25 February 2016
EMA/647097/2015
Committee for Medicinal Products for Human Use

Overview of comments received on '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 (EMA/CHMP/509951/2006, Rev.1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Alexion Pharma GmbH
2	ANSM (French Health products Safety Agency) – Evaluation Division
3	BEUC – The European Consumer Organisation
4	BIO Deutschland e.V. – the German Biotech Industry Association
5	Cancer Research UK
6	Centre for Health Technology Evaluation, National Institute for Health and Care Excellence (NICE)
7	EFPIA - European Federation of Pharmaceutical Industries and Associations
8	EORTC: European Organisation for Research and Treatment of Cancer
9	EuropaBio - the European Association for Bioindustries
10	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
11	European Organisation for Rare Diseases (EURORDIS)
12	Health Action International (HAI), the International Society of Drug Bulletins (ISDB) and Medicines in Europe Forum (MiEF)
13	IABS-EU as a member of the IMI – Zoonoses Anticipation and Preparedness Initiative
14	International Plasma Fractionation Association (IPFA)
15	Norwegian Medicines Authority (NOMA)
16	Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel (Federal Institute for Vaccines and Biomedicines)

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Stakeholder no.	Name of organisation or individual
17	Pharmaceutical Group Of the European Union (PGEU)
18	REGenableMED consortium (REGenableMED is a United Kingdom Economic and Social Research Council (ESRC)-funded project)
19	Teva Pharmaceutical Industries Ltd

1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
General messages on Conditional marketing authorisation and the guideline		
1	Alexion welcomes the revision of the guideline for the practical arrangements of the Conditional Marketing Authorisation (CMA) to include learning experience of assessment of past applications.	
4	BIO Deutschland welcomes the opportunity to respond to this public consultation, which is of particular interest to our members.	
5	Adaptive pathways Cancer Research UK believes that all cancer patients should have access to the best, evidence-based interventions for their disease. This means that while it is imperative to get new treatments to patients as soon as possible, particularly in life-threatening diseases such as cancer, it must be done in a robust and evidence-based way. We have welcomed the EMA's efforts to improve timely access for patients to new medicines, notably its Adaptive Pathways pilot. Whilst national schemes, such as the UK's Early Access to Medicines Scheme (EAMS), are being explored, we believe that the real value to accelerating the development pathway will be found in the delivery of an effective adaptive approach that is relevant across all member states. Whilst it has been argued that the existing regulatory framework could allow for an effective adaptive pathway, we are concerned that current mechanisms are not well understood by smaller commercial developers and may be under used as a result. Accelerated Assessment and Conditional Marketing Authorisation are key mechanisms to accelerate patients' access to medicines that address unmet medical needs. We welcome the EMA's intention to revise guidance relevant to these schemes in order to optimise their use by	The EMA recognises the importance of providing clear guidance and support during the development phase of the products. Various tools already exist for this purpose (e.g. SME office support, scientific advice) whilst new activities are being undertaken (e.g. PRIME scheme). Regarding the proposal to publish case studies, we would like to clarify that the European public assessment reports contains the relevant information and the products with conditional marketing authorisation can be identified on the search page for human medicinal products (using "browse by type" tab). The EMA is consolidating the information on this authorisation type and other tools for early access to medicines in a dedicated page on the EMA's website, and will also be summarising the 10-year experience with conditional marketing authorisations.

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	companies developing new medicines. Having assessed the revisions, we do think that they go some way to clarifying these mechanisms. Following its introduction, it will be important for the EMA to seek feedback from companies on whether this updated guidance is effective in its intended purpose of clarifying these schemes. We welcome that the revised guidance emphasises the importance of early dialogue with the EMA. Such an approach gives the organisations developing new treatments more certainty about the approach they take to gathering evidence and how it will be treated during assessment. In addition to amending guidance, it is important that the EMA explores mechanisms to better communicate adaptive pathways. This would help ensure wider participation, for example of SMEs who may have limited prior experience of applying for Conditional Marketing Authorisation or Accelerated Assessment. In addition to better signposting of these mechanisms to both academic and commercial developers, the EMA should also consider developing case studies of medicines that have had an Accelerated Assessment or been granted a Conditional Marketing Authorisation to clearly demonstrate (where relevant): • The value of early dialogue with the EMA and how best to approach this • How to justify fulfilment of major public health interest • The fulfilment of unmet clinical needs • How a positive benefit-risk balance will be substantiated where that are less complete data • The extent and type of data required to be included in annual renewal submissions Relevant information could be taken from an appropriate selection of	

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	European Public Assessment Reports in order to develop these case studies.	
7	EFPIA welcomes the revisions to the Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation (CMA) for medicinal products for human use falling within the scope of Regulation (EC) No 726/ 2004.The relatively small number of CMAs indicates a revision to the guidance is needed in particular to increase the applicability in the oncology field and beyond. While the system would benefit from changes of regulatory and scientific approaches, EFPIA is convinced that there is a need for a renewed holistic perspective on CMA in combination with and demarcation to other regulatory tools (full authorisation, PAES/PASS, etc.).	The comments are noted. The revision of this guideline is indeed conducted in parallel with other activities aimed at facilitating early access to medicines addressing unmet medical needs, and further analysis of the experience will also be carried out in the future.
7	A review of and report on the experiences with the revised system latest within 1-2 years after adoption of the guideline will be important to allow adjustments in scope with expectations.	The Agency intends to review the experience following the update of the guideline within an appropriate timeframe (the timing remains to be determined, as information on the completion of specific obligations is required for a meaningful analysis).
7	Finally, in commenting on the draft guideline EFPIA makes reference to its " Proposal for Options to Improve the Application of the Conditional Marketing Authorisation System in the EU (not requiring legislative changes)": http://www.efpia.eu/uploads/Modules/Documents/2015_07_10_efpia-cma-options-for-improvement-(1).pdf	
9	EuropaBio welcomes the opportunity to respond to this public consultation, which is of particular interest to our members. Increasing MAHs' understanding of when to use and how to apply for the Conditional Marketing Authorisation (CMA) procedure more	The EMA recognises the importance of providing clear guidance and support during the development phase of the products. Various tools already exists for this purpose (e.g. SME office support, scientific advice) whilst new activities

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	efficiently is very important for our corporate members, as they develop and manufacture innovative biotechnology products that address unmet medical needs. Within the pharmaceutical industry, EuropaBio represents companies and national associations that are active in the biological market, representing both innovator and biosimilars developers. EuropaBio has had sight of the response to this consultation by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and supports the comments submitted by EFPIA.	are being undertaken (e.g. PRIME scheme). The advantages and importance of prospective planning of applications for conditional MA are being highlighted in the Guideline.
10	With reference to a recent discussion with different Stakeholders, it is important that the CMA procedure is used and seen in a positive manner. To reinforce the idea that CMA is an indicator of innovation, Stakeholders would need to see positive precedents of submissions of CMA (upon request from MAH) converted to a full approval (upon review by EMA). To support this it may be important to introduce and clarify the difference between specific obligations versus post-follow up commitment. EUCOPE understands that the new pharmacovigilance tools may also allow and support this; examples would be welcomed and could be added to the Section 4.1.2.	The EMA is consolidating the information on this authorisation type and other tools for early access to medicines in a dedicated page on the EMA's website, and will also be summarising the 10 year experience with conditional marketing authorisations. Starting in Q2 2016 the EMA will also publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed). Difference between specific obligations and other post authorisation measures is currently addressed in the questions and answers on the EMA's website (see sub-section "Post-authorisation measures: questions and answers" under Human regulatory > Post-authorisation section of the EMA's website).
13	The IMI-ZAPI members welcome the draft GL and are happy to have the possibility to comment. The comment made conclude the ongoing discussions and actions within the project how to ensure quick licencing of platforms (vectors) in case of emergency situations.	
15	The revised guideline has been discussed in the management board	Some editorial improvements to the text of the guideline

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	at NOMA. We support and appreciate the proposed changes. However, it should be possible to develop a more reader-friendly and better structured document. We find the revised guideline on Accelerated assessment more easy to read and understand.	have been implemented. Since multiple aspects of conditional marketing authorisation (e.g. scope, requirements for recommending CMA, provision of comprehensive data after authorisation, annual renewals) need to be addressed in the guideline, it is not considered possible to simplify the structure of the document.
17	We welcome the opportunity to comment on 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.	
18	All the partners of the REGenableMED project are aware of the existence of this draft Guideline. We welcome the opportunity to review this 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.	
General comments on the extent to which the conditional marketing authorisation provisions should be applied		
3	BEUC welcomes the opportunity to comment on the EMA's guidelines on the scientific application and practical arrangements necessary to implement conditional marketing authorizations. Licensing medicines on the basis of less comprehensive data than is normally required should only be done in narrowly defined and duly justified situations. There are concerns that requirements for post-marketing studies are not enforced, which means there is little oversight of the higher risks patients are exposed to and little data is generated to improve the situation. Evidence from Canada's early access policy shows that	The Guideline elaborates the principles set by Regulation (EC) No 507/2006 that conditional marketing authorisation is restricted to certain product types and requires fulfilment of several criteria, in particular the positive benefit risk balance and fulfilment of unmet medical needs. The CHMP considers that these requirements are being followed, as explained in the European Public Assessment Reports of the products with conditional marketing authorisation.

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	there is little oversight of manufacturers' duties to confirm medicines' clinical benefits in post-marketing studies. Studies are executed for some medicines in as early as 1.4 years after authorisation, while for other medicines these commitments were still unfulfilled after seven years.1 With these concerns in mind, we have made several specific recommendations below for the guideline on conditional market authorization.	
12	The pharmaceutical marketing authorisation procedure is a health protection measure. EU pharmaceutical legislation provides that, as a general rule, before a medicine is authorised it has to undergo ''extensive studies to ensure that it is safe, of high quality and effective for use in the target population''. The importance of maintaining the requirement for solid evidence about benefits and harms before a medicine is approved as the corner stone of pharmaceutical regulation must be emphasised. Pre-market efficacy evidence is an important health protection measure as it protects patients from a potentially harmful exposure to medicines without solid scientific evidence of a benefit to health. The current marketing authorisation procedure emerged as a response to a series of drug-induced disasters and has been in place for more than 50 years. However, several attempts have been made to expand the use of premature and accelerated approvals for new drugs, particularly over the last decade. The paucity of new medicines that offer even a modest therapeutic advantage stands in stark contrast to the large number of new products that expose patients to unjustified risks. The majority of new medicines are "me-too" drugs and not "innovative" since they do not demonstrate any added therapeutic value. A recent study found that 66% of phase III trials conducted between 2007 and 2010 were	The CHMP does not regard the conditional marketing authorisation as entailing lowering the requirements, but rather as a legitimate opportunity for the patients to have earlier access to a new therapeutic option and thus satisfy an unmet medical need, with careful weighting of benefits and risks of such an earlier authorisation. This approach also ensures that comprehensive data are still generated on the product in line with agreed timelines.

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	terminated for lack of efficacy. This is a failure that adaptive licensing won't address. Rather than lowering the requirements for marketing authorisation, the EMA should favour the demonstration of a new drug's therapeutic advance when compared to the best available therapeutic option. This would act as an incentive to reorient research and development towards unmet health needs and true therapeutic progress. It is regulation for innovation.	
12	Several mechanisms are already available to allow faster patient access to new medicines. Over the last 20 years, regulatory approaches have been adopted both in the US and in the EU to ensure that patients have early access to new medicines. In the US, several expedited drug approval schemes have been put in place from 1992 onwards, such as the "accelerated approval" and "priority review" (1992), "fast-track" (1997) and "breakthrough therapy" or "special medical use" (2012). In the EU, mechanisms providing faster patient access to new medicines include "approval under exceptional circumstances" (1993) and "conditional marketing authorisations" (2005). Approval under exceptional circumstances in the EU covers those medicinal products for which the applicant can demonstrate that comprehensive data on efficacy and safety cannot be provided due to specific reasons foreseen in the legislation (e.g. it could apply to very rare diseases). Conditional approvals can be granted in the absence of comprehensive clinical data but are subject to specific obligations to ensure that the missing data is provided subsequently, in a short timeframe. According to EU legislation, this mechanism is to be used in exceptional circumstances in order to meet unmet medical needs of patients and in the interests of public health. The submission of	The Guideline elaborates the principles set by Regulation (EC) No 507/2006 that conditional marketing authorisation is restricted to certain product types and requires fulfilment of several criteria, in particular the positive benefit risk balance and fulfilment of unmet medical needs. The CHMP considers that these requirements are being followed, as explained in the European Public Assessment Reports of the products with conditional marketing authorisation.

