10 July 2015

EFPIA Proposal for Options to Improve the Application of the Conditional Marketing Authorisation System in the EU (not requiring legislative changes)

Summary

In 2006, the EU fully established the conditional marketing authorisation (CMA) system to support early regulatory approval on the basis of potentially less comprehensive data to address situations of unmet medical need. Last year, the Escher Group published the results of a survey on 11 oncology products approved under the scheme for the period from 2006-2013. The analysis revealed challenges with the complexity of the procedure due to the application of standard evaluation criteria for data assessment. Moreover, the conditional marketing authorisation was often considered relatively late during an assessment procedure following application for a normal marketing authorisation procedure and thus became a "rescue option". In conclusion, assessment timelines for CMA were longer as compared to standard authorisations, and an accelerated assessment (AA) of 150 days (versus 210 days) was never applied for CMAs for oncology products. The perception in companies has been that there is a lack of sufficient incentives to request a conditional marketing upfront as a prospectively planned pathway.

Following the Escher survey EFPIA conducted a specific root cause analysis on the basis of company examples and identified problems in the following areas:

- long timelines for the assessment and lack of practice of acceleration (e.g. through combining conditional marketing authorisation with accelerated assessment);
- application in practice currently almost solely limited to the oncology therapeutic area;
- challenges with complexity of scientific discussions on specific concepts in relation to the benefit-risk assessment, such as surrogate endpoints and single arm studies (known to have led to EMA' s reluctance or discouragement for choosing the CMA route);
- approval of new indications for existing conditional marketing authorisations;
- high administrative efforts related to the annual renewal process and overlap with the PSUR assessment;
- specific challenges with complexity in adjusting specific obligations with evolving science and data;
- conversion into a normal authorisation;
- increased (perceived or real) complexity of discussions with HTA bodies and subsequent reimbursement;
- overall perception of the tool as lacking attractiveness due to a questionable balance of administrative complexity and incentives.

Evolving concepts such as "Medicines Adaptive Pathways to Patients" (MAPPS), which is expected to build on existing regulatory tools, reinforce the need to optimise the application of the CMA system.

On the basis of the analysis, EFPIA identified options to improve specific areas of interpretation and application of existing legislation and guidelines (but without changing the legislation) to ultimately encourage a CMA as more pro-active pathway while maintaining the possibility to switch during an ongoing application for a marketing authorisation (rescue option). Proposed options include scientific and procedural aspects and are detailed in the Annex. In summary:

Patients and pharmaceutical companies would benefit from improvement in the following areas:

- scope of "seriously debilitating" and "life threatening diseases" accepted to include long-term chronic disease areas such as **Alzheimer and Parkinson Disease** (1.1);
- the requirement for addressing "unmet medical need" to include **major improvements in patient care** as a quality criterion (1.2);
- **acceleration of the process** through the possibility to apply a "rolling review" (2.3), an "accelerated assessment" by the CHMP (2.1, 2.2) and an accelerated decision making" by the European Commission (2.5).

Pharmaceutical companies are expected to more proactively request a conditional marketing authorisation if the following areas are addressed:

- early scientific advice to kick off an **early and regular dialogue** and prospective planning as part of the EU Network' s planned **"European early stage innovative medicines designation"**[1] with a view to optimise and accelerate the development and assessment for individual products (2.4 and 3.1);
- **scientific re-assessment** of the current position and interpretation of alternative **study designs, outcomes and surrogate endpoints** across therapeutic areas (4.1);
- evolving science and integrated evidence generation over the lifecycle of a product to be considered in the assessment of a **positive benefit-risk ratio** of a medicine (5.1);
- improving efficiency of administrative efforts through streamlining detailed provisions for the **annual renewal process** for conditional marketing authorisations while avoiding duplications (6.1. 6.2);
- opening up the possibility to submit a **variation** to an existing marketing authorisation for a CMA (7.1) or to vary a CMA with new indications (7.2).

Timely, planned and consistent involvement of HTA bodies into the dialogue process, which is currently being addressed through other discussions (i.e. parallel scientific advice, SEED, adaptive pathways) is of key importance, in particular for CMA and final access of medicines authorised under this scheme to patients.

EFPIA is convinced there is a need to communicate, once established, a **renewed holistic perspective on CMA** in combination with and demarcation to other regulatory tools (full authorisation, PAES/ PASS, adaptive pathways etc.). This could be established through discussion, including examples of real life assets, and as part of a broad stakeholder change management process (8.1).

Finally, certain aspects have been identified as potential roadblocks in the application of the conditional marketing authorisation scheme, however addressing those most likely requires legal change. These include, in particular, the annual frequency of the renewal, a limited company benefit from the data protection incentive since the clock starts with the CMA (and not with the full authorisation) and the complex decision making process at the European Commission (and not at the European Medicines Agency which is currently responsible for the scientific assessment but not for decision making). Other challenges beyond regulatory include the development of new concepts for pricing and reimbursement. These aspects may equally be bottlenecks for a scaling up of the adaptive pathways concept.

EFPIA is prepared to participate in a constructive dialogue on the above options and points, including on developing and fine-tuning criteria and processes for the "European early stage innovative medicines designation" concept and to further contribute to the discussions with additional data, pilot projects, real life and modelled examples.

[1] See consultation draft for an „EU Medicines Agencies Network Strategy 2020" including „European Early Stage Medicines Innovation" (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500185138.pdf)

Annex

Key Improvement Area	Proposed Option	Reference
1 CMA: Scope of application and requirements	1.1 Scope of application: The interpretation of **"seriously debilitating"** or **"life-threatening" diseases,** for the purposes of granting CMA, should be clarified as to also encompass disease areas where serious debilitation or life-threatening outcomes are expected in the mid to long-term (e.g. Alzheimer and Parkinson Disease).	• EMA (CHMP) Guideline 509951/2006 (CMA), Point A 1.1 (1) • EMA (CHMP) Guidelines for different therapeutic areas
	1.2 Requirements: The interpretation of **"unmet medical need"** and in particular the reference to **"major therapeutic advantage"** should be clarified to encompass • **major improvements in patient care** alternatively to the currently required "meaningful improvement of efficacy or clinical safety". Improvements in patient care could, for instance, be achieved with optimised formulations or be measured through improved patient reported outcomes or quality of care. Examples: ○ reduced hospitalization, ○ prolonged independent living for a longer period (e.g. Alzheimer), ○ preventing blindness (age-related macular degeneration), ○ replacement of high interventional by low interventional procedures (e.g. bone marrow transplantation replaced through medication in oncology), ○ patient reported outcomes, e.g. in patient diaries or by healthcare professionals (survival, morbid events (stroke, myocardial infarction), disease recurrence, caregiver burden), improvement of compliance showing improvements on effects on serious conditions; • medicinal products which have been identified to bring a **"significant benefit**" (which may include superiority over an existing treatment) under the Reg. 141/2000 (OMP), whereas the interpretation of what constitutes a **"satisfactory method of diagnosis, prevention, treatment"** should ○ refer, but not be limited to the regulatory situation (i.e. approved drug in a given indication) and ○ take appropriate account of the clinical aspects (e.g. enhanced efficacy or a better safety profile) or ○ take appropriate account of the short term benefits for patients (and health care professionals) or of the long term benefit for society (e.g. antibiotics/	• COM Reg. 507/2006 (CMA), Art. 4 (1c) & 4 (2) Art. 4 (2): '**unmet medical need'** 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 concerned will be of **major therapeutic advantage** to those affected. • EMA (CHMP) Guideline 509951/2006 (CMA), Point A 1.2 (c) • Reg. 141/2000 (OMP), Art. 3(1) A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish (a) (…) 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. • COM Reg. 847/2000 (OMP), Art. 3(2) For the purpose of implementation of Art. 3 of Reg. 141/2000 (…) **significant benefit** means "**a clinically relevant advantage or a major contribution to patient care."**

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	antimicrobial resistance).	
2 Shorten timelines for CMA Approval	2.1. Clarification: A product which **"fulfills unmet medical needs"** and which is planned to be submitted for a conditional marketing authorisation automatically falls under the category of **"major interest from the point of view of public health and from the point of view of therapeutic innovation"** stipulating the possibility for the applicant to request an accelerated assessment procedure.	• COM Reg. 507/2006 (CMA), Art. 4 (1c) & 4 (2) • Reg. 726/2004, Art.14 (9) • EMA (CHMP) Guideline 419127/05 (AA)
	2.2 **Upon request by the applicant** the **application for an accelerated assessment procedure** (AA) of **150 days** will automatically be accepted for requests for Conditional Marketing Authorisations (CMA). Specific considerations: Applicants accept that the application of the accelerated assessment procedure continues to include the obligation to respond within 1 month (30 days) after Day 120. If companies need more than 30 days for responding to questions, it is accepted that the AA may be converted into a procedure with normal timelines of 210 days.	• Reg. 726/2004, Recital 33 and Art. 14 (9) • COM Reg. 507/2006 (CMA), Recital 7
	2.3 **Upon request by the applicant or the Agency** a **rolling review process** (following rolling review experiences with pandemic and provisions for ebola vaccines) will be applied for products intended to be submitted for a conditional marketing authorisation with a view to speed up the assessment process. The following **elements** are critical for an efficient and successful establishment of a rolling review process: • need to discuss and mutually agree the rolling review between the applicant and the (Co)-Rapporteur latest at the pre-submission meeting; • formal request to be submitted with the letter of intent; • need to mutually agree specific deliverables and a time schedule; • as a general rule, deliverables should include complete sections, such as the entire CMC, toxicology or clinical section unless ○ subsections would constitute a reviewable unit and be useful in making the review process more efficient, e.g. ▪ section on CMC data incorporating risk based approaches could be submitted in iterative steps, ▪ section lacking final consistency lot data and long-term stability data, ▪ toxicology section lacking chronic toxicology data, ▪ final study reports for some or all of the principal controlled trials without integrated summaries, or ○ justified for reasons for addressing urgent public health needs;	• US Guideline on Expedited Programs Relevant US guidance • EMA Work Instructions on Rolling Review: IPM 7.2 Non-core dossier approved MA: rolling review (prior to submission of marketing authorisation application) as part of the EMA Pandemic Influenza Crisis Management Plan

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	• the Agency will start the review of sections submitted before the full the dossier has been submitted; • the formal assessment procedure (and clock) will start once the full dossier has been submitted by the applicant; • the shortening of the formal assessment procedure will be considered (latest following submission of the dossier); • accelerated assessment (2.2) and rolling review (2.3) are not mutually exclusive but both will be triggered through specific request. Rationale: especially during an accelerated assessment a rolling review may significantly support acceleration of timelines by enabling the start of the review of certain sections of the dossier before official clock start.	
	2.4 The **Agency will support the early preparation of the CMA**, in particular through • enhanced early interactions with the regulators and HTA bodies, • early consideration of accelerated assessment and rolling review, in particular once the Rapporteur/ Co Rapporteur are appointed (see also 3.1 below), • ensuring that other activities and considerations (e.g. concerning orphan medicines) will not prolonging the timelines of the assessment process).	
	2.5 EU COM to automatically combine accelerated assessment (and upon applicant request CMA) with an **accelerated decision making** by the European Commission. Expected acceleration (reduction) for the full procedure: from max. 67 to max. 30 days. Particular focus should be given to the reduction of the Standing Committee procedure to significantly less than 22 days (max. 5 days for situations where there is a high public health interest and which stipulate an "urgency" or "extreme urgency").	• Reg. 726/ 2004, Art. 10 and 87 (3) • Rules of Procedures for the Standing Committee on Medicinal Products for Human Use (SANCO/D/3/PB/SF/ddg.1.d.3 (2011)1118442), in particular Art. 3 (2) and 8
3 Early and frequent stakeholder dialogue	3.1 Early scientific advice to kick off an **early and regular dialogue and prospective planning** as part of the EU Network' s planned **"European early stage innovative medicines designation"** involving relevant stakeholders (in particular regulatory agencies, HTA bodies, companies, payers, patients, HCPs). Objective: The objective of the dialogue should be to optimise and accelerate, on a case-by-case basis, the development and assessment for individual products. This can be established by taking a holistic approach (regulatory and HTA assessment) for an improved mutual understanding of expectations for regular, conditional marketing authorisations and authorisations under exceptional circumstances with a view to support patients' early access to medicines.	• EU Medicines Agencies Network Strategy to 2020 (EMA/HMA), Consultation draft 27 March 2015, Ch.3, Theme1, Objective 3 • New specific EMA guidelines need to be established to implement above Network Strategy

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4 Acceptance of alternative trial designs and surrogate endpoints	4.1 **Scientific re-assessment** of current position and interpretation of **alternative designs** (e.g. single arm studies), **surrogate endpoints** (e.g. Overall Response Rate (ORR) in Oncology) and **outcomes** should be considered across therapeutic areas taking into account evolving science, e.g.: • better understanding and stratification of diseases; • increased potential to better select and target suitable patient populations (e.g. biomarkers, Next Generation Sequencing); • new trial designs, such as basket trials targeting various diseases with the same biomarker; • increased potential to establish high quality efficacy data in smaller patient populations leading to early approvals (recent examples discussed by FDA and EMA); • possibility to generate further safety data post marketing (including real world data) with regulatory tools which allow legal enforceability (e.g. post marketing conditions and specific obligations: post authorisation safety studies (PASS), registries, specific monitoring with black symbol)	• Relevant sections in therapeutic area guidelines (in particular Oncology, Alzheimer)
5 Positive Benefit-Risk Balance	5.1 Interpretation of "the **benefit-risk balance** to be positive" in the case of unmet medical need if • the evidence provided in the application is <u>reasonably likely to</u> establish a positive benefit-risk balance for a conditional marketing authorisation; • there is a substantial benefit and a lack of potential significant harm. <u>Rationale:</u> • An approval on the basis of strong efficacy data in a limited number of patients (e.g. stratified patient populations, rare disease populations) may have to be based on limited safety data in order to make the product accessible to a broader patient community at an early stage. Consequently, there may be a degree of uncertainty with respect to the assessment of the risk while the efficacy data may be strong. • In situations of high unmet medical need the application of traditional clinical trial methodologies may be limited, e.g. where ○ the only current option is palliative/best supportive care, ○ no randomised comparison may be acceptable; ○ ethical considerations lead to cross over of patients from best supportive care to the new experimental drug after a short period of time or progression. In these situations the benefit-risk ratio of a medicinal product can be established relative to the high unmet need setting, while fully	• COM Reg. 507/2006 (CMA) Article 4 (1) • EMA (CHMP) guideline 509951/2006 (CMA), Point 1.2 (a) and 4 • Reference to specific case studies in the US (currently under development by EFPIA)

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	confirmative data may only be generated in clinical trial settings where no methodological limitations exist (e.g. with settings with established standard of care). Yet, the data from this setting should be requested and provided as condition to the CMA.	
6 Annual renewal process	6.1 **Refine interpretation for the annual renewal system** for conditional marketing authorisations with a focus on updating information which has changed: • The applicant should be requested to confirm in a simple way which information remains unchanged. • The requirement to submit documents/ information should be limited to the following: ○ **Addendum to clinical overview** to include only new information or data from the external environment (whereas the submission of the safety part in the clinical overview will be streamlined with the PSUR – see point 6.2); ○ **Interim report** (as part of the addendum to the clinical overview) on the fulfilment of specific obligations including an assessment of new data; ○ **Listing of any variations** and **notifications** submitted since authorisation or last renewal (line listing). • Changes to other aspects than the above will require submission of a variation. Rationale: To rationalise administrative efforts there should be a strong reliance on data/information previously submitted. Therefore, the focus of any application for renewal should be exclusively on data/information which has changed since the granting of the first CMA/ latest renewal and on new data (as opposed to current practice of duplications).	• COM Reg. 507/2006 (CMA), Art. 6 • EMA (CHMP) guideline 509951/2006 (CMA), Point B • EMA Guideline on post authorisation procedural advice May 2015 EMEA-H-19984/03 Rev. 51, No. 10 (in particular 10.3)
	6.2 Streamline submission date for **safety part of annual renewal** (as presented in the addendum to the clinical overview) with date of PSUR "birthdate" through synchronization of data lock points (DLP). Allow for the safety-related content in the renewal clinical overview addendum to cross-reference with the PSUR.	• COM Reg. 507/2006 (CMA), Recital 11, Art.6 & 9 • EMA (CHMP) guideline 509951/2006, Point B • EMA Guideline on post authorisation procedural advice May 2015 EMEA-H-19984/03 Rev. 51, No. 10

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7 Flexibility in applying variations	7.1 Establish interpretation that a **CMA may apply to new indications** submitted as part of a type II **variation or extension procedure to a normal marketing authorisation.** Such a concept should in particular • allow to limit only the new indication to be categorized as CMA (with an information about the CMA status of the indication in the label and SPC); • establish the possibility to make the CMA subject to fulfillment of specific obligations (as with the "regular" CMA); • establish an annual review for the new indication in alignment with the requirements for the CMA, for example through inclusion in the specific obligations (see 6.1, 6.2). Example: a medicine may have received normal authorisation in lung cancer as a first indication; the envisaged second indication will be in liver cancer but needs to be based on less comprehensive data. Such examples are expected to increase with a stronger focus on biomarker driven research (e.g. basket trials).	
	7.2 Establish interpretation that **CMA may be varied for new indications** if the collection of comprehensive data to convert the initial CMA into a normal authorisation is very long term. Example: a medicine may have been authorised under conditional marketing for the indication in Alzheimer and the fulfillment of specific obligations will take a longer period. In the meantime, efficacy may be established for other neurological indications which should be submitted as a variation.	• EMA (CHMP) guideline 509951/2006 (CMA)
8 Renewed holistic perspective – stakeholder change management process	8.1 With the renewed interpretation a **stakeholder change management process** should be proactively set up with a view to • establish and inform about a renewed holistic perspective on the application of the conditional marketing authorisation in combination with and demarcation to other regulatory tools; • set up stakeholder interactions, including workshops with focus on ○ implications of evolving science and data generation in medicines development (see 4.1) for ▪ regulatory risk based decision making, ▪ revised thinking on applying post authorisation regulatory measures, ▪ application and combination of existing regulatory tools (e.g.including PASS, PAES) ○ developing and informing on a renewed approach for applying CMA (following agreement on options for improvement); ○ addressing the overall (currently negative) perception of CMA as a challenging concept (including handling	

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	and adaptations of specific obligations and conversion into full authorisation); ○ reassessing the benefits from incentives (e.g. regulatory data protection); ○ learning and improving the system through real life assets (pilots) in a safe harbor; whereas • stakeholders in the discussion should include at least the scientific level (CHMP), HTA, payers, industry, patients, healthcare professionals (HCPs).	

References:

- **Regulation (EC) No 726/2004** of the European Parliament and the Council of 6 November 2001 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended (herein "Reg. 726/2004")
- **Commission Regulation (EC) No 507/2006** of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council (herein after referred to as "COM Reg. 507/2006 (CMA)")
- **Regulation (EC) No 147/2000** of the European Parliament and the Council of 16 December 1999 on orphan medicinal products (herein after referred to as "Reg.147/2000 (OMP)")
- **Commission Regulation (EC) No 847/2000** of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority (herein after referred to as "COM Reg 847/2000 (OMP)")
- Consultation Draft of **CHMP Guideline** on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No. 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (herein after referred to as "EMA (CHMP) Guideline **509951/2006** (CMA)")
- **CHMP Guideline** on the procedure for accelerated assessment pursuant to Art. 14 (9) of Regulation (EC No 726/2004 (herein after referred to as "EMA (CHMP) Guideline **419127/05** (AA)")
- **EMA Guideline on post authorisation procedural advice** May 2015 EMEA-H-19984/03 Rev. 51 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf)
- **EMA Work Instructions on Rolling Review**: IPM 7.2 Non-core dossier approved MA: rolling review (prior to submission of marketing authorisation application) as part of the EMA Pandemic Influenza Crisis Management Plan http://www.ema.europa.eu/docs/en_GB/document_library/Work_Instruction_-_WIN/2009/09/WC500003249.pdf)
- **Rules of Procedures for the Standing Committee** on Medicinal Products for Human Use (SANCO/D/3/PB/SF/ddg1.d.3(2011)1118442); (http://ec.europa.eu/health/files/pharm_stand_comm/2011_09_13_human_scrutiny.pdf)
- **EU Medicines Agencies Network Strategy to 2020 (EMA/HMA)**, Consultation draft 27 March 2015 (EMA/MB/151414/2015) (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500185138.pdf)
- **Procedural Guidance by U.S.** Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) May 2014: Procedural **Guidance for Industry - Expedited Programs for Serious Conditions – Drugs and Biologics** (herein after referred to as "US Guideline on Expedited Programs") (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)
- **Escher Report:** Improving the EU system for the marketing authorisation of medicines: Learning from regulatory practice (http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf)