



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Legal basis & types of approvals

Regulatory considerations for human medicines development: Legal basis for marketing authorisation applications & conditional marketing authorisations and authorisations under exceptional circumstances

SME info day on 26 October 2018

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Scientific and Regulatory Management Department

An agency of the European Union



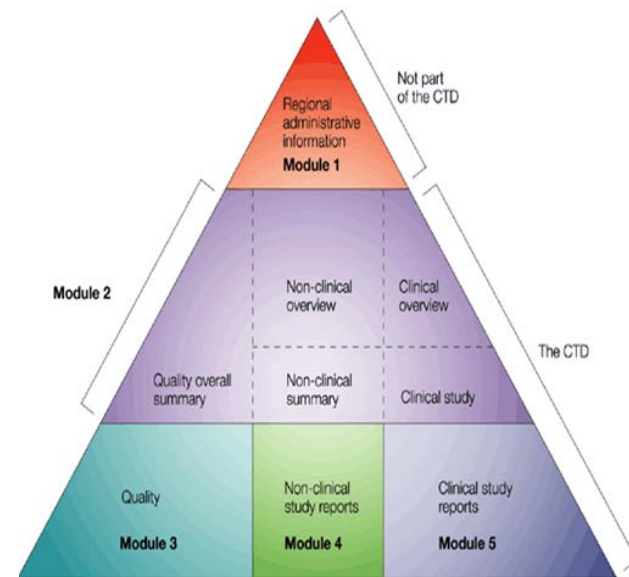


EU Marketing Authorisations – Legal basis and dossier requirements



Dossier requirements

- Detailed pharmaceutical, non-clinical and clinical **data** required (CTD format).
 - Specified in Annex I of Directive 2001/83/EC.
 - Further clarified in scientific guidelines.
 - Need to properly and sufficiently demonstrate quality, safety and efficacy & establish a positive B/R balance.
- Product development and data generation needs to be compatible with the **legal basis** of the application.



<http://www.ich.org/products/ctd.html>

Legal basis of the application in the EU

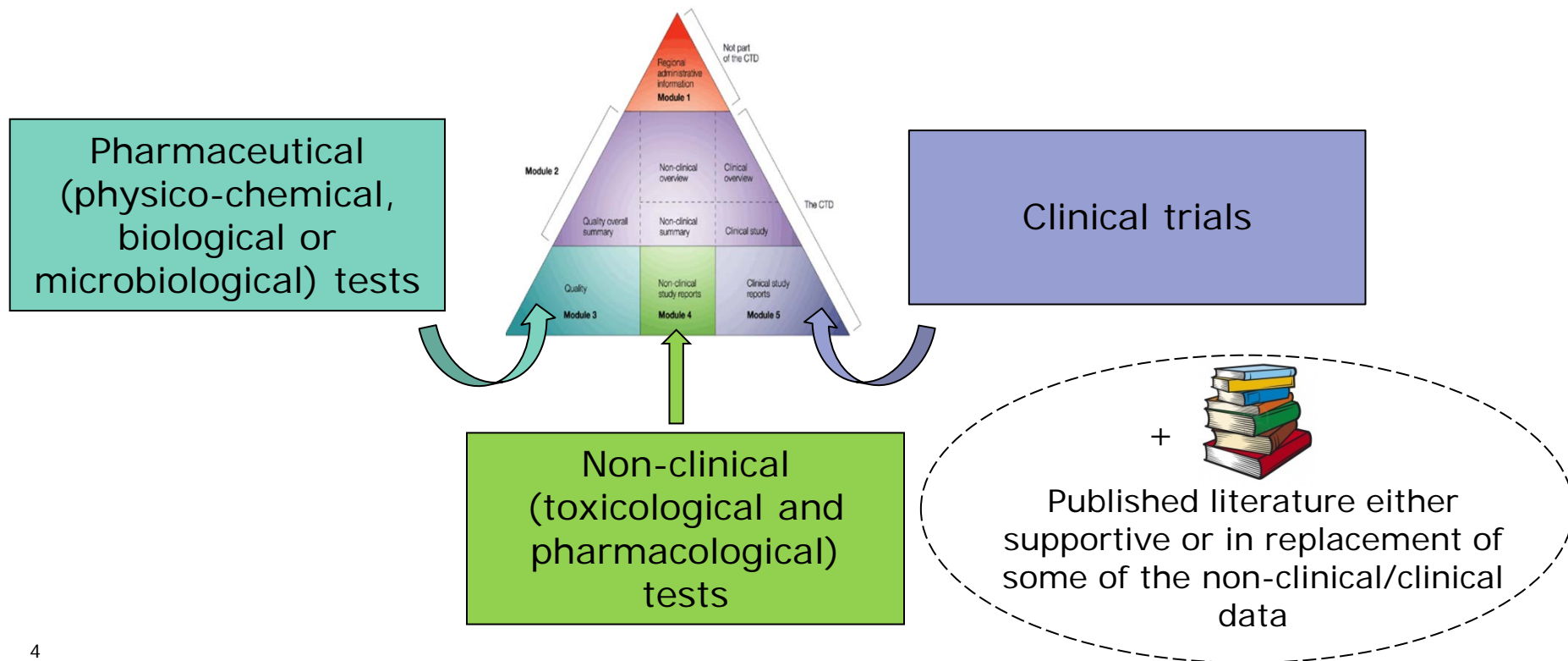
Art. *	Type of application
8(3)	Full or full-mixed application (complete dossier)
10(1)	Generic medicinal product application
10(3)	Hybrid medicinal product application
10(4)	Similar biologic product application
10a	Well established use application (literature only)
10b	Fixed dose combination (components already authorised separately) application
10c	Informed consent application

* **Directive 2001/83/EC**

Simplified registration procedures foreseen for some homeopathic (Art. 14 and 15) and traditional use herbal medicines (Art. 16a).



Article 8(3) Stand-alone application (so called 'Full' or 'Mixed')





Article 8(3) Stand-alone application - continued

- Expectation to include all particulars and documentation in accordance with Annex I of the Directive (own data or literature).
- **Absence of certain tests or trials** may be **acceptable if justified**, e.g.
 - if specifically foreseen in CHMP Guidelines,
 - if additional tests or studies are unlikely to further the scientific knowledge or would not be applicable/relevant to their medicinal product.

Abridged applications (generic, hybrid, biosimilar)

- **Article 10(1), 10(3) and 10(4)** of Directive 2001/83/EC.
- Derogation from the requirements for a full marketing authorisation.
- Development *versus* a **reference medicinal product**, which has been granted a marketing authorisation
 - **in the Union** (a non-EU/EEA medicinal product cannot be used as reference product), and
 - on the basis of a full dossier, i.e. Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC.
- Submission only possible once **data protection period** of reference medicinal product **has expired**.



Abridged applications – continued

- Access to **centralised procedure**
 - automatic access if **reference medicinal product is a centrally authorised product**.
 - mandatory for biosimilars produced by **biotechnological** processes.
 - optional if **innovation** or in the **interest of patients at Community level**.










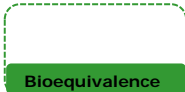
Article 10(1) - Generics



- same **active substance**,
- same **amount** of **active substance** (strength),
- same **pharmaceutical form**, and
- **bioequivalence** has been demonstrated by appropriate bioavailability studies (where necessary).

⇒ **No need to provide additional non-clinical tests or clinical trials**



CTD Module	Originator	Generic
1		
2		
3		
4		
5		

Cross-reference



Article 10(1) Generics - continued

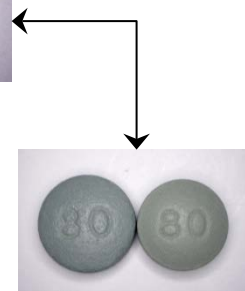
- The various immediate-release oral pharmaceutical forms (tablets, capsules, oral solutions and suspensions) are considered to be one and the **same pharmaceutical form**.
- A **biowaiver** may be possible (i.e. no need for BE studies) in line with criteria defined in the *Guideline on the investigation of bioequivalence*.
- The **SmPC should in all relevant respects be consistent** with that of the reference medicinal product (except for patent/SPC protected indications and dosage forms).

Article 10(3) Hybrids

For medicinal products when

- the **strict definition of a generic** medicinal product is not met,
- where **bioequivalence cannot be demonstrated** through bioavailability studies, or
- in case of **changes** in active substance(s), therapeutic indications, strength, pharmaceutical form, or route of administration compared to the reference medicinal product.

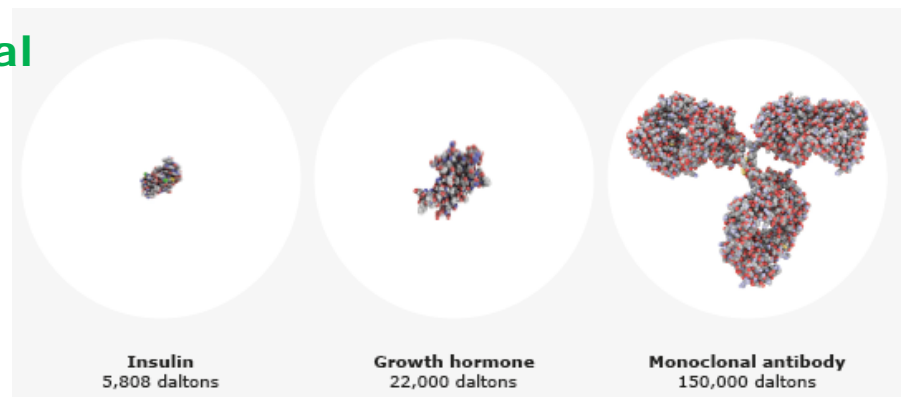
⇒ **Rely in parts on dossier of the reference medicinal product + results of appropriate own non-clinical and/or clinical studies**



Article 10(4) Biosimilars

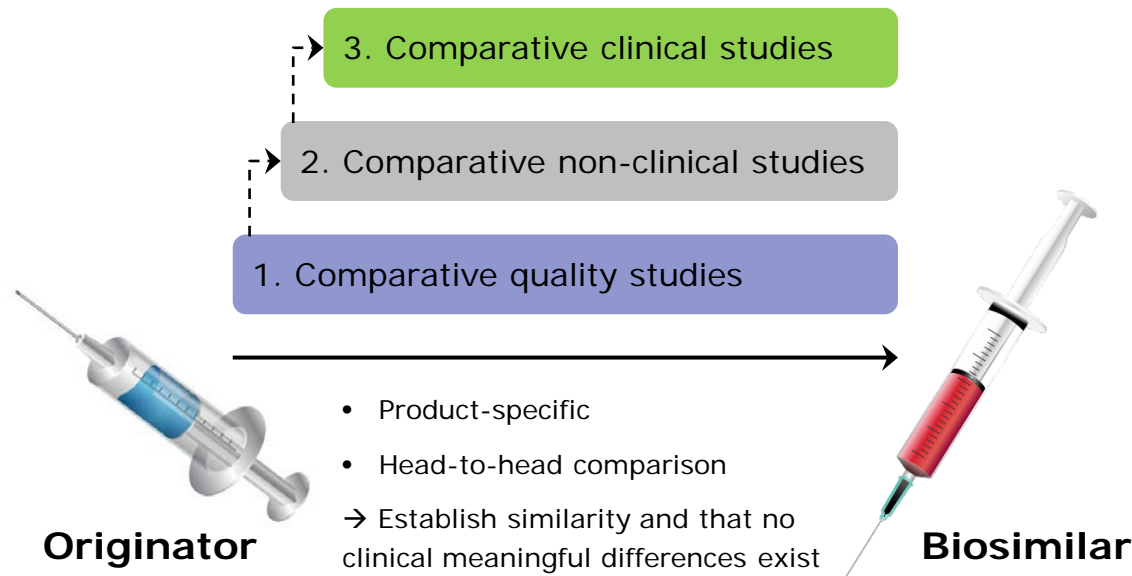
For **biological** medicinal products which are **similar to a reference biological product**, but do not meet the conditions in the definition of generic medicinal products, owing to, in particular, **differences relating to raw materials or differences in manufacturing processes**.

- ⇒ **Results of appropriate non-clinical or clinical studies needed.**
- ⇒ **Comparability exercise to demonstrate similarity.**

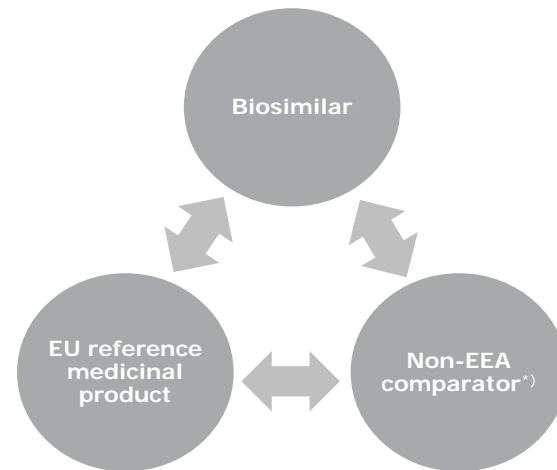


Article 10(4) Biosimilars - continued

Comparability exercise



Global development



^{*)} Non-EEA authorised version of reference medicinal product, approved by regulatory authority with similar scientific/regulatory standards (e.g. ICH country)

Article 10a Well established use / bibliographical

‘the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in **well-established medicinal use** within the Community for at least **ten years, with recognised efficacy and an acceptable level of safety** in terms of the conditions set out in Annex I.

In that event, the **test and trial results shall be replaced by appropriate scientific literature.**’





Article 10a Well established use – continued

1) Well-established medicinal use in the claimed therapeutic indication within the Union, based on

- **time** over which a substance has been used & **quantitative aspects** of the use including geographic spread (systematic and documented use ≥ 10 years)
- degree of **scientific interest** & the **coherence** of scientific assessments

For applications for **orphan medicines**, possible to refer to **supply on a named patient basis**.

2) Positive B/R balance

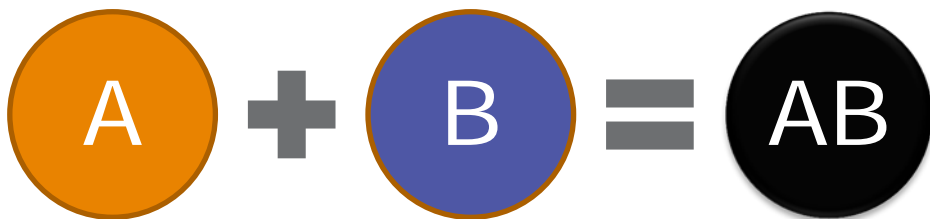
- **Safety and efficacy** need to be **demonstrated by published scientific literature** (i.e. available in public domain, published by reputable source/peer-reviewed).
- **Assessment reports** (e.g. EPARs) **not acceptable** for this purpose.
- **Studies** may be provided **only for bridging** to support relevance of the literature.



Article 10b Fixed Dose Combinations

What is a Fixed Dose Combination (FDC)?

- A combination of active substances within a single pharmaceutical form



Distinct from Combination packs = combination of active substances included in separate pharmaceutical forms (very exceptional only).

- Possible to submit FDC under different legal bases.

Article 10b Fixed Dose Combinations - continued



In the case of medicinal products containing active substances used in the composition of **authorised medicinal products** but not hitherto used in combination for therapeutic purposes, the results of **new pre-clinical tests or new clinical trials relating to that combination** shall be provided in accordance with Article 8(3)(i), but it **shall not be necessary to provide scientific references relating to each individual active substance**.

Individual substances must have been authorised in the EU

Own non-clinical/clinical data on the combination is needed

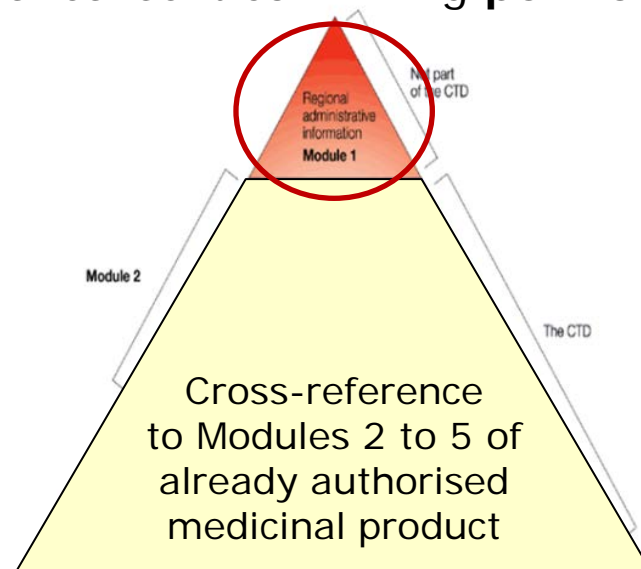
Derogation from the requirement of providing data on individual components

Article 10c – Informed Consent

Permission to make use of the pharmaceutical, non clinical and clinical documentation contained in the dossier of another medicinal product for the purpose of a subsequent application → *Letter of consent* confirming **permanent access** to the data.

Both medicines must have

- the **same qualitative and quantitative composition** in terms of active substance(s), and
- the **same pharmaceutical form**.



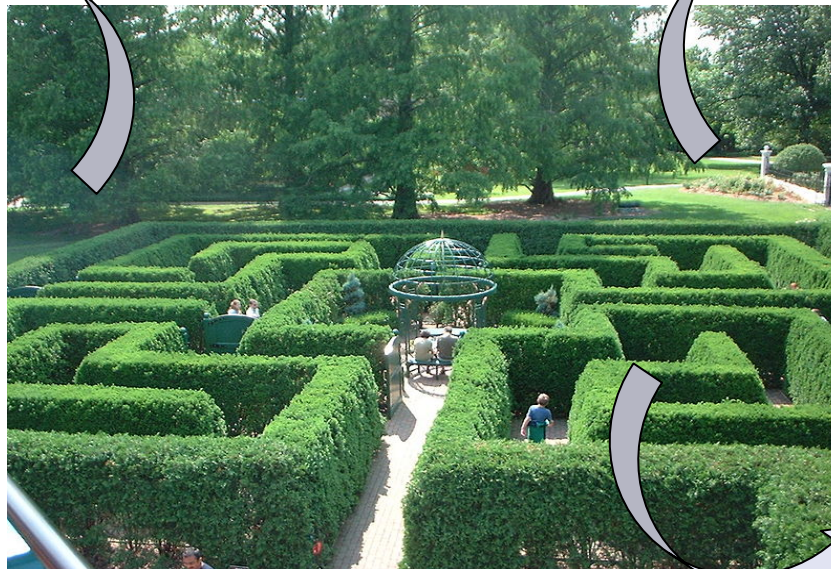
Choice of legal basis – What to consider?

Is there a reference medicinal product? If yes, has the data protection period elapsed?

→ *Articles 10(1), 10(3) and 10(4)*

Is there well-established medicinal use within the Union for at least 10 years in the proposed therapeutic indication for the active substance?

→ *Article 10a*



Development of a medicine, e.g. with a new active substance or in a new indication, conducting all the appropriate non-clinical tests and clinical studies?

→ *Article 8(3)*

Each legal basis is associated with specific data requirements
Legal basis is the choice of the applicant

Non-Standard Marketing Authorisations (MAs)

Granting of a marketing authorisation based on a **dossier containing less than comprehensive data** possible for certain medicines.

- **Marketing Authorisation under exceptional circumstances**
 - Comprehensive clinical data not expected.
- **Conditional Marketing Authorisation (CMA)**
 - Comprehensive data expected to be obtained post-approval within defined timeframe.

MA under exceptional circumstances



Criteria (at least one):

- the indication(s) is/are so **rare** that the applicant cannot reasonably be expected to provide comprehensive evidence;
- in the **present state of scientific knowledge**, comprehensive data cannot be provided;
- if contrary to **ethical** principles to collect the information.

- ➡ MA subject to **specific obligations (SOBs)**, in particular relating to safety.
- ➡ Standard validity of MA (5 years): **Annual re-assessment** of B/R based on progress of SOBs.

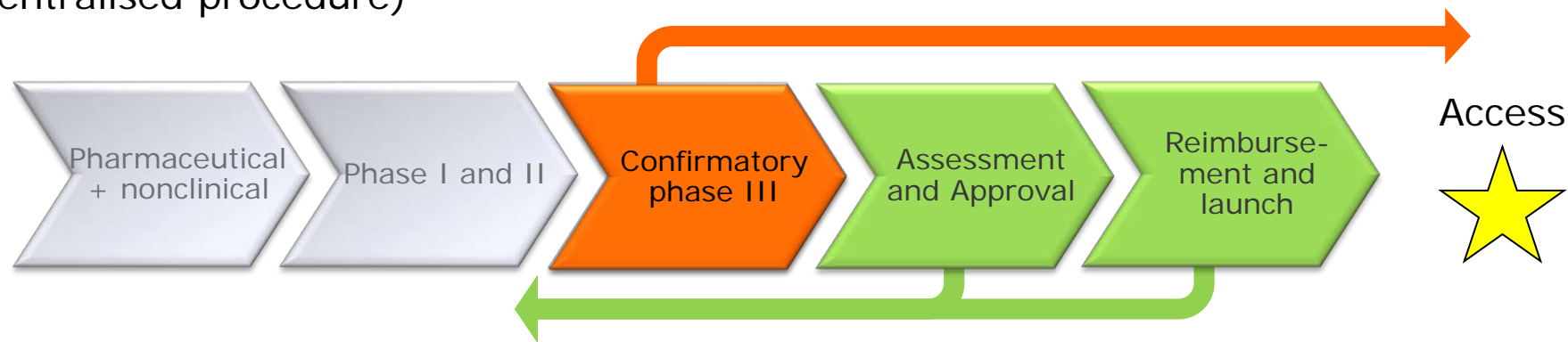


Specific obligations (some examples)

- Data from **ongoing study**
- Data from a **post-marketing safety study (PASS)** in the indicated patient population
- **Registry** to **collect long-term safety and efficacy data**
- Data from **observational cohort study**
- **Immunosurveillance programme including antibody testing** in the event of a possible immune reaction or lack of efficacy.
- **Monitoring and reporting of toxicity** in all ongoing and planned clinical trials.
- **Carcinogenicity testing** in an appropriate model.

Conditional Marketing Authorisation

MA before comprehensive (clinical) data are available in order to address unmet medical needs, when benefits of early access outweigh the risks due to limited data (centralised procedure)



A key tool for early access:

- Promising products can be authorised several years earlier.
- Comprehensive data are still generated after authorisation.

Conditional Marketing Authorisation - continued



Scope (at least one):

- Intended for treatment, prevention or diagnosis of **seriously debilitating diseases or life-threatening diseases**;
- To be used in **emergency situations**, in response to public health threats;
- Designated as **orphan** medicinal products.

Requirements (all):

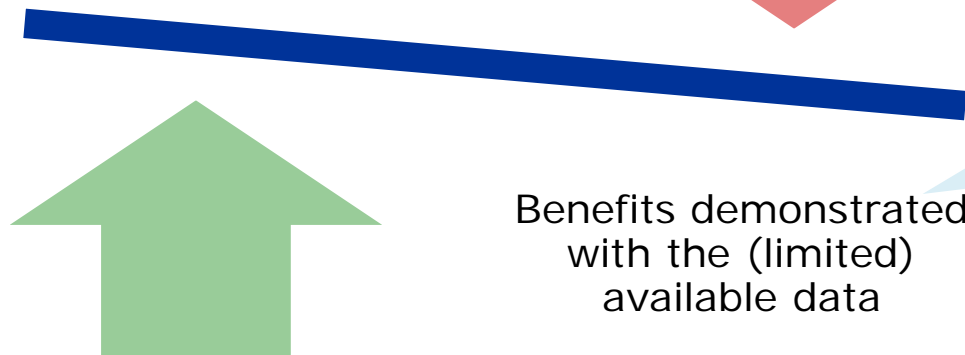
- The **benefit-risk balance** is **positive**;
- It is **likely** that the applicant can **provide comprehensive clinical data**;
- **Unmet medical needs** will be fulfilled;
- The **benefit to public health of the immediate availability** of the medicinal product outweighs the risk inherent in the fact that additional data are still required.

B/R balance in absence of comprehensive data

Risks identified in the studies conducted + risks related to the absence of some of the data



Disproportionate from the public health perspective to delay the approval of the medicinal product



Benefits demonstrated with the (limited) available data

could potentially be based on intermediate endpoints that are reasonably likely to translate into clinical benefit, but do not directly measure the clinical benefit (benefits must outweigh the uncertainties about the extent of the clinical benefit it translates to)

Switch of CMA to 'full' MA

- CMA **valid for 1 year** → annual renewals including interim report on fulfilment of SOBs
- Switch when **comprehensive data submitted** (all SOBs completed) confirming a **positive B/R balance**.
- Can be made in a **renewal procedure or another procedure**.
- Based on CHMP Opinion, **EC issues decision on a 'full' Marketing Authorisation** (=not subject to specific obligations) with standard **5 year** validity.





Analysis on 10 years of experience with CMA: Key findings

'Typical' CMA includes **evidence from 2 phase II or III studies** at the time of approval.

For most CMAs, **specific obligations** were **fulfilled** in line with agreed scope and timelines.

On average **within 4 years** CMAs were **converted** into standard MAs.

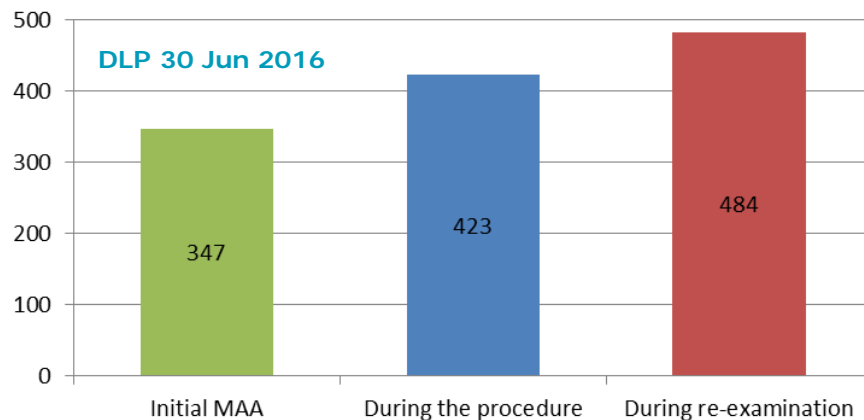
Pro-active use by Applicants linked to shorter assessment periods.

Most experience with CMAs in the **therapeutic areas of oncology and infectious diseases**.

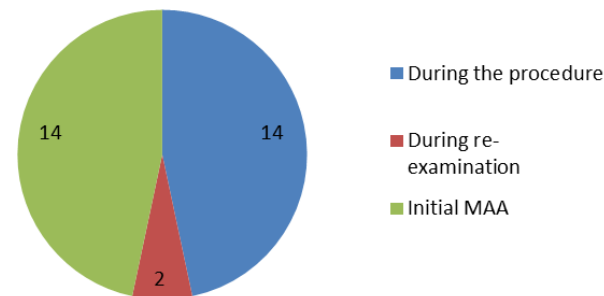


Prospective planning of CMA can facilitate the assessment

Mean duration of assessment (including clock-stops) by stage of first consideration of CMA (N=30)



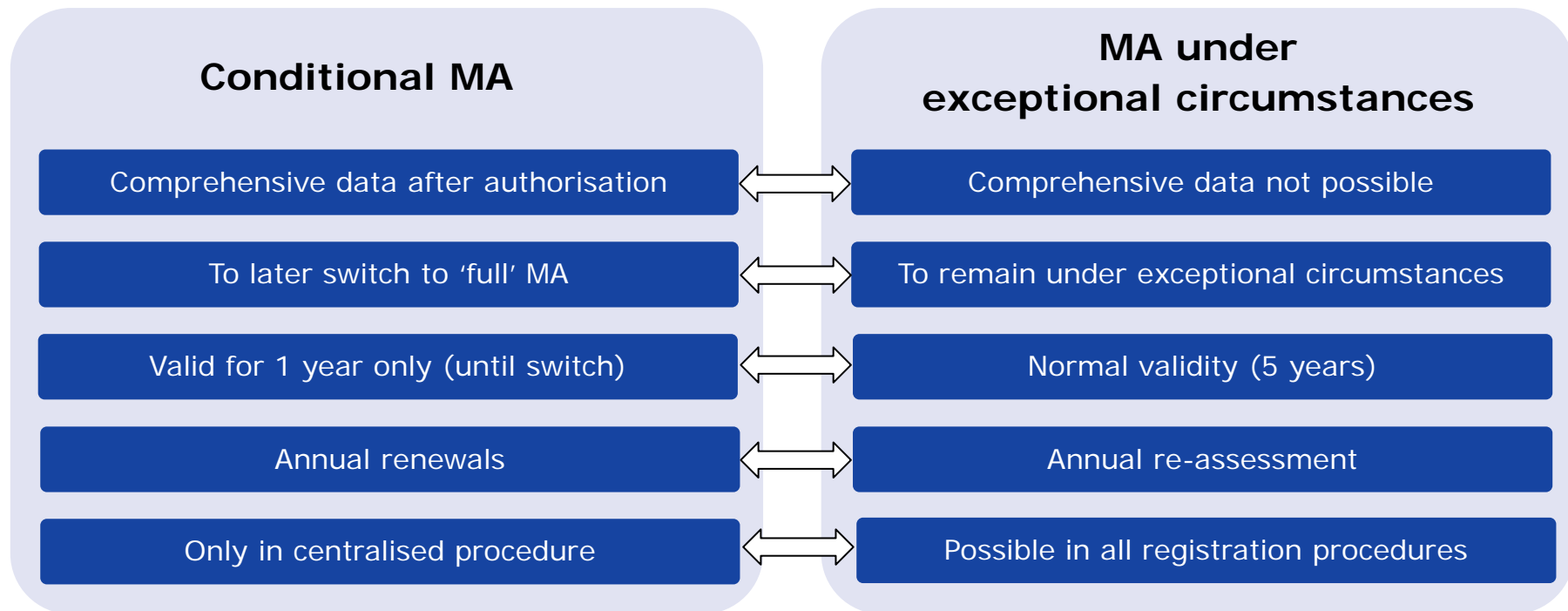
Stage of procedure, when CMA was first considered, all CMAs (N=30)



➤ Pro-actively consider

- the type of product and available data,
- adequate specific obligations,
- early interaction with the Agency (e.g. scientific advice).

Recap: CMA vs. MA under exceptional circumstances



Take home message

- Product development and choice of legal basis are interrelated.
- Consider proactively whether to apply for a conditional MA or a MA under exceptional circumstances and how additional data can be best generated post-approval (SOB).
- Consider engaging early with the Agency, in particular
 - if certain tests or trials are to be omitted or if the development deviates from guideline requirements.
 - to discuss most suitable type of MA and post-authorisation studies/SOBs.



Any questions?

Further information

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