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	less complete data does not preclude the fact that there needs to be a positive risk-benefit balance at the time of conditional approval. In addition to these two schemes, "compassionate use" mechanisms are available in many Member States. They allow physicians and patients to apply for access to an unapproved therapy, or one that is still under consideration for approval if they have a life-threatening condition and approved treatments have failed, or there are no treatments currently approved. Legitimate when there is an unmet health need. These "expedited" schemes are legitimate when there is a real unmet health need. But just like any other patient, those suffering from rare diseases or life-threatening conditions also deserve drugs approved on the basis of concrete evidence of benefit, not just hope value or interim clinical trial results. As recently stated by seasoned AIDS activists and health researchers: "patients need knowledge—answers about the drugs they put in their bodies—not just access". Unsuccessful previous attempts to introduce premature new drug approvals in the EU. During the last 15 years, the European Commission has made several attempts to deregulate the framework for new drug approvals in the EU. For example, the proposal for a new pharmacovigilance regulation and directive foresaw the expansion of "conditional marketing authorisations" to all new drugs and not just for unmet medical needs. The aim of the European Commission was to reduce R&D costs and provide pharmaceutical companies with "a faster return on investment". To prevent exposure to insufficiently evaluated medicines and their adverse drug reactions, the European Parliament and the Health Ministers of Member States reiterated the need to ensure that "a strengthened system of pharmacovigilance does not lead to the premature granting	

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	of marketing authorisations". Ultimately, the proposal to expand "conditional marketing authorisations" to all new medicines was rejected and is not part of the 2010 pharmacovigilance legislation.	
12	Lessons learnt from the last decade about accelerated-access schemes: faster marketing authorisations have implications for health outcomes and patient safety. Faster patient access to medicines also means increased health risks and fails to guarantee better therapy. The findings from initiatives providing faster patient access to new medicines are even more worrying. In the US, after 16 years of follow-up, researchers have found that drugs approved following legislative changes introduced to speed up the approval process were more likely to be withdrawn or receive new "black-box warnings" than drugs authorised prior to the bill's passage. A black box warning is the FDA's most serious safety warning and often refers to life-threatening risks. According to another study, drugs approved under expedited review were not as thoroughly tested as those that received a standard review. This implies that many hundreds of thousands or even millions of people may be exposed to a drug later considered to be unsafe. In Canada, drugs approved through the priority pathway had a 34% chance of receiving a serious safety warning compared to a 19% chance for drugs approved through the standard pathway. According to data from the European Commission, the timelines for drug licensing have dramatically shortened over the last 10-20 years, sometimes posing threats to patient safety. Premature licensing is achieved at the expense of proper evaluation, leading to more pharmacovigilance problems down the line. The EMA should not shorten the timelines for decision-making, as that is likely to speed up approvals based on weak evidence.	The Guideline elaborates the principles set by Regulation (EC) No 507/2006 that conditional marketing authorisation is restricted to certain product types and requires fulfilment of several criteria, in particular the positive benefit risk balance and fulfilment of unmet medical needs. The CHMP considers that these requirements are being followed, as explained in the European Public Assessment Reports of the products with conditional marketing authorisation. The importance to ensure access to medicines (and not just their approval) is recognised, therefore the Guideline encourages involvement of health technology assessment bodies in early dialogue. This is regarded important for facilitating a timely decision regarding the reimbursement.

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	Drugs approved under expedited procedures do not necessarily offer a therapeutic advantage to patients. The independent drug bulletin Prescrire has assessed 21 drugs "approved conditionally" in the EU since 2006 and rated them as follows: 24% as "not acceptable" (e.g. "product without evident benefit but with potential or real disadvantages"); 29% as having "judgement reserved" (e.g. "rating postponed until better data and more thorough evaluation become available"); 10% as nothing new, only 19% as "possibly helpful" and only 19% as clearly "offering an advantage" (See Chart 1). These results indicate that most medicines approved conditionally do not meet patients' needs and that for more than one third there is insufficient evidence. A recent study from Banzi and colleagues covering the same period of conditional marketing approvals states that ''the benefit-risk profile of medicines conditionally allowed is rarely reassuring and strong enough to make the expected public health advantage outweigh the risk of limited clinical information''. Furthermore, the authors argue that while medicines granted market authorisation under conditional approval could benefit patients who suffer from severe diseases where there is no available treatment, conditionally-approved drugs are not justifiable when effective treatments are already available (e.g. breast and colorectal cancer drugs). Chart 1. EMA Conditional Approvals (2006-2014) and their Prescrire ratings (per indication)	

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	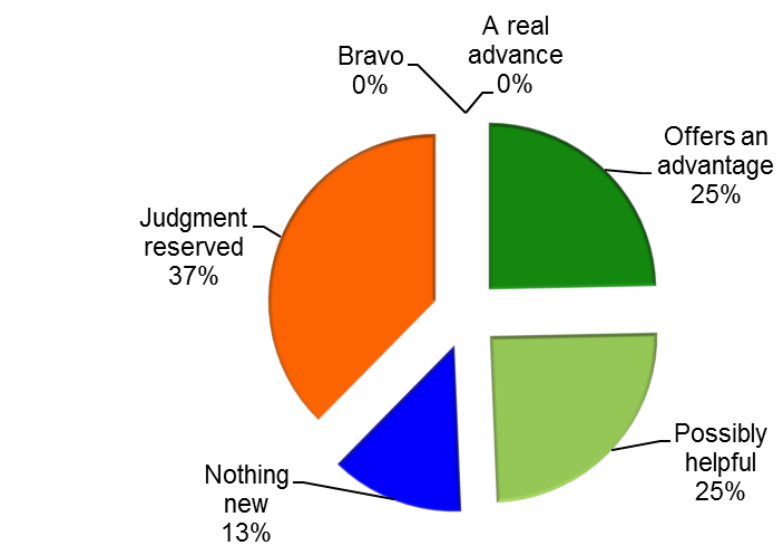 Post-authorisation commitments are often not honoured. Expedited or "conditional drug approvals are often granted by drug regulatory agencies with the requirement that the manufacturer must conduct additional post-market safety or efficacy studies within a defined timeframe ( ). However, years of experience now show that these commitments are often not honoured. A frequent reason provided is that participants are too difficult to recruit. Patients are less likely to participate in a clinical trial with all its constraints if the medicine is already available on the market. In 2007, the US Institute of Medicine reported that many drugs were allowed to remain on the market even though many of the required post-marketing studies had not been completed and confirmatory studies had not shown the expected impact on true health outcomes. In Canada, the Notice of Compliance with conditions (NOC/c) policy	

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	allows Health Canada to approve new drugs on the basis of incomplete evidence with the companies promising to do confirmatory studies. A recent study revealed that drugs approved using the NOC/c policy are much more likely to get a post-market safety warning than drugs with a standard approval. Furthermore, many of the required post-market studies are still not completed even 10 years after conditional approval was granted. It is much more difficult for regulators to remove a drug from the market once it has been approved than to refuse approval in the first place, particularly when regulators have been working closely with companies (scientific advice). In the post-marketing scenario, even in the face of new evidence of higher risks or questionable efficacy, withdrawing drugs can be a lengthy and complicated process, often faced with opposition from patient groups. In addition, shifting the burden of proof from pre-marketing to post-marketing implies that regulators have to rely on the marketing authorisation company to submit additional data to conclude the clinical assessment. In the EU, the new pharmacovigilance regulation explicitly allows drug regulatory authorities to withdraw marketing authorisations when pharmaceutical companies fail to conduct post-marketing studies. In short. The current drug approval system already offers opportunities allowing patients who suffer from conditions with an unmet medical need to have early access to a new drug. There are already specific procedures in place to allow earlier access in exceptionally justified cases. Additionally, orphan drugs are not subject to the same efficacy requirements as other new drugs. The current drug approval process does not need to be weakened. It rather needs a critical review.	

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	It is imperative to separate out these exceptional situations from the needs of the general population suffering from a condition where there are already plenty of therapeutic options available (e.g., drugs to treat hypercholesterolemia, cardiovascular conditions, psycho-active drugs, etc.). Faster patient access should not take place at the expense of a thorough evaluation of the efficacy and the safety of new drugs. Moreover, a market authorisation is not equivalent to 'patient access' as the prices of new medicines can be unaffordable to health systems and individual patients. Moves to accelerate regulatory approval could further contribute to a spiral of escalating drug prices and meet the demands of a new pharmaceutical business model: the niche-buster. By targeting specialty markets with no established therapy exists, companies can demand higher prices than the ones that can be demanded in already saturated markets.	
17	We would like to stress that patient safety and product effectiveness should not be compromised in any way, and that any conditional MA granted should not come at the cost of less robust assessment procedures. Any conditionally granted MA should adhere to the same standards as the regular assessment procedure.	Please see the response above.
Conditional authorisation for extensions of indication		
1	The CMA is limited in Europe to initial Marketing Authorization. Alexion believes that it would be needed to have this type of option also for the review of new indication for an already approved product as well. Indeed, even if a product is already approved, high unmet medical need exists for indication(s) irrespective of the product registration status, justifying an early indication approval based on less comprehensive data than usually expected to allow quick access of the patients to the product. This would also limit off label use of	Change of a marketing authorisation not subject to specific obligations into a Conditional marketing authorisation in the framework of an extension of indication is not considered possible within the existing legal framework; therefore this cannot be addressed by the CHMP Guideline.

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	the approved product for a not yet approved indication. Our proposal for CMA would be to apply the same criteria and same conditions as for initial MAA. This means that a product could have a full MAA for 1 indication and a CMA for a 2nd indication (with specific post authorization measures to be completed). Similarly, the mandatory yearly renewal would apply to the CMA indication. It is important to note that other Health Authorities (eg. FDA) offers CMA/accelerated assessment for new indication(s) of existing product in case of high unmet medical need and/or orphan indications.	
7	EFPIA would also welcome additional EMA guidance as to how the principle on conditional marketing authorisations can apply to Type II variation (e.g. for new indications) and extension applications. This is considered not to require a legal change and such guidance could further detail how specific obligations could support a conditional approval. Even with a variation or an extension application the unmet medical need can be justified and could relate to seriously debilitating or life-threatening diseases justifying an approval within the same principles as currently outlined in the draft guidance.	Please see the response above.
9	EuropaBio would like to provide some additional comments of relevance to the biotechnology sector: • In the current draft the CMA is foreseen only for new MAs. For the majority of new biotechnology products significant new indications, strengths and/or pharmaceutical forms solving an unmet medical need can be developed during the course of their Life Cycle. Therefore, EuropaBio recommend extending the use of the CMA pathway to applicants for Type II variations and extensions, when appropriate and without changing the current legislative framework. • It should be clarified in the new guidelines if it is possible for	Please see the response above.

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	companies to submit an application for a Type II variation (e.g. adding a new indication) or an extension (e.g. adding a new strength and/or a new pharmaceutical form) on the basis of limited documentation when it has been justified that this covers an unmet medical need.	
19	We would welcome an extension of the guideline to include variations. For example the provision of a 'conditional approval' of an extended indication (based on limited data) might be useful and would give more patients access to medicine where there is an unmet medical need.	Please see the response above.
Other comments on the legal framework		
4	For all categories within the scope of Article 2 of the commented Draft Guideline a conditional marketing authorisation should be possibly granted with less preclinical, pharmaceutical and/or clinical data. Independently from the source of uncertainty in the dossier the application for conditional marketing authorisation should be reviewed and approval should be considered as long as the data package provided is sufficient to support a risk profile outlining that the benefits demonstrated with the available data outweigh the risks.	Restriction of conditional marketing authorisation in case of less comprehensive pharmaceutical or pre-clinical data to products to be used in emergency situations is foreseen in Art. 4(1) of Regulation (EC) No. 507/2006 and this cannot be amended by the CHMP Guideline.
13	The current drafted GLs are intended for medicines for human use only. It would be welcomed when comparable approaches for veterinary medicinal products would be available as well.	Both the CHMP guideline and the Regulation (EC) No. 507/2006 are limited to medicinal products for human use only.
16	The Paul-Ehrlich-Institut acknowledges the update of the guideline. Specific obligations related to the Paediatric regulation (EC) No 1901/2006 should be considered and reflected in the guideline.	Although in a particular individual case a study could be at the same time a measure in the Paediatric Investigation Plan (foreseen in Regulation (EC) No 1901/2006) and a Specific obligation for a conditional marketing authorisation (foreseen in Regulation (EC) No 507/2006), not all PIP measures would necessarily be specific obligations, and *vice versa*. It is therefore considered that a cross reference to

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		Regulation (EC) No 1901/2006 is not required and could also be misleading.
Serious debilitation		
7	EFPIA welcomes the expansion of the definition of 'seriously debilitating disease by including 'well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages' as described in lines 94-99.	
Addressing unmet medical needs		
7	A product which fulfils the unmet medical need criterion for an application for a conditional marketing authorisation could be viewed as automatically falling under the criterion of 'major interest from the point of view of public health and from the point of therapeutic innovation' allowing a request for an accelerated assessment procedure.	At the time of submission of an application for marketing authorisation its suitability for a conditional authorisation is still to be assessed, while decision on granting an accelerated assessment should be taken in advance of the procedure start. It is therefore not supported to 'grant' automatic accelerated assessment in case of request for a conditional marketing authorisation (i.e. a claim that is not yet assessed), but rather continue to decide on accelerated assessment based on high level results, without a prejudice to the outcome of the actual assessment of the application. Nevertheless, further references to suitability of products addressing unmet medical needs for both the Conditional marketing authorisation and accelerated assessment are being added to the guideline.
12	Timely access to medicines shall not be to the detriment of patient safety. Whilst timely access to needed medicines is important, it should not be in detriment of patient safety. In addition, the concept of ''innovative medicines'' shall be understood to refer to medicines that meet true unmet medical needs. The criteria for granting marketing authorisation for medicines should move towards an approach where	It is recognised that direct comparative data are the best possible evidence to substantiate fulfilment of unmet medical need based on major therapeutic advantage. Nevertheless, it is not possible to generate such data in all cases and indirect data in some cases can be sufficiently convincing. Therefore, the sufficiency of the available data for substantiation of major therapeutic advantage has to

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	comparative-trials against the best available treatment are requested and the question of the added therapeutic value is a determining factor in granting approval. Existing flexibilities for market access (i.e. conditional approval, exceptional circumstances, compassionate use and accelerated assessment) must apply in fully justified circumstances only. Communication to patients and their relatives about the potential benefits of medicines that have been granted a conditional authorisation shall not be overestimated. As important is that the risks from a drug granted conditional authorisation should never be downplayed. Treatment with medicines approved under conditional marketing authorisation needs to be closely monitored and any adverse drug reaction reported and published. It is also important to emphasise that unmet medical need shall be interpreted as a medical condition that has a significant effect on someone's quality of life or leads to serious morbidity or mortality and for which there is no or no adequate medical treatment available. For example, infectious diseases such as HIV in the 80's, some orphan diseases, cancers without well-established therapy, and so on. The existence of an unmet medical need must be duly justified by the company through sound evidence at the point of marketing application. The EMA's guideline on conditional marketing must reinforce these criteria.	remain a case by case decision. A blanket requirement that only direct data from comparative trials against the available therapies would be acceptable is not supported. Access to EudraVigilance data on adverse drug reaction reports is limited by the need to protect personal data of subjects; therefore it is not seen possible to foresee an approach for conditional marketing authorisations that would be different from the general approach on access to ADR report data. Please also note that a revised EudraVigilance access policy has been adopted in December 2015.
8	In the document terms "unmet need" are sometimes used in a neutral form and the eventual justification of risk/benefit assessment comes in addition of the justification of unmet need as such; in some instances (see comment to lines 56-57) those terms seem to refer to risky or life-threatening conditions (while unmet needs could concern less critical conditions situations that do not justify any risk-taking)	The scope of conditional marketing authorisation is restricted to certain product categories therefore it is not felt necessary to provide specific guidance for "less critical conditions".

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	The text shall be reviewed for consistency from this point of view (it shall be clear that "unmet need" shall always be considered in combination with a risk benefit assessment in the scope of this document.	
7	Once unmet medical need has been confirmed for a product and CMA has been obtained for molecules of the same class and same indication, the "unmet medical need" should not be considered to have been met as long as the status of the first product is still conditional. Once a full license has been obtained for subsequent applications the unmet medical need should be justified on and individual basis. There should be an appropriate level playing field considering the need to address overall public health objectives.	It is recognised that the extent to which conditionally authorised products address unmet medical needs is comprehensively demonstrated only after authorisation, through completion of specific obligations. The guideline text is therefore revised to indicate that while specific obligations are still to be completed, another product could potentially aim to address the same unmet medical need, and could also be recommended for a conditional marketing authorisation if it is has at least equivalent chances to address the unmet need. This is in line also with the understanding that conditional marketing authorisation is not intended as an exclusivity provision, and that it is in the public interest to have multiple products available, provided that uncertainties involved are balanced against the benefits (which is addressed by the requirement that benefits of immediate availability must outweigh the risks related to the fact that further data are still required).
Significant benefit		
10	EUCOPE welcomes in particular the considerations around orphan medicinal products (218-221) when requesting a conditional marketing authorisation and the complexity of justifying a significant benefit while having less comprehensive data than normally required. The cooperation between CHMP and COMP in their assessments (lines 269 to 272) is seen as a positive new process. It is understood that in case a product fulfils an unmet medical need	Granting of conditional marketing authorisation and confirmation of significant benefit have different legal basis and assessment bodies, therefore it is not seen appropriate that CHMP by recommending a conditional marketing authorisation would also conclude on confirmation of a significant benefit, which is in the remit of the COMP. In addition, as recognised also in the case law of European

Stakeholder no.	General comment	Outcome (if applicable)
	and is benefiting public health by the immediate availability on the market: this, by definition, would be sufficient to demonstrate the significant benefit over existing therapies.	Court of Justice, the orphan medicinal product provisions are aimed at protecting certain products from competition and the "significant benefit" may thus require a stricter interpretation. The cooperation between both committees though is encouraged.
Involvement of health technology assessment bodies		
6	We support the EMA in their acknowledgement of the potential downstream impacts of early access procedures. We support statements in the documents about the need to consult with other stakeholders. We suggest that these statements are further strengthened throughout the document as engagement with those responsible for downstream medicines access policy is crucial to the successful implementation of regulatory early access procedures.	The guideline aims at encouraging involvement of health technology assessment bodies in the early dialogue. The wording of the guideline is amended to make this encouragement stronger.
12	A marketing authorisation is not the same as access to a drug. Especially for orphan drugs, cancer treatments, and more recently also for other treatments (i.e., hepatitis C), the major factor limiting patient access is their exorbitant prices, which make these drugs simply unaffordable in the EU. In the meantime, it is important to remember that: "from the patient's perspective, an unaffordable treatment is no more effective than a non-existent treatment".	Please see the response above.
Evidence requirements and compliance with specific obligations		
7	EFPIA also welcomes the renewed interpretation for evidence generation in demonstrating benefit/risk in order to obtain CMA (lines 120-123) while strengthening the criteria for the MAH to fulfil the specific obligations (lines 339-342).	
Compliance with specific obligations		
12	Post-authorisation evaluation: all but 'wishful thinking'.	The Guideline elaborates the principles set by Regulation

Stakeholder no.	General comment	Outcome (if applicable)
	Shifting the burden of evidence from the pre-market period to the post-market period is at best naïve: experience with expedited drug approvals or "conditional marketing authorisations" shows that commitments to post-authorisation evaluation are generally not honoured and sanctions are not enforced Other problems include: • There are many examples of post-market studies carried out by manufacturers showing no harm, when independent studies have shown the contrary. The pre-market requirements for double-blind randomized controlled trials establish an indispensable level of scientific rigour that is often not present in the post-market period. • A proposal is put forward based on the use of ''big data'': observational studies exploring national health services data. However, this approach has limitations and does not provide the required level of proof. Observational studies are of weaker quality than randomised clinical trials as differences in patient characteristics often affect outcomes; and there are fewer methodological standards. • Lack of incentives for pharmaceutical companies to actually conduct post-marketing studies which could reveal that a drug is less effective or more harmful than initially presumed; • Public authorities will face opposition from patients when deciding to stop reimbursing a drug or to withdraw its marketing authorisation. According to an example from a US study, "this tension emerged (…) around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival,	(EC) No 507/2006 that conditional marketing authorisation is restricted to certain product types and requires fulfilment of several criteria. The CHMP considers that these requirements are being followed, as explained in the European Public Assessment Reports of the products with conditional marketing authorisation. The Guideline clearly states that regulatory action may ned to be taken in case of non-compliance with specific obligations. The most appropriate regulatory action though needs to be identified for each individual case, taking into account the known risks and benefits of the product, the level of uncertainties, the extent of non-compliance, as well as the interests of public health and the individual patients.

Stakeholder no.	General comment	Outcome (if applicable)
	withdrawing the indication took nearly a year and generated substantial opposition. Some insurers even still cover off-label use of the drug for this non–evidence-based purpose". According to a recent study on conditionally-approved drugs, the median time taken by companies to meet the specific obligations was four years (range 0.2 to 7.7) and there were delays or discrepancies in the fulfilment of obligations in more than one third of the authorisation procedures. In contrast to the approach proposed by the EMA in its consultation document, concrete measures to dissuade, penalties and sanctions should be applied to those marketing authorisation holders which do not comply with their obligations. The EMA must closely monitor marketing authorisation holders and apply sanctions in case of non-compliance (i.e. in the form of fines; removal of conditional approval).	
Products for use in emergency situations		
13	The tabulated overview , EMA/480969/2015, on the two GLs: *Guideline on the scientific application and the practical 4 arrangements necessary to implement Commission 5 Regulation (EC) No 507/2006 on the conditional 6 marketing authorisation for medicinal products for human 7 use falling within the scope of Regulation (EC) No 8 726/2004, EMA/CHMP/509951/2006, Rev.1* and *Guideline on the scientific application and the practical 4 arrangements necessary to implement the procedure for 5 accelerated assessment pursuant to article 14(9) of 6 regulation (EC) No 726/2004, EMA/CHMP/697051/2014-Rev. 1* indicates that these GLs should be applied the use in emergency situations as well. Based on the experience so far, licensing under emergency use requires extremely flexible approaches. As the text of the proposed draft GLs	It would not be seen appropriate to exclude products for use in emergency situations from the scope of the guideline, since only some procedural aspects could exceptionally be more flexible, while the scientific assessment principles would still apply. It Is considered that flexibility on procedural aspects in emergency situations can be provided on a case by case basis, depending on the urgency.

Stakeholder no.	General comment	Outcome (if applicable)
	does not reflect in detail the needs for licensing particularly for immunological products in emergency situations, it is proposed either to exclude licensing in emergency situations from these GLs or the provide some more details. For example: the pre-application period described for conditional licensing procedures is too long.	
13	Currently, platforms are either under development and as well already under use, which allow to produce "vaccines on demand" especially in emergency situations. It would be of great value, if these developments could be considered as well.	The guideline aims at addressing the general principles for use of conditional marketing authorisation. Aspects specific to individual categories of products can be discussed on a case by case basis.
Accelerated assessment		
7	EFPIA believes it is important that applications for a conditional marketing authorisation automatically qualify for an accelerated assessment procedure upon request from the applicant and proposes further amendments to Section 4.4 to support this.	At the time of submission of marketing authorisation suitability for a conditional marketing authorisation is still to be assessed, while decision on granting accelerated assessment should be taken in advance. It is therefore not supported to 'grant' automatic accelerated assessment. Nevertheless, further references to suitability of products addressing unmet medical needs for both the Conditional authorisation and accelerated assessment are being added to the guideline.
10	With reference to the Introductory (7) of the COMMISSION REGULATION (EC) No 507/2006 stating: "It should also be made clear that applications containing requests for conditional marketing authorisations may be the subject of an accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) No 726/2004" and in light of the new draft guidance for accelerated assessment, EUCOPE would welcome more cross-reference in order to highlight the possibility of having a CMA within a AA timing.	Cross reference to the accelerated assessment is being strengthened through the 'unmet medical need' criterion.
Other early dialogue initiatives		
7	EFPIA also believes that other changes would allow to incentives	Except for products for use in emergency situations,

Stakeholder no.	General comment	Outcome (if applicable)
	applicants to submit CMA instead of it being used as a rescue pathway and expects the recently announced PRIME (Priority Medicines) scheme to enable this (amongst others): a more flexible dialogue with the authorities flexibility in terms of the timing of submission of some pre-clinical and pharmaceutical data.	comprehensive pharmaceutical and pre-clinical data has to be available at the time of authorisation in line with Art. 4 of Regulation (EC) No 507/2006.
Interactions with Industry		
1	While interactions between the sponsor and (Co)-Rapporteurs are well defined in the guideline, Alexion would recommend to enhance further those interactions during the CMA assessment procedure. For example, we would welcome the possibility to have a teleconference with the (Co)-rapporteurs after draft assessment report and before final assessment reports are available. This would be in addition to clarification meeting offered during clock stop. We believe that it is important to include this possibility in the guideline to favour harmonization of procedure and options among rapporteurs. Also, we believe that this is particularly important for CMA because there may be a need for additional interactions to discuss the design of the post authorization measures. Waiting for the official interactions options during clock stop have shown to prolong the assessment procedure to finetune the design of post authorization measure.	Use of early dialogue prior to submission of the marketing authorisation application is encouraged. Proposed additional interactions during the assessment procedure (after the circulation of first reports but before the position of other CHMP members is known) are not foreseen. The applicants are instead encouraged to engage in early dialogue with the regulators before the submission of the application, in order to ensure that prompt assessment is possible.
12	Early, scientific and parallel advice = risk of regulatory capture In both public consultation documents, the EMA proposes close dialogue with pharmaceutical companies. The provision of confidential "advice" to pharmaceutical companies on their development plans for new medicines in exchange for fees is a practice of concern, particularly when the objective is to lower regulatory standards to allow for earlier approval of medicines based on limited data and their subsequent reimbursement. The EMA pilot	The guideline does not foresee any change in assignment of scientific advice coordinators and CHMP Rapporteurs, which remain independent processes. Information on most relevant aspects of scientific advice is discussed in the CHMP assessment reports. More detailed information on the scientific advice provided can be requested through access to documents process (following the authorisation of the product). The proposal to anticipate the disclosure of the

Stakeholder no.	General comment	Outcome (if applicable)
	project on parallel scientific advice with national health technology assessment (HTA) bodies in the European Union (EU) takes place in the context of the Agency's plans on adaptive pathways. The provision of confidential scientific advice by regulators to the regulated, in exchange for fees, carries an inherent risk of regulatory capture. This is further accentuated when the members of the committee responsible for providing advice on marketing authorisation procedures are concomitantly involved in the provision and endorsement of scientific advice. To minimise the risk of regulatory capture, committee members deciding on marketing authorisation should not be involved in the provision of scientific advice. Scientific advice should be transparent to allow independent scrutiny and enhance public trust. Detailed reports of the scientific advice provided by regulators to pharmaceutical companies during drug development and the pre-registration process should be published ideally at the time of decision on trial, or not later than 12 months after the end of the trial. This information cannot be considered commercially confidential information as there is a clear overriding public interest in disclosure. Instead of providing customised advice to pharmaceutical companies based on regulatory standards that are not guided by therapeutic value, we urge the EMA to write up ad hoc guidelines that help drug manufacturers make development decisions that address genuine public health needs. Potential guideline deviation should be addressed through written exchange only and subject to transparency requirements. European public assessment reports (EPARs) and similar national regulatory documents should include an additional section summarising scientific advice given by the EMA at each stage of the	scientific advice, or excerpts thereof, prior to the decision on the authorisation of the product, cannot be supported, as it has no legal basis.

Stakeholder no.	General comment	Outcome (if applicable)
	development process. This information would not only facilitate better understanding of the data provided, but also allow for an assessment of the role of scientific advice in the approval of new medicines.	
Renewal of MA and switch to MA not subject to specific obligations		
7	EFPIA welcomes the update of the list of general and administrative requirements for the **annual renewal** (section 5.1) in particular concerning the addendum to Clinical Overview (ACO) that is no longer required. EFPIA does not follow why the requirements for the annual renewal (Section 5.1) should remain high. The revision of the guideline provides an opportunity to reduce administrative burden which should not be missed: The value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD submissions (including PSURs) which are accessible to EMA and all CHMP members. Therefore, EFPIA continues to request to reduce the requirements for an annual renewal and only include those items which have changed and are critical to assess that the MAH is fulfilling its commitments (see lines 339-342).	It has to be noted that renewal is not to be regarded as purely administrative procedure and in line with requirements of the Regulation (EC) No. 507/2006 should include the re-assessment of the benefit-risk balance. The requirements for the information to be included in renewal applications is seen as appropriate for assessment of compliance with specific obligations and the benefit-risk balance. It is reminded that the guideline does not require re-submission of previously submitted data, which can be cross referred in eCTD.
7	EFPIA welcomes the possibility to proceed to a normal marketing authorisation not subject to **specific obligations** without the need to submit a separate 'switch' application as included in the previous guidance (section 6). However, in line with the comments related to the yearly renewal, EFPIA would welcome further simplification for obtaining a full approval based on the fulfilment of all specific obligations associated with the conditional approval. Such specific obligations are subject to separate assessments for which CHMP opinions are rendered hence it would be possible for the CHMP to render a normal MAA based on the completion of the last specific obligation and therefore no separate switch application is required.	The guideline describes the process in lines 455 – 461 (in the draft version for public consultation).

<table>
<tr><th>Stakeholder no.</th><th>General comment</th><th>Outcome (if applicable)</th></tr>
<tr><td>7</td><td>In addition, EFPIA would welcome the possibility for EMA to reconsider the validity of some specific obligations based on the existing scientific knowledge and regulatory environment at the time of the CMA. Certain obligations may no longer be relevant or outdated because either scientific or medical knowledge has evolved from another source since approval or the understanding of the benefit-risk of the drug in the approved indication has been further complemented from knowledge gathering or analyses.</td><td>Modification of specific obligations, when justified, is considered possible and compatible with the legislation and proposed Guideline. When the (potentially modified) specific obligations are completed and comprehensive data are available on the product, the CHMP can recommend granting a Marketing Authorisation not subject to specific obligations.</td></tr>
<tr><td>14</td><td>Thank you for providing this Draft Guideline for public consultation. IPFA notes that:
- Annual renewal is still required (with obligation to file the request six months in advance of the anniversary date) comparable to what already exists, so no relief compared to the existing.
- Structure is given on the annual progress report of the requirements; thereby fit well the Agencies expectations.</td><td>Annual renewal is required in the legislation, which cannot be amended by a CHMP Guideline.</td></tr>
<tr><td colspan="3">Renewal of MA and switch to MA not subject to specific obligations, transparency</td></tr>
<tr><td>11</td><td>Eight orphan medicines were granted conditional marketing authorisation since 2004 when this provision was introduced in the legislation. Of note, other orphan medicines had been authorised with post-marketing obligations to be fulfilled by the MAH, e.g. Onsenal® (withdrawn), but there is no public catalogue of these obligations.
<table>
<tr><th>Brand name</th><th>MA date</th><th>Conditions</th><th>Condition linked to the significant benefit</th><th>Renewal dates (CHMP opinion)</th><th>Number of renewals</th></tr>
</table></td><td>A limit to number of renewal is not foreseen in the legislation. The guideline stresses that the specific obligations should be completed within an appropriate timeframe. However, what duration would be appropriate has to be assessed on a case by case basis, taking into account various aspects, in particular the nature of the comprehensive data required (e.g. long term outcomes).
In case of a conditional marketing authorisation, the 5th renewal does not differ from other annual renewals. The first five year period for the renewal starts only after the conditional authorisation is switched to an authorisation not subject to specific obligations.
In order to increase the transparency on completion of</td></tr>
</table>

Stakeholder no.	General comment						Outcome (if applicable)
	Adcetris	25/10/2012	Long-term effects, such as duration of response and survival, which are needed to confirm the positive benefit-risk balance.	Yes, long term outcome part of the significant benefit	26/06/2014 27/06/2013	2	specific obligations and the corresponding data generated, the EMA is increasing the information included in the European Public Assessment report, in particular by starting to publish in Q3 2016 the assessment reports for annual renewals and procedures in which specific obligations are being fulfilled.
	Bosulif	27/03/2013	Larger study with Bosulif in patients with Ph+ CML previously treated with one or more tyrosine-kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options	Yes, improvement of the treatment of patients who do not respond to existing treatments part of the significant benefit	18/12/2014	1	
	Cometriq	21/03/2014	Safety and effectiveness of different doses of Cometriq, and its benefit in patients lacking the RET gene mutation or whose cancer has changes in another family of genes called RAS	Not exactly, significant benefit is on the improvement of long term outcome	20/11/2014	1	
	Deltyba	28/04/2014	To confirm the long-term effectiveness and safety of Deltyba. A further study will also be carried out to confirm the most appropriate dose.	Yes, long term outcome part of the significant benefit	26/02/2015	1	

Stakeholder no.	General comment	Outcome (if applicable)

Holoclar	17/02/2015	To provide data on the benefits and risks of Holoclar from a prospective clinical study	Not clear, as significant benefit only mentions Holoclar might act differently from other methods		NA
Sirturo	05/03/2014	Additional data on the medicine's benefits and safety when used with different combinations of medicines. The company will also provide longer term safety data on the medicine	Yes, long term outcome part of the significant benefit	20/11/ 2014	1
Translarna	31/07/2014	Further data on the effectiveness and safety of the medicine from an ongoing confirmatory study in DMD patients with the nonsense mutation	Significant benefit not mentioned in Summary of Opinion on Orphan Des.		NA
Votubia	02/09/2011	The long-term effects of the medicine and the duration of the response to treatment	Significant benefit not mentioned in Summary of Opinion on Orphan Des.	22/05/ 2014 25/04/ 2013 24/05/ 2012	3

Out of these 8 medicines, 2 were authorised too recently to have reached the end of the first year after conditional authorisation. Of the remaining 6, 4 obtained 1 renewal of the conditional authorisation, 1 obtained 2, and 1 obtained 3. There are no limits in the number of renewals that can be obtained.

Stakeholder no.	General comment	Outcome (if applicable)
	This shows that the condition could never be fulfilled in just one year; no conditional authorisation could be transformed in a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations') yet. However, as initial marketing authorisations are re-evaluated after five years for their renewal, these guidelines could indicate a limit of 4 renewals. Among products other than orphan medicines, one authorised product received a conditional authorisation in 2011 and has been renewed four times already	

Medicine Name	MAH	Authorisation date	Indication	Condition	CHMP opinion on renewal
Fampyra	Biogen Idec Ltd	20/07/2011	Improvement of walking in adult patients with multiple sclerosis with walking disability (Expanded Disability Status Scale 4-7)	"To conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment. The study report is to be submitted by **30 June 2016**.	26/03/2015 20/03/2014 25/04/2013 15/03/2012

From the European Register on Clinical trials, two trials correspond to the necessary study described in the condition. One is completed (120 subjects)

EudraCT number 2012-000368-90

Stakeholder no.	General comment	Outcome (if applicable)
	A.3 Full title of the trial A Multicenter, Randomized, Double-Blind, Placebo-Controlled Exploratory Study to Assess the Effect of Treatment With Prolonged-Release Fampridine (BIIB041) 10 mg Twice Daily on Walking Ability and Balance in Subjects with Multiple Sclerosis (MOBILE) The end of trial date is 09/08/2013 and its results should have been submitted for the renewal evaluation 20/03/2014. Another trial still in progress only recently started in 2014 for a1 year duration for each subject (560 subjects): EudraCT number 2013-003600-40 A.3 Full title of the trial A Multicenter, Randomized, Double Blind, Placebo Controlled Study to Assess the Long-Term Efficacy and Safety of Prolonged Release Fampridine (BIIB041) 10 mg, Administered Twice Daily in Subjects with Multiple Sclerosis (ENHANCE) E.2 Objective of the trial E.2.1 Main objective of the trial The primary objective of Study 218MS305 is to determine whether prolonged-release fampridine (10 mg BID) has a clinically meaningful effect on patient-reported walking ability over a 24-week study period. E.2.2 Secondary objectives of the trial The secondary objectives are as follows: o To determine whether prolonged-release fampridine 10 mg BID has a clinically meaningful effect on dynamic and static balance, physical impact of MS, and upper extremity function over a 24-week study period o To evaluate criteria for early assessment of response to fampridine that can predict clinically meaningful benefits in walking ability and	

Stakeholder no.	General comment	Outcome (if applicable)
	balance This illustrates cases where the condition might be difficult to fulfil, where a first trial could not conclude and a second one was therefore initiated. However this can only be assumed: EMA public documents do not mention the content of the CHMP or PRAC discussions at the time of renewal; the renewal itself is announced in the "Procedural steps taken and scientific information after authorisation" with no other information. A general comment would be to provide more information on these discussions, particularly for products benefiting from a long-lasting conditional authorisation where the public may question why it seems so difficult to fulfil the post-marketing obligations. Other than this, in general Eurordis approves the clarification proposed by these guidelines in terms of scope of the conditional MA, of the information required to request conditional MA, and of the requirements to report on the obligations.	
12	No public assessment report is available reviewing the implementation of the accelerated and the conditional marketing authorisation procedures. While the EMA claims that the documents subject to consultation are based on "the experience accumulated with Conditional Marketing Approvals" and "accelerated assessments", no detailed report is available evaluating the implementation of the accelerated or the conditional procedures. The EMA has not published any review, nor shared any quantitative or qualitative data with the public to document eventual shortcomings. It is therefore surprising to read that the Agency is considering implementing, through soft guidelines, several measures that would de facto change the existing flexibilities	The EMA is revising the templates for CHMP assessment reports for initial MA applications, in order to consolidate in a single location with a clear subtitle the discussion on recommending a conditional marketing authorisation, or rejecting such request from the applicant. The EMA also plans to publish in 2016 a consolidated analysis of 10 years of experience with conditional marketing authorisations.

Stakeholder no.	General comment	Outcome (if applicable)
	for early market access.	
12	Transparency: It is imperative to provide and improve the information to the public on accelerated and conditionally-approved drugs. The EMA's transparency requirements are enshrined in the EU directive 2001/83/EC which regulates pharmaceutical products, as well as in the EU freedom of information Regulation (Regulation 1049/2001) which governs public access to documents in the European Union's institutions and agencies. The accountability and public scrutiny of health authorities' decisions are only possible when the public has access to both the body of evidence and the rationale on which decisions are based. With respect to accelerated and conditional marketing authorisations, the information provided to the public by the EMA is sparse, particularly during the initial period of marketing authorisation. The European Public Assessment Reports are summaries of discussions and very thin in content. There are also no reports provided during the annual evaluation of conditionally-approved drugs, nor thorough evaluation reports of the Periodic Safety Update Report studies. To be actively engaged in healthcare and make informed choices about treatment, both professionals and patients have the right to know what to expect from a medicine. This means being aware of the treatment's benefits and harms. Against this background, product information should: • Easily identify products subject to additional monitoring; • Easily identify whether a medicine's marketing authorisation has been granted under special conditions or exceptional circumstances; • Identify recent clinically relevant changes to the product	The EMA is revising the templates for CHMP assessment reports for initial MA applications, in order to consolidate in a single location with a clear subtitle the discussion on recommending a conditional marketing authorisation, or rejecting such request from the applicant. The EMA is also increasing the information included in the European Public Assessment report, in particular by starting to publish in Q2 2016 the assessment reports for annual renewals and procedures in which specific obligations are being fulfilled.

Stakeholder no.	General comment	Outcome (if applicable)
	information, in particular those due to safety reasons; • Enable patients to grasp the meaning of harm-benefit balance; • Encourage health professionals and patients to report any suspected adverse drug reactions and put in place optimal means for reporting. • All promotional material should clearly state that products were approved under special conditions or exceptional circumstance	
17	Transparency towards, patients, the general public and healthcare professionals of the conditional nature of any granted MAs must be established and maintained.	The information that a product is authorised conditionally is included in the product information, and the conditionally authorised products can be identified on the EMA website in the search page for human medicinal products (using "browse by type" tab).
Involvement of patients		
11	For discussions on the renewal of the conditional authorisation, with or without an oral explanation with the marketing authorisation holder, patients should be consulted and invited in a CHMP meeting, particularly when the opinion is likely to be negative, or if key questions can benefit from the dialogue with patients, e.g. difficulties in relation to the recruitment or the retention of patients in clinical studies requested by the conditional approval.	The importance of involvement of patients in the decision making process is recognised and reflected in various documents, e.g. the CHMP work plan. In the context of Conditional marketing authorisation it is felt that involvement of patient representatives should not be specific to renewal of the authorisation, but could be even more important for the review of the initial application. The scope of the guideline, however, does not cover the organisational aspects of CHMP meetings, oral explanations, scientific advisory groups and other fora suitable for involvement of patient representatives. The need for patient involvement remains to be considered on a case by case basis.
Differences from MA under exceptional circumstances		
1	The revised guideline definitely provides very useful information on the specific criteria that a product would have to fulfill to get a CMA. However, we believe that additional information on the concrete	Differences between standard MA, Conditional MA and MA under exceptional circumstances are already described in the CHMP Guideline on procedures for the granting of a

Stakeholder no.	General comment	Outcome (if applicable)
	differences between a dossier to support a CMA and a dossier to support an exceptional circumstance MA (ECMA) would be welcomed. Some specific examples of a dossier and associated post authorization measures to support CMA vs ECMA would be helpful for Sponsor to clearly identify the best route for a specific dossier.	marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004, as well as in the EMA procedural and regulatory guidance. The examples of products that have been authorised with either marketing authorisation type can be identified on the search page for human medicinal products (using "browse by type" tab).
1	It may be useful to notify in the guideline that for application for which CMA is not considered applicable by the EMA (during scientific advice for example), ECMA may be considered.	Please see the response above.
Differences from 'standard' MA		
7	EFPIA calls for clarification and a more flexible interpretation on what should be understood as "comprehensive data" as well as "(less) comprehensive data" in relation to situations where a CMA can be applied as well as flexible processes allowing case-by-case justifications and assessment.	Comprehensive data are defined by Directive 2001/83/EC (in particular Annex I), as well as the general and therapeutic area specific guidelines. It is therefore considered not possible to provide a concise definition of comprehensive data, which has to be assessed on a case-by-case basis. A general description of comprehensive data with reference to Directive 2001/83/EC has been added.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
56 - 57	8	Comment: The example provided ("i.e. medicines with an established potential to address an unmet medical need") does not fit the sense of lines 54-56 and 119-123. Indeed, the potential to address the unmet need has to be always outwaited against the uncertainty and there are unmet needs that would not be critical enough to justify the additional risk-taking. Proposed change (if any): the example can be changed to: "i.e. medicines with an established potential to address an unmet medical need in a severe life-threatening condition"	Not accepted. The scope of Regulation 507/2006 is not limited to severe life-threatening conditions only, therefore restricting the scope already defined by law would not be appropriate.
59 - 61	7	Comment: The previous paragraph that stated that CMAs do not apply to new indications has been removed. We would welcome confirmation that this implies that CMAs can now be applied to new indications and line extensions. If this is the case, further clarity on practical aspects would be welcomed (e.g. will this be applied per indication or for all indications in the same MA?)	Not accepted. It is not regarded compatible with the current legislation to change a marketing authorisation not subject to specific obligations into a conditional marketing authorisation in the framework of an extension of indication or another post-authorisation procedure. At the same time, a conditional marketing authorisation could have changes to the indication and/or specific obligations (not affecting the 'type' of authorisation), therefore the referred to statement from the previous guideline version could be misinterpreted and is therefore removed.
68 - 71	7	Comment: While applicants are invited to notify EMA of their intention to request a CMA in the letter of intent, it is EFPIA's understanding that this can be discussed later in pre-submission meetings as in many cases the company may not be in a position to have decided on this at time of the	If the applicant has not indicated at the time of letter of intent their intentions to request a CMA, this does not prevent from making such request at the time of submission. Nevertheless, the applicants are encouraged to plan CMA prospectively and engage in early dialogue on this aspect. As in the letter of intent it is required to indicate the intended

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		letter of intent	submission date, it is expected that by that time it will be known what data will be available at the time of submission of the application.
72	2	The importance of planning the CA as early as possible in advance of the submission of the MAA is underlined in the document (line 211), and pre-submission meetings with EMA and Rapporteurs where the intention to request a CA would be addressed are mandatory. The possibility evoked line 72 to present a request for a CA at the time of the MAA appear contradictory to the above. Thus, the intention of submitting a CA should be made in advance of the MAA, sufficiently to enable pre-submission meetings and eventually a scientific advice to verify the unmet-need eligibility criterion. Proposed change: Line 72 "The Applicant ~~may~~ **should** present a request for a conditional marketing authorisation **sufficiently, and at least 2 -3 months, in advance** of the application for marketing authorization **to allow for a scientific advice to be possibly organized to verify eligibility criteria, and for the organization of the necessary pre-submission meetings where the development plan and timelines for provision of data would be discussed (refer to section 4 .1.2 (b) and section 4.2)**".	Not accepted. The applicant is strongly encouraged to engage in early dialogue for potential applications for CMA, nevertheless, however it is felt that such exchanges cannot be imposed as mandatory.
75 - 77	7	Comment: a complete reference to the Regulation EC 507/2006 would clarify the text.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: (Article 2 of Commission Regulation (EC) No 507/2006) (Article 4 of Commission Regulation (EC) No 507/2006)	
75 - 77	10	Comment: a complete reference to the Regulation EC 507/2006 would lead to a greater clarity of the text. Proposed change (if any): (Article 2 of Commission Regulation (EC) No 507/2006) (Article 4 of Commission Regulation (EC) No 507/2006)	Please see above.
75 - 79 204 - 206 Lines 75-79	9	The draft guideline does not mention risk management plans, nor if there are any special risk management considerations in case of a CMA. It is twice mentioned that specific pharmacovigilance obligations might (in some instances) apply and that intense safety monitoring may be needed. We would suggest incorporating such monitoring obligations in the Risk Management Plan (RMP) assessed by the PRAC to ensure consistency with full marketing authorisations. The guideline could make this clearer. *"The request should consist of justifications to show that the medicinal product falls within the scope of the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional marketing authorisation are fulfilled (Article 4), together with the applicant's proposal for completion of ongoing or new studies and, if applicable, also specific proposals for collection of pharmacovigilance data* ***to be included in the Risk Management Plan (RMP)".***	Not accepted. The guidance on Risk Management plans already foresees that specific obligations focused on safety are also reflected there (as 'category 2 studies' in the pharmacovigilance plan). The guideline text cited refers to obligations that would eventually become specific obligations to the marketing authorisation and reflected in Annex II to the MA (in addition to the RMP).
77 - 78	12	Remove 'if applicable'. The collection of pharmacovigilance	Not accepted. Text refers to additional specific activities (as

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		data is a prerequisite of the conditional approval and should be deemed necessary, not optional.	specific obligations), not the routine pharmacovigilance activities that apply to all products.
82-109	11	Maybe there is a fourth situation when conditional approval could be granted: in case a long-lasting shortage has occurred for an authorised medicine and another one is being evaluated for the same indication (cf Fabrazyme and Cerezyme shortages for example). Here a conditional authorisation could be granted for patients who are the most affected by the shortage so that they can benefit from the new alternative, the condition being to continue the development of the experimental product as planned.	Not accepted. Shortages can be transient and they would have to be exceptionally severe to warrant granting marketing authorisation for another product based on less comprehensive data. Such decisions would have to be taken exceptionally and on a case by case basis.
82-109	11	On the same line, one question is whether or not a product could be granted a conditional authorisation because at the time of the authorisation the MAH is not yet able to manufacture enough product for all possible patients and the manufacturing capacity will reach its full potential in a year or so? The condition would be to be able to produce enough supply within a year. During the first year, priority should be given to the most severely ill patients. Such cases have occurred (Crixivan® in 1996, paediatric formulation of Viracept in 1998…).	Not accepted. The described situation does not appear to refer to a case of less comprehensive clinical data, therefore would not be suitable for a conditional MA.
84 - 97	9	Addition highlighted **in bold** below: "*The applicant should justify that the medicinal product falls within the scope of the conditional marketing authorisation regulation. The categories of medicinal*	Not accepted. Products for treatment, prevention and diagnosis are potentially within the scope, depending on the unmet medical needs identified. It is not supported to restrict the scope only to treatment or prevention, contrary to the provisions of the legislation.

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		products that fall within the scope of the conditional marketing authorisation regulation are defined in Article 2 of Commission Regulation (EC) No 507/2006. These are products for human use falling under Article 3(1) and (2) of Regulation (EC) No 726/2004, and belonging to at least one of the following categories *1. Seriously debilitating diseases or life-threatening diseases* *[…] For a disease to be considered seriously debilitating it would need to have a well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages. These aspects should be quantified in objective terms, as far as possible.* ***Medicinal products that treat these diseases or prevent or delay progression would be considered to be within scope.*** Justification: Unmet medical need is always mentioned in relation to *treating* diseases, however, many biotechnology products help *preventing* occurrence of disease instead of just treating. EuropaBio members recommend the point above be reflected in the guidance for greater clarity to applicants.	
90 - 91	3	In relation to the justification that the medicinal product falls within the scope of the conditional market authorization, the category of seriously debilitating diseases or life-threatening diseases should be justified	Not accepted. It is recognised that such information would be useful, if it was available at the time of authorisation. However, it is not felt that it should be mandatory in all cases, as it may not always be available.

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		based on objective and quantifiable medical or epidemiological information such as Disability-Adjusted Life Years (DALYs)	
93-96	19	Comment: Seems a bit repetitive regarding the definitions of seriously debilitating disease and maybe the paragraph could be consolidated/split to read more clearly '...justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. For a disease to be considered seriously debilitating it would need to have a well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages.' Proposed change (if any):	Not accepted. Merging the two sentences would create a sentence that is too long. Although both sentences refer to the impact on day-to-day functioning, the first one introduces it as a criterion for assessing debilitation, while the second quantifies the impact that would correspond to serious debilitation.
94 - 96	2	A disease would be considered as seriously debilitating, thereby justifying a conditional MA, even if the disease-induced rnajor impact on activities of daily living would be anticipated only at late stages in the disease course. If the drug developed is targeting even early stages of the disease (which can be anticipated most of the time), then the applicant would have to provide a thorough justification that, for those patients at an early stage, delaying the administration of the drug until the complete data set is available (i.e. until a full MA could be granted) would have detrimental effects in terms of disability at the later disease stages. This justification is not straight forward in	Not accepted. Conditional marketing authorisation can be recommended only if it is considered that the benefits of immediate availability outweigh the risks inherent in the fact that additional data are still required, therefore such addition is not considered necessary.

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		case several decades separate the early stages and the stages corresponding to a seriously debilitated health status. Proposed change: Line 96 "for a disease to be considered seriously debilitating, it would need to have a well- established major impact on patients' day-to-day functioning, either already early in the course of the disease, or in the later stages. **In the latter case, the applicant would have to provide a thorough justification that, for those patients at an early stage, delaying the administration of the drug until the complete data set is available (i.e. until a full MA could be granted) would have detrimental effects in terms of disability at the later disease stages. This justification is not straight forward in case several decades separate the early stages and the stages corresponding to a seriously debilitated health status**".	
94-99	11	To document on the seriousness of the disease, the guidance could advise the applicant to consult with patients' organisations particularly when quantitative information is missing. Proposed changes: For a disease to be considered seriously debilitating it would need to have a well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages. These aspects should be quantified in objective terms, as far as possible. Furthermore, serious debilitation, or fatal outcome should	Not accepted. The importance of involvement of patients in the decision making process is recognised and reflected in various documents, e.g. the CHMP work plan. However, such specific reference for assessment of whether the condition is seriously debilitating is not seen necessary.

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		be a prominent feature of the target disease and therapeutic indication, i.e. affect an important portion of the target population. *Consultation with relevant patients' organisations can help measuring the impact on patients' day-to-day functioning or collect quantitative data.*	
100 - 105	7	Comment Decision 1082/2013/EU has been recently adopted with the intention of combating serious cross-border threats to health and includes, within its scope, "health emergencies of international concern" and the relevant medicinal products. This should be referred to in this chapter. Proposed change: Add After lines 100-105 "2. Medicinal products to be used in emergency situations A justification should be provided that the medicinal product is intended for use in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No. 2119/98/EC). A reference to the relevant WHO Resolution or Decision, or to the measures adopted by the Commission in the framework of Council and Parliament Decision No. 2119/98/EC should be provided. Medicinal products falling within the scope of Decision 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health also qualify as "medicinal products to be used in emergency situations" within the meaning of Article 2 of	Accepted with a modified wording.

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		Commission Regulation (EC) No 507/2006" (addition of last sentence)	
103, 105	18	Comment: Decision No 2119/98/EC has been repealed by Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health. To replace "Decision No 2119/98/EC" by "Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC". Proposed change (if any): "**Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC** ~~"Decision No 2119/98/EC~~	Accepted with a modified wording.
103, 248	18	Comment: The European Community has been replaced by the European Union Proposed change (if any): "**European Union** ~~Community~~ (Decision…"	Accepted.
106-109	11	How does it work for orphan products when the condition is to further substantiate the significant benefit over existing products, if any? If this turns out not to be the case, does the product looses its orphan drug status but can remain authorised if the benefit/risk is still positive?	The non-confirmation of the orphan designation does not have an automatic effect on the validity of the marketing authorisation (provided that for a conditional marketing authorisation the product remains within the scope of the regulation), but rather affects the authorisation of the product as an orphan.
112	7	Comment:	Accepted.

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		Please remove 'Regulation' from line 112 Proposed change: The requirements for a conditional marketing authorisation ~~*Regulation*~~ are described in Article 4 of Commission Regulation (EC) No. 507/2006.	
112-113	19	Comment: Minor error Proposed change (if any): The requirements for a conditional marketing authorisation ~~Regulation~~ are described in Article 4 of Commission Regulation (EC) No. 507/2006.	Accepted.
117	1	Comment: This section reports that one of the criteria for granting of a conditional marketing authorisation is that the risk/benefit balance of the medicinal product is positive while it is understood that it should read that a benefit/risk balance is positive instead. Proposed change: "one of the criteria for granting of a conditional marketing authorisation is that the benefit/risk balance of the medicinal product is positive"	Accepted. Regulation (EC) No 507/2006 uses term 'positive risk-benefit balance', but that is regarded interchangeable with 'positive benefit/risk balance'. The term is changed to 'benefit-risk balance' throughout the guideline, with a footnote explanation that both terms are regarded as interchangeable.
119 - 120	12	Remove 'in particular'. The evidence to be reviewed by the EMA in order to evaluate a benefit-harm ratio must consist of clinical trials only to establish a base level of scientific rigour.	Not accepted. Even though clinical trials are required, also further supportive evidence is needed (e.g. non-clinical studies).
122 171 253 and	7	Comment: In reference to recent discussion across stakeholders (STAMP meeting), it is important that the CMA procedure is	Not accepted. Term 'risk' is maintained in line with the terminology used in Regulation (EC) No 507/2006 (e.g. 'risk inherent in the fact that additional data are still required').

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254		seen in positive manner. In the proposed draft guideline, the absence of data is always referred as a risk. The previous version was referring to uncertainty related to the absence of some data. In the same logic as for the risk management plan, missing data are not to be seen as necessarily a risk but as missing information or undefined certainty that could be managed through the specific obligations or post-follow-up commitment. Proposed change: "Risk" to be replaced by "uncertainty"	
122 171 253 and 254	10	Comment: With reference to a recent discussion amongst Stakeholders (STAMP meeting), it is important that the CMA procedure is seen in a positive manner. In the proposed draft guideline, the absence of data is always referred as a risk. The previous version was referring to uncertainty related to the absence of some data. In the same logic as for the risk management plan, missing data are not to be seen as a risk but as missing information or undefined certainty that could be managed through the specific obligations or post-follow up commitment. Proposed change (if any): "Risk" to be replaced by "uncertainty"	Please see above.
124 - 130	7	Comment: For all products falling under the scope of Article 2, it may be appropriate to allow the applicant to submit less	Not accepted. Comprehensive data are data that from perspective of current scientific standards are considered sufficient for a

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		comprehensive **clinical data relating to the safety and efficacy (clinical parts)** of the application dossier, i.e. data that are "less complete than normal", whilst not being "incomplete" (refer to Recital 4 and Article 4 of Commission Regulation (EC) No 507/2006). EFPIA acknowledges the clarification on elements of comprehensive clinical data which do not need to be available at the time of authorisation. In addition, consistent with Article 4(1) a conditional marketing authorisation may be granted with less comprehensive **pre-clinical or pharmaceutical (including quality/CMC) data** only in the particular case of emergency (Article 2(2)). Yet, on this point also drugs falling under the scope of Article 2(1) and (3), by nature, justify a degree of flexibility at submission in order to allow for more timely applications. For those cases, EFPIA proposes to specifically define, on a case-by-case basis, what "comprehensive data" in relation to pharmaceutical or pre-clinical data entails following prior agreement from the CHMP, (Co-) Rapporteur and the EMA. This would allow for a more timely submission and give an incentive to applicants to submit via the conditional marketing authorisation. This possibility is currently not fully reflected in the guidance. Alternatively, some pre-clinical or pharmaceutical data not essential to allow regulators to establish the benefit/risk balance of the product could be submitted as an additional specific obligation to the conditional marketing authorisation as appropriate.	marketing authorisation not subject to specific obligations. Such data are defined by Directive 2001/83/EC (in particular Annex I), as well as the general and therapeutic area specific guidelines. It is therefore considered not possible to provide a concise definition of comprehensive data, which has to be assessed on a case-by-case basis. A general description of comprehensive data with reference to Directive 2001/83/EC has been added to the guideline. Seeking the CHMP input on a case by case basis on what is to be considered comprehensive data for a particular product is encouraged, but that should be part of early dialogue (e.g. through scientific advice), which is already encouraged in other parts of the guideline. Non-comprehensive quality and non-clinical data outside emergency situations are not foreseen by Regulation (EC) No 507/2006.

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		Line 124-130 (replacement): "Products to be used in an emergency situation, in response to recognised health threats, may provide particularly important benefits, therefore higher uncertainties related to the absence of some data may be acceptable**.** Art. 4(1) states that in such cases a conditional marketing authorisation can be granted also if preclinical or pharmaceutical data are not comprehensive. Specific consideration will also be given to and applications will be assessed for what constitutes "comprehensive preclinical or pharmaceutical data" at the time of submission for cases which are not classified as being used in emergency situations. Each of those applications will be assessed on a case-by-case basis, taking into account the respective health threats and expected effects of the product. In addition, consistent with Article 4 (1) of Regulation (EC) 507/2006 for all products within the scope of Article 2 the clinical data referring to the safety and efficacy can be less comprehensive than normally the case."	
131-134	7	Comment: Clarification to avoid misreading. Proposed change: "The elements of the comprehensive data that are not available at the time of authorisation should be discussed by the applicant and their acceptability justified based on the strength of available results and taking into account the requirement for a positive benefit-risk balance. If justified, such elements that may be waived at the point of	Not accepted. Previous sentence describes 'the elements'. In addition, the need to provide this data is not waived, but rather requested post-authorisation.

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		time of authorisation could include:….”	
131 - (134) - 165	7	Comment: The process for accepting less comprehensive data, the justification thereof would benefit from further clarification. Proposed change: “The elements of the comprehensive data that are not available at the time of authorisation should be justified on a case-by-case basis and discussed by the applicant and their acceptability justified based on the strength of available results and taking into account the requirement for a positive benefit-risk balance. If justified, such elements could include (….) *New addition after line 165:* “Prior to submission, a mutual understanding of the data package that is planned to be included in the application should be agreed between the applicant, the (Co)-Rapporteur and the EMA. In case the applicant might foresee that relevant supplemental data will become available during the evaluation, details should be provided about timelines and how these supplemental data are considered of relevance for their conditional marketing authorisation application. In addition some pre-clinical or pharmaceutical data not essential to the establishment of the benefit/risk balance of the product could be submitted as an additional commitment (specific obligation) to the conditional marketing authorisation as appropriate.”	Not accepted. The guideline encourages early dialogue, nevertheless the extent of non-comprehensive data still allowing establishment of the benefit risk balance in the context of conditional marketing authorisation can be confirmed only upon assessment of the data and depending on the strength of effects seen. It would therefore not be appropriate to ‘agree’ on or impose extent of data prior submission. If applicants were to wish to receive CHMP opinion on comprehensiveness of data, such questions can be discussed in a scientific advice procedure. Regulation (EC) No 507/2006 requires (except for emergency situations) that non-clinical and quality data should be comprehensive. Please see also the response above to comment on lines 124 – 130.
135 - 136,	3	We note that the use of intermediate endpoints is most	Not accepted. If an intermediate endpoint has been properly

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145 - 146, and 149 - 150		valuable and certain when their relationship with clinical outcomes is validated. Therefore, we recommend the phrase 'validated intermediate endpoint(s)' be used in lines 135-136, 145-146, and 149-150.	validated, it could provide data sufficient for a marketing authorisation not subject to specific obligations.
135 - 144	7	Comment: Please add to the list an example that is applicable for vaccines Proposed change: • Vaccines effectiveness data (having used immunogenicity data and/or data from a human challenge study at the time of authorisation)	Accepted with a modified, more concise wording.
137	7	Comment: In reference to the Medicines Adaptive Pathway to Patients (MAPPS) concept and the possible use of real world data as well as registries (which are suggested to be added and listed here), reference to data set instead of database would clarify the possibilities. Proposed change: "database" to be replaced by "data set"	Not accepted. "Database" is not considered as restricting the sources of data to clinical trials only; change to "data set" not considered necessary.
137	10	With reference to Adaptive pathways and the possible use of real world data as well as registry (those should be added and listed here), reference to data set instead of database would clarify the possibilities. Proposed change (if any): "Database" => "data set"	Please see the response above.
137 - 138	7	Comment: "with the same endpoint(s) and in same population" reads inflexible and may not always be possible.	Not accepted. These lists are only examples of possible scenarios, therefore not exhaustive. The particular example refers, e.g. to a case when the same pivotal study is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "Same" to be replaced by "similar"	continued. Change not regarded necessary.
137 - 138	10	The wording "with the same endpoint(s) and in same population" is too narrow. Proposed change (if any): "Same" replaced by "similar"	Please see the response above.
138	7	Comment: EFPIA would welcome clarification of the definition of "same population" as it can read in different ways and results in different situations: 1- Same line of treatment or 2- Different treatment line in the same disease or 3- Across different disease with the same biological target receptor (mechanism of action). What would be important is how data and scientific evidences are bridged to support a full product assessment; by having more flexibility in the next clinical step this will help the specific obligations fulfilment.	Please see the response above.
138	10	Comment: EUCOPE would welcome clarification of the definition of "Same population" as it can read in different ways and results in different situations: 1- Same line of treatment or 2- Different treatment line for the same disease or 3- Across different diseases with the same biological target receptor (mechanism of action). What would be important is how data and scientific evidences are bridged to support a full product assessment; by having more flexibility in the next clinical step this will help the specific obligations fullfilement.	Please see the response above.

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141 - 144	7	Comment: EFPIA recommends limiting the list of possible elements with less than comprehensive data to the most important ones, by removing the reference on sub-populations and impact on other medication. If further data is important for sub-populations or on the impact of other medications, and if these are the only missing elements to a comprehensive data set, the approval should not be classified as "conditional". Instead, it could be classified as "standard/ normal" with respective post-approval commitments. Proposed change: delete: ~~further data in important sub-populations, e.g. patients with resistance or a particular biomarker that may be important, further data on impact of other medication, e.g., efficacy data with other co-medication for combination therapies~~.	Not accepted. Data on certain subgroups of the proposed indication may be limited at the time of granting conditional marketing authorisation. In certain cases such data on subgroups may need to be provided post-authorisation, in order to consider the overall data comprehensive. The same applies to data on use of the product on the background of the current standard of care (e.g. co-medication).
145 - 156	7	Comment: EFPIA conducted a root cause analysis on problems with the use of the conditional marketing authorisation tool. Across the cases analysed in the oncology sector certain scientific elements, i.e. the use of "overall response rate" and the application of single arm studies lead to complex scientific discussions and a more stringent alignment on those will be key for future overall attractiveness of the tool. Proposed change: Considerations for the establishment of beneficial effects	Partly accepted. Example of overall response rate is included. The guideline does not explicitly exclude single-arm studies, but addition of a general reference to single-arm studies is not seen appropriate.

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		should explicitly name and acknowledge some of the surrogate markers, such as "overall response rate" as well as specific study designs, such as single arm studies, as applied in the oncology area.	
145 - 156	2	The definition of a surrogate "reasonably likely" to translate into a clinical benefit appears too unclear, it should at least be specified that not only a justification would have to be submitted, but that the CHMP reserves the right to reject the justification; moreover, as it is stated later that a fully validated surrogate would normally deserve a full MA, the cases when a surrogate not fully validated would nevertheless be sufficiently likely to translate in a clinical benefit outweighing the risks need to be further clarified, and clear examples should be given. Proposed changes: Line 146"«the establishment of beneficial effects at the time of MA could potentially be based on intermediate endpoints that are **sufficiently validated to be** ~~reasonably~~ **highly** likely to translate into a clinical benefit…, **and their acceptability to that respect will be assessed on a case by case basis**» .. Line 147: the cases when a surrogate not fully validated would nevertheless be sufficiently likely to translate in a clinical benefit outweighing the risks need to be further clarified, and clear examples should be given.	Not accepted. The proposed concept of 'partial validation' is regarded as confusing. Some examples of intermediate endpoints are already provided in the guideline.
151 - 153	12	Delete text. Validated surrogate endpoints should not be used to allow unrestricted conditional marketing authorisation (no specific obligations from marketing authorisation holders). Patient safety is at stake.	Not accepted. The purpose of validation of a surrogate endpoints is to allow authorisation and that is considered in line with current scientific standards for comprehensive data.

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152	7	Comment: The expectation on benefits outweighing "any" uncertainties in relation to a conditional marketing authorisation seems unrealistic and inconsistent with the concept of a CMA. Proposed change: "Conditional marketing authorisation could be appropriate when an intermediate endpoint shows benefits that outweigh any the uncertainties about the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required."	Accepted.
153 - 156	7	Comment: In line with the general comment above that CMA should be seen in a "positive way", the paragraph starting from line 153 "it has to be also ...." to 156 could be added to the paragraph 157 to 161 to give a perspective of potential case where the submitted data would not need specific obligations; i.e. full approval.	Not accepted. It is not seen appropriate to provide general guidance on evidence standards outside the context of conditional marketing authorisation in this particular guideline.
153 - 156	10	Comment: In line with the general comment above that CMA should be seen in a "positive way", the paragraph starting from line 153 "it has to be also ...." to 156 could be added to the paragraph 157 to 161 to give a perspective of potential cases where the submitted data would not need specific obligations; i.e. full approval. Clarification of potential situations where the risk management plan are sufficient to be handled as post follow-up commitment should be included.	Please see the response above.

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157 - 161	7	Comment: In line with the above comment, the examples mentioned in this sentence should reflect the most important elements. Proposed change: Scenarios of establishing a positive benefit-risk balance with less than comprehensive data include also situations when comprehensive data would require other additional data (e.g. with longer duration, larger database or additional endpoints ~~more data on particular subgroups~~), but the benefits demonstrated with the available data outweigh the risks and it would be disproportionate from the public health perspective to delay the approval of the product. Furthermore, it should be clarified that this paragraph does not signal an intent that such products would in the future be granted a CMA by default.	Changes in the guideline text accepted. If comprehensive data are not available (As described in the lines cited), a marketing authorisation not subject to specific obligations cannot be granted.
172 - 174	7	Comment: What is the definition of "… beneficial effects are particularly strong for the respective endpoint" in this context? A harmonized language as compared to other EMA guidelines (e.g. Reflection paper on methodological issues in confirmatory clinical trials planned with adaptive design) would be useful. Proposed change: "it is expected that beneficial effects observed are partic*ularly clinically meaningful".*	Partially accepted. For intermediate endpoints the clinical meaningfulness may be not direct, therefore a modified wording is included.
172 - 174	10	Comment: "it is expected that beneficial effects observed are	Please see the response above

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		particularly strong". EUCOPE would welcome clarification on the meaning of "strong" (i.e. clinically meaningful)?	
181ff	16	Comment: In the introduction the guideline references the underlying regulation (EC) No 507/2006) for further detailed background information. The missing scenario, however, is the fact that the later approved Paediatric Regulation (EC) No 1901/2006 encompasses specific obligation for the filing of marketing authorisation application. Although this is a general guidance on a specific form of MAA, obligations agreed in the PIP opinion to conduct clinical trials in children need to be reflected. Especially for those rare cases concerning a "Paediatric only condition". For those cases a conditional MA is difficult to obtain. Proposed change (if any): Applications for conditional MA approval related to a paediatric only medicinal product development should be reviewed by the PDCO with regard to the applicability of the compliance check according to Article 23 of the regulation (EC) No 1901/2006.	Not accepted. Although it cannot be excluded that in an individual case a particular study could be at the same time a measure in the Paediatric Investigation Plan (foreseen in Regulation (EC) No 1901/2006) and a Specific obligation for a conditional marketing authorisation (foreseen in Regulation (EC) No 507/2006), not all PIP measures would necessarily be specific obligations, and *vice versa*. Addition of a reference to Regulation (EC) No 1901/2006 not considered necessary.
183, 197, 198	12	The timelines for completion of obligations (and deadlines) must be publicly accessible to allow public scrutiny. Sanctions must be applied in case of non-compliance.	The due dates for completion of specific obligations are published in Annex II to the Marketing Authorisation.
184	7	Development of quality documentation is usually not final at the time of a CMA. There will often be a need to include pharmaceutical data obligations. Proposed change: ~~"In emergency situations~~ (delete), specific obligations to provide comprehensive non-clinical or pharmaceutical data	Not accepted. Pharmaceutical data has to be comprehensive at the time of authorisation (exceptions possible only for products for use in emergency situations).

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		may also be required."	
191 - 192	10	Comment: "specific obligations should aim to obtain evidence that has consequence on confirming the benefit-risk in the approved indication"; as explained on line 200 to 203, performing trial in the exact same population may be difficult while in similar or complementary one this would assess efficiently the benefit/risk of the product. In reference to that same point, advice from EMA on the use of real world data, registry, or early access programme and how it could efficiently supplement the "comprehensive data".	Partly accepted. A reference is included in the Guideline that specific obligations do not necessarily have to be randomised clinical trials in all cases. Obtaining of comprehensive data through completion of specific obligations is still required.
191 - 195	7	Comment: EFPIA would welcome if EMA could specify in which document (e.g. the risk management plan) the explanation and rationale on what are the remaining questions and how fulfilment of the obligation will result in a resolution of these questions.	These elements should be addressed in the justification for conditional marketing authorisation from the applicant and will be reflected also in the CHMP AR. Clarification on this aspect in the CHMP guideline is not considered necessary.
196 - 197	8	Comment: It is indeed important that work is being done to reduce uncertainty as soon as possible, but terms used are very vague and in particular the term "indefinitely" is not clear in the scope of a yearly follow-up. For some rare conditions it makes take quite long time to gather the evidence that would provide sufficient certainty. Proposed change (if any): It may be useful at time of the yearly review to re-evaluate the risk/benefit ratio in the view of new data available; not only the date from the research performed by the applicant, but also other available information that may	Information from all available sources should be taken into account in annual benefit-risk assessments, as already stated in the guideline. Re-assessment on an annual basis after the authorisation of whether unmet medical need still exists is not foreseen in Regulation (EC) No 507/2006.

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		impact this ratio. Insofar as condition is still an unmet need and the risk/benefit is acceptable, it should be possible to re-evaluate whether to continue the development or not.	
198 - 203	2	"The Applicant should explain how comprehensive data can be provided in an agreed timeframe"; The importance of a timeframe as short as possible and of complying with this timeframe could be underlined, referring to lines 371 and 381 that specify that the maximum duration of the CA will be 5 years and that noncompliance with the time frame of submission of the specific obligations might be interpreted as a non- confirmation of the positive benefit/risk ratio. Proposed changes: Line 198: "*The Applicant should explain how comprehensive data can be provided in an agreed timeframe****, and justify that the proposed timeframe is the shortest feasible one. In case promised delivery dates are not adhered to, the benefit/risk might be considered not confirmed at the time of the next renewal (Please refer to section 5)***".	Not accepted. Limitation of a general maximum duration of conditional marketing authorisation is not supported and also not foreseen in the legislation – it would have to be assessed on a case by case basis. The guideline already states that comprehensive data should be obtained in an appropriate timeframe, and that regulatory action can be taken in case of a non-compliance.
200	6	Comment: Less comprehensive data at the point of (conditional) regulatory approval materially impacts the ability of downstream stakeholders (including physicians and patients) to make informed decisions. As a consequence, unless mitigation plans are developed, it will reduce the ability of early access regulatory policies from achieving its aims. It is therefore vital that the impact of the lack of data is made transparent and plans are developed to address the evidence gaps. Where possible, we strongly suggest that regulatory approval under early	The guideline encourages early dialogue with various stakeholders. However, it is not considered that such engagement can be imposed as mandatory.

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		access should include provisions for data generation that have been agreed via multi-stakeholder dialogue. Joint early dialogue alongside scientific advice could be used as a mechanism to achieve this. Otherwise the burden of providing the evidence will fall to the healthcare systems. It is not tenable for healthcare systems to support early access for medicines with lower evidence unless plans are developed, at the point of regulatory approval, that mitigate the risks their risks alongside regulatory risks. Lines 188- 203 highlight some of the risks that need to be managed in this context as it indicates clearly that the provision of a licensed medicine can make it difficult for further studies to be undertaken. This needs very serious consideration. Proposed change (if any):	
204	12	Replace 'may' by 'shall'. Safety monitoring is not an option, but a necessity.	Partly accepted – wording modified to 'may need particularly intense monitoring'.
205	12	Replace 'may' by 'shall'. Safety monitoring is not an option, but a necessity.	Not accepted. Routine pharmacovigilance and Risk Management Plan activities may be sufficient in some cases; therefore it is not regarded necessary to impose in all cases additional specific pharmacovigilance activities as specific obligations. Also the Regulation (EC) 507/2006 states 'specific obligations may be imposed in relation to the collection of pharmacovigilance data'.
205 - 206	3	Concerning fulfilling the requirements for conditional marketing authorization, when it is likely that the applicant will be able to provide comprehensive data, specific obligations **shall** be imposed in relation to the collection of	Please see the response above

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		pharmacovigilance data. (lines 205-206). Patients using medicines with conditional authorization take higher risks because less comprehensive data is available for these products. Therefore, to ameliorate these risks for future patients, it is essential that specific obligations to collect pharmacovigilance data be imposed on the applicant and that this data be reviewed at the annual renewal and made public.	
211	2	The Applicant is strongly encouraged to discuss, in advance of the MAA, the overall development plan and design of studies planned to be completed before MA or later as specific obligations. However, pre-submission meetings with EMA and Rapporteurs, where the intention to request a CA would be addressed, are mandatory (lines 308-310), and the timeframe for provision of comprehensive data should be agreed. To leave the time for assessment of the grounds for the proposed timeframe and content for specific obligations, those discussions in advance of the MAA should be mandatory. Proposed change: Line 211 « the Applicant ~~is strongly encouraged to~~ **should** discuss… ; **depending on the anticipated key issues to be discussed, scientific advices would need to be applied for shortly after the first presubmission meeting**".	Not accepted. While early dialogue is encouraged, it is not considered that is could be imposed as mandatory.
211 - 217 and 297	6	Comment: Conditionally licensed medicines present particular challenges for HTA and payer processes. Companies should be strongly encouraged to discuss clinical development plans with other stakeholders through	Not accepted. It is considered that engagement in early dialogue with health technology assessment bodies cannot be made mandatory, while just an evidence of such engagement would not guarantee eventual reimbursement in all cases

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		Scientific Advice routes. The EMA might go as far as to indicate that evidence of this type of engagement would be taken into account when assessing to what extent the company has provided sufficient justification with respect to plans for post-regulatory approval evidence generation. Developing these multi-stakeholder mechanisms will be vital if the number of medicines going through the early access procedures is increased. Proposed change (if any):	(and consequently feasibility of post-authorisation activities). Interactions with HTA bodies in the early dialogue are supported and the guideline already encourages that.
218 - 221	7	Comment: The section "it is likely that the applicant will be able to provide comprehensive data" now includes a reference to the orphan medicinal product and the obligation "to consider the suitability of the data to be generated for confirmation of the orphan designation at the time of the conditional marketing authorisation". EFPIA understands that following Protocol Assistance to agree on the level of evidence required to confirm the orphan designation (i.e. significant benefit), the data submitted for the conditional marketing authorisation would be sufficient for the confirmation of the orphan status at that time. Proposed change: Line 221: at time of **conditional** marketing authorisation.	Text amendment accepted. Protocol assistance is expected to be useful to ensure that sufficient data are generated to confirm the significant benefit for maintaining the orphan status. However, as protocol assistance is not mandatory and not always such questions are raised in the protocol assistance, all applicants are reminded about importance of generating sufficient data for confirmation of orphan designation.
218 – 221	10	Comment:	Please see the response above.

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		Under the section "it is likely that the applicant will be able to provide comprehensive data" is now included a reference to the orphan medicinal product and its obligation "to consider the suitability of the data to be generated for confirmation of the OD at the time of the marketing authorisation". EUCOPE understands that following Protocol Assistance to agree on the level of evidence required to confirm the orphan designation (i.e. significant benefit), the data submitted for the conditional marketing authorisation would be sufficient for the confirmation of the orphan status at that time. Proposed change (if any): Line 221: at time of **conditional** marketing authorisation.	
218 -220	16	Comment: A decision taken by the PDCO on significant therapeutic benefit for a paediatric medicinal product development needs to be reflected. Proposed change (if any): The applicant for an orphan medicinal product for which the designation is based on significant benefit over existing therapies, when preparing and discussing the development programme, is encouraged to consider also suitability of the data to be generated for confirmation of the orphan designation at the time of marketing authorisation. Decisions taken by the PDCO on the medicinal product development for the paediatric population should be	Not accepted. The concept of "significant therapeutic benefit" is considered by the PDCO at the early stages of development and is not necessarily identical to "major therapeutic advantage" in the context of conditional marketing authorisation, to be assessed at the time of authorisation. E.g., the European Commission Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01) states that "As experience with the use of the medicinal product in the paediatric population might be unavailable or very limited at the time of submission of the application, significant therapeutic benefit could also be based

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		reflected in the conditions agreed to the MA.	on well-justified assumptions" (emphasis added), while for recommending a conditional marketing authorisation the claim of major therapeutic advantage needs to be based on actual (even if not yet fully comprehensive) data generated. Also, in order to justify an authorisation based on less comprehensive data, stronger benefits may be required to conclude on 'major therapeutic advantage' for a conditional marketing authorisation, as compared with significant therapeutic benefit in the context of paediatric investigation plan. Similarly, measures in the paediatric investigation plan are not automatically to become specific obligations in case of a conditional marketing authorisation.
218-221	11	Same comment than above. For an orphan drug with a positive benefit/risk at the time of the conditional approval, but more information is needed to confirm the significant benefit over existing alternatives. If the MAH fails to fulfil its commitments, or the significant benefit does finally not exist: - is the product no longer authorised? - or is it authorised, but loosing its orphan drug status?	Demonstration of significant benefit may be required to maintain orphan status, but failure to demonstrate it does not have an automatic impact on the validity of market authorisation itself (provided that for conditional marketing authorisation the product remains within the scope of the regulation), only on the non-orphan or orphan status.
230	3	Moreover, in the summary of new or ongoing studies, a justification of the patient population and number of patients to be included in studies (line 230) should be given.	Accepted. Clarification accepted.
230	7	Comment: Please consider development of a vaccine which is administered to healthy subjects instead of patients Proposed change (if any):	Accepted. Clarification accepted.

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		• ***Study ~~Patient~~*** population and the number of ***subjects/***patients to be included	
233 - 234	8	Comment: examples given are all very conventional, mostly referring to randomised designs: "Kind of control(s) (e.g., placebo, no treatment, active drug, dose-response) and study configuration (parallel, cross-over)" and it has been debated that for many conditions that would fit the scope of this document would need alternative solutions as some of the above designs would not be feasible or even unethical… Use of real life data has been under debate and though it is still under discussion and methodology is yet to be defined; it would be welcome to provide some room for innovation in this area. Proposed change (if any): To add a remark such as "other types of controls or benchmarks may be acceptable, but would require a case by case discussion"	Partly accepted. The lines cited refer to examples for a 'typical clinical efficacy study' (See line 225 in the version released for public consultation). A reference is added to the guideline that not all specific obligations are necessarily randomised clinical trials.
244 – 280 (section 4.1.2(c))	3	The guideline should provide a clearer definition of what an unmet medical need is, as this is currently only guided by broad examples. (section 4.1.2(c)) A lack of a definition could enable the excessive use of the conditional market authorization, which would unnecessarily expose patients to higher risks of medicines for which there is less comprehensive data available.	Not accepted. Unmet medical need is already defined in Regulation (EC) No 507/2006 as absence of treatments, or the new product providing major therapeutic advantage. Lines 260 – 265 in the version released for public consultation provide further guidance on the latter.
247	7	Comment: For clarity of the reference Proposed change:	Not accepted. Change not considered necessary.

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		Also Article 4 paragraph 2 of the Commission Regulation EC No 507/2006 specifies that....	
247	10	Comment: For clarity of the reference Proposed change (if any): Also Article 4 paragraph 2 of the Commission Regulation EC No 507/2006 specifies that....	Not accepted. Change not considered necessary.
247 - 254	8	Comment: It is not clear from the context if terms "unmet need" as used here include that seriousness of the condition or its life-threatening nature or not. The risk/benefit evaluation shall clearly take into consideration the nature of the condition itself. Proposed change (if any): Check terms "unmet need" throughout the entire document to ensure consistency; consider adding a definition or referring to an existing definition for clarity Add I the line 253 "… authorisation, the nature of the condition to be treated, but also the risks…	Not accepted. The scope of the regulation restricts the conditional marketing authorisation to seriously debilitating or life threatening conditions, orphan conditions or recognised emergency situations.
255, 259, 266	12	Replace 'should' by 'shall'. Again, it is not a recommendation, it is an obligation.	Not accepted. Change not considered necessary.
262 - 265	2	The notion of of a major therapeutic advantage as an eligibility criterion for unmet need is already existing in the definition of the significant benefit to be demonstrated to maintain an orphan status. In case the major therapeutic advantage justifying the unmet need is not "based on a meaningful improvement in efficacy or safety" but to "a major improvement m patient	Not accepted. As recognised also in the case law of European Court of Justice, the orphan medicinal product provisions are aimed at protecting certain products from competition and the "significant benefit" may thus require a stricter interpretation. In addition, the conclusion that unmet medical needs will be met has to be adopted already at the time of recommending a conditional marketing authorisation, as this

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		care" addressing e g. "serious existing issues with treatment compliance" (justified on a case by case basis), the demonstration that the treatment actually met its goals and e.g. improved compliance should be provided as part of the specific obligations. Proposed change : **Line 265, add** **"In the former case, the demonstration that the treatment actually met the expectations and meaningfully improved compliance and thereby efficacy will be requested as part of the specific obligations dataset."**	is one of the requirements.
262 - 272	7	Comment: The revised draft guideline provides clarification on fulfilment of unmet medical needs, and provides an additional situation when medicines that provide major improvements in patient care over existing therapies can be eligible in certain cases. However the guideline states "In exceptional cases …" which, however, does not seem to be opening up the eligibility to fulfil unmet medical need and thereby facilitating future uptake for CMA. By making reference to "improvements to patient care", this section primarily captures the caregiver's perspective. It would also be relevant to consider fulfilment of an unmet need from the patient's perspective, which would be achieved by assessing improvements in health-related Quality Of Life. This would also allow to further align with the description of unmet need provided in the guideline on accelerated assessment (lines 90-99) Proposed change:	Not accepted. Improvements in patient care are expected to warrant major therapeutic advantage in exceptional cases. If the improvements in patient care provided by the medicinal product in question would be shown to result in improved safety, the fulfilment of unmet medical need could potentially be substantiated by 'meaningful improvement of clinical safety' (lines 260 – 261 of guideline version released for public consultation). Product's impact on quality of life could be regarded as indicative of the efficacy.

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		It is suggested that "major improvement" should also include an improved safety profile of the medicinal product concerned. 'In justified cases, also major improvements to patient care or health related quality of life could provide a major therapeutic advantage, e.g. if the new treatment is expected to address serious existing issues including major safety improvements with treatment compliance or if the treatment allows ambulatory treatment instead of treatment in hospital only.'	
264 - 268	8	Comment: Ambulatory versus in hospital treatment is a delicate aspect to consider as it related to both, added value for the patient, but also potential substantial savings of costs for healthcare systems, which can constitute as such a motivation to accept more uncertainty (which is comprehensible in the view of debate on the affordability of the healthcare). Nevertheless, it shall be kept in mind that at this stage little information is available about costs of medication and the risk related to potential costs of innovative drug as compared to the standard care shall also be taken in consideration. Proposed change (if any): To incorporate this additional aspect in the evaluation of advancement in patient care with anticipated economic impact.	Not accepted. Pharmacoeconomic assessments are outside the scope of assessments for granting marketing authorisations.
269 - 272	7	Comment: We welcome the close collaboration between CHMP and COMP in such a situations. A more dynamic and synergic	Not accepted. The procedural aspects of cooperation are to be developed and may need to be elaborated based on first experiences

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		collaboration will help avoiding recent case of delay. Clarification on timelines and impact on the COMP procedure would be welcomed. In addition, it would be helpful if the guidance could clarify the process regarding the maintenance of orphan designation report that is submitted by the applicant at the same time as the MAA.	when the process is initiated. It is not considered necessary to provide details of procedure in this guideline (especially, since involvement of applicant is not expected to be affected at this stage). Procedure of confirming maintenance of orphan designation is not specific to conditional marketing authorisations and is dealt with in other guidance documents.
272	10	Comment: EUCOPE welcomes the close collaboration between CHMP and COMP in such a situations. A more dynamic and synergic collaboration will help avoiding recent case of delay. Timelines and impact on the COMP procedure would be welcomed.	Not accepted. It is not considered necessary to provide details of procedure in this guideline (especially, since change in involvement of applicant is not expected at this stage).
273	12	Replace 'is expected' to by 'shall'. Again, it is not a recommendation, it is an obligation.	Accepted.
273 - 279	6	Comment: The guideline focuses on the positive risk benefit balance for individual medicines. When considering the public health importance of these medicines, which is one of the explanations for this regulatory route being made available, it is vital that further precision is provided on what justification is required to demonstrate 'public health unmet need' in the bullet points in Line 273. We note that this is not included in the legal provisions. The current statements are inadequate for a robust evaluation of high public health unmet need and risk medicines being made available via conditional routes which are not a public health priority. Additionally, the guideline notes that the evidence package for these medicines will not necessarily comprise comparative data. This implies the	Not accepted. The guideline elaborates on Regulation (EC) No. 507/2006 and is based on 'unmet medical need' as defined in the regulation (i.e. not necessarily from public health perspective only). Development of novel methodologies for quantification of unmet needs could be supported, but is not regarded feasible within the update of the guideline.

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		need to undertake some form of indirect comparisons/network meta-analysis in order to assess the extent to which the new medicine addresses adequately the public health unmet need. Proposed change (if any): We suggest EMA develop methodologies that quantify the magnitude of public health unmet need and the degree to which the new medicines meets that need and also develop transparent decision rules for eligibility based on this methodology	
283	12	Replace 'will have to', by 'is to'	Not accepted. The current wording regarded as suitable to reflect that the concerned justification is needed.
291	12	Add: 'the applicant has the obligation to provide detailed justifications. These shall be made publicly accessible, to allow public scrutiny and for information purposes'.	The CHMP assessment report discusses the fulfilment of requirements for a conditional marketing authorisation on the basis of the report provided by the Applicant and the content of the CHMP assessment report is proactively published by the EMA following the completion of the procedure. The documentation submitted by the applicant in Module 1 (including section 1.5.5) are currently not proactively published by the EMA, but as any documents in the possession of the Agency can be requested through an access to documents request.
297 - 313 (section 4.2)	3	In relation to the Agency advice prior to the submission of a request for conditional market authorisation (section 4.2), it is vital to ensure that regulators' involvement in scientific advice or protocol assistance does not undermine their independence. To avoid any potential conflict of interest, those individuals involved in scientific advice or protocol assistance on behalf of the EMA should not be	Not accepted. The guideline does not foresee any change in assignment of scientific advice coordinators and CHMP Rapporteurs, which remain independent processes.

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		involved in the evaluation of the marketing authorization application.	
304	2	"Please see also section **4** .1.2 (b) "	Accepted.
304 320 395	7	Comment: Section to be corrected Proposed change: Please see also section 4.1.2 (b)	Accepted.
304 320 395	10	Comment: Section to be corrected Proposed change (if any): Please see section 4.1.2 (b)	Accepted.
304	19	Comment: Correction Proposed change (if any): Please see also section **4.1.2.(b)** above regarding the scientific advice on development	Accepted.
304 - 305	7	Comment: Clarification regarding the section numbering. Proposed change: "Please see also section 4.1.2.(b) above regarding the scientific advice on development programme for products intended for conditional marketing authorisation and the recommended approach of prospective scenario building".	Accepted.
306	12	Transparency is needed on the provision of scientific advice. Add: 'the public will have access to reports of the scientific advice provided'.	Not accepted. Currently proactive publication is not foreseen for product specific scientific advice outcomes. As any information contained in the marketing authorisation application dossier, documents can be requested after

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			authorisation through an access to documents request.
306-307	1	Comment: the EMA may also suggest parallel EMA/FDA scientific advice for this type of development that are usually global development Proposed change (if any):	Not accepted. The EMA/FDA parallel scientific advice is not specific to conditional marketing authorisation and therefore no specific statement on this option is included in the guideline. It also has to be noted that regulatory and legal provisions for early access to medicines differ between the EU and US.
319 - 320	7	Comment: Clarification regarding the section numbering Proposed change: "To ensure consistency of application the response should address the elements set out in section 4.1.2."	Accepted.
319-320	19	Comment: Correction Proposed change (if any): To ensure consistency of application the response should address the elements set out in **section 4.1.2.**	Accepted.
328 - 346 (Section 4.4)	7	Comment: EFPIA believes it is important that such applications for a conditional marketing authorisation automatically qualify for an accelerated assessment procedure upon request by the applicant and proposes further amendments to Section 4.4 to support this. Proposed change: Applications which are submitted for a conditional marketing authorisation should on request of the applicant be granted an accelerated assessment based on the	Not accepted. At the time of submission suitability for a conditional marketing authorisation is only a claim, while suitability for an accelerated assessment would need to be assessed separately before procedure start. Nevertheless, the accelerated assessment for conditional marketing authorisation applications is encouraged and guideline text is being expanded, stressing the link between both tools through 'unmet medical needs'.

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		overlapping criteria described in Article 14(9) of Regulation (EC) No 726/2004 and Articles 2 and 4 of Regulation (EC) 507/2006 on the conditional marketing authorisation.	
329 - 330	7	Comment: It would be helpful for the applicant to specify when during scientific review the CHMP assessment/acceptability of a request for CMA will be available, Proposed change: "If a conditional marketing authorisation is requested at submission by the applicant, the acceptability will be part of the scientific review (Day 120 Assessment Report)."	Not accepted. Acceptability of a conditional marketing authorisation is linked to, *inter alia*, conclusions on benefit-risk balance, and therefore it can be confirmed only upon completion of the procedure. If request for a conditional marketing authorisation was to be included in the initial application, it is to be assessed together with other claims in the dossier, but specific wording on this in the guideline is not regarded necessary.
330	12	Add: The CHMP shall summarise 'and make publicly available' its assessment of the request…	Not accepted. The assessment of suitability for a conditional authorisation is included in the final CHMP assessment report, which is already made public as part of European Public Assessment Report. Earlier assessment reports circulated and adopted throughout the procedure are not proactively published.
343 - 346	4	Comment: The wording of the obligations published in the EPAR should be agreed with the MAH before publishing. Proposed change (if any): Upon granting of a conditional marketing authorisation, the specific obligations and the timeframe for their completion will be clearly specified in the conditional marketing authorisation (Annex II to the Commission Decision), and will be made publicly available by the Agency as part of the	Not accepted. Though the applicant is consulted, the conditions to the marketing authorisation that are needed in order to recommend authorisation of the product are defined by the CHMP.

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		European Public Assessment Report after agreement of the wording with the MAH.	
345	12	Replace 'will' by 'shall'	Not accepted. These activities do take place.
347 - 354 (Section 4.5)	7	Comment: To ensure product information is tailored to the users, feedback from physicians and patients on the usability of the information should be collected to prove the added value of the information versus the increased complexity of information. Usually, a statement in the SmPC or package leaflet is not sufficient to explain a regulatory concept to lay persons. In order to provide adequate context around this concept, EFPIA believes that the EPAR is the suitable document to explain the regulatory concept of conditional approval and the scientific rationale for its application. A reference in the product information to the EPAR can ensure that full transparency is provided to interested parties.	Statement on the conditional status of the authorisation in the Product Information is required by Art. 8 of Regulation (EC) No 507/2006, therefore this needs to be maintained. The EPAR scientific report contains a discussion on the acceptability of conditional marketing authorisation and therefore provides further details. The EMA is revising the templates for CHMP assessment reports for initial MA applications, in order to consolidate in a single location with a clear subtitle the discussion on recommending a conditional marketing authorisation, or rejecting such request from the applicant.
349	12	Replace 'should' be 'shall'	Not accepted. Difference in text not seen important.
351	12	Replace 'will' by '' shall'	Not accepted. These statements are being included.
355 - 359	7	Comment: Since PSUR (now the PBRER) include an assessment of the benefit/risk of the product periodically, timelines of specific obligations should, where possible, follow the PSUR timelines to avoid a double assessment.	Not accepted. Specific obligation outcomes should be provided as early as possible, irrespective of PSUR or renewal timelines. The guideline already foresees including specific obligation results in renewal submissions, if timelines allow that.
356 – 359	10	Comment: Since PSUR (now the PBRER) are assessing the benefit/risk of the product periodically, timelines of Specific Obligations	Please see the response above.

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		should follow the PSUR timelines to avoid a double assessment.	
358	12	Add: …following the granting or renewal of a conditional marketing authorisation. These reports shall be 'made publicly available as soon as possible'.	Partly accepted. Starting in Q2 2016 the EMA will publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed).
360	6	Comment: The EMA might consider developing mechanisms to ensure optimum transparency of the outcome of their review of conditional authorisations, perhaps by producing a 'compliance statement' to highlight whether the conditional requirements are being met. Proposed change (if any):	The guideline foresees that most appropriate regulatory action will be considered in case of non-compliance. Starting in Q2 2016 the EMA will also publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed).
360	7	Comment: The details for the timetable for a renewal have been removed. EFPIA believes this information was of value for applicants and requests re-introducing the timetable details should be considered.	Not accepted. Detailed timetables for annual renewal procedure are published on the EMA website.
360 - 381	8	Comment: it can be understood from the text proposed that if no new data are produced, for any reason (failure to comply, difficulty to enroll the promised study, etc.) the situation of the drug remains as it was 1 year before. In other words it is still "established potential" etc (see above), because the available data are the same. It is not clear from this paragraph whether the application will be rejected in such case. From the point of public health, the rationale is to keep it	Not accepted. The guideline already states that in case the MAH is not compliant with specific obligations, the CHMP will consider the most appropriate action, which may differ from one case to another, taking into account, e.g. the benefits demonstrated and the uncertainties remaining. As pointed out in the comment, public health considerations may dictate the need to maintain the product on the market, therefore it is not possible to provide a 'blanket' recommendation for all cases.

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		on the market (ie. assessment is the same, because data is the same). The conflict between 1. the "obligation" of the applicant to produce data and 2. The continued non-changed assessment of established potential in absence of new data is not addressed. Proposed change (if any): The document should clarify the consequences for the applicant in case of failure to comply with conditions, specifically when the failure is not justified by solid scientific background.	
360 - 453 (Section 5)	19	In Section 5 on renewals the timetable has been removed versus the original guideline. It might be useful to state here where the renewal assessment timelines can be found and if these follow the same renewal procedure as a 'normal' MA (with the exception of submitting 6 m before rather than 9 m before for a 'normal' MA). Most preferable would be to have the timetable included again.	Not accepted. Detailed timetables for annual renewal procedure are published on the EMA website.
367	3	Considering the purpose of the renewal of a conditional market authorization is to re-evaluate the benefit-risk balance based on evidence generated since the approval, we recommend that the Committee for Medicinal Products for Human Use assess the renewal application in contact with the Pharmacovigilance Risk Assessment Committee (line 367).	Not accepted. The detailed timetables (with PRAC related steps) and other further details of procedural guidance are published on the EMA website.
367	7	Comment: It would be helpful to specify for in cases where the applicant assesses that the timeframes agreed for the	Not accepted. If modification is not done in another procedure (e.g. a renