particular with respect to scientific criteria, procedures, standardised documents (e.g CUP protocol templates).

Future/aditional legislative changes

- **National framework for cohort CUPs**: Systematic national implementation of a framework for cohort CUPs in all MSs to allow operation of Article 83 across all MSs.

Human regulatory

Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Ethical use of animals
Innovation in medicines
Medicines for older people

Compassionate use

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Table of contents

Compassionate use is a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials.

The European Medicines Agency (EMA) **provides recommendations** through the Committee for Medicinal Products for Human Use (CHMP), but these do not create a legal framework. Compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures.

Established by Article 83 of Regulation (EC) No 726/2004, this tool is designed to:

Discussion

Quo vadis CU in the EU?

„There is nothing worse for a patient, from a psychological and human standpoint, than being severely ill or even dying from a disease, when experimental treatments are out there, pending final evaluation.”
/EURORDIS/

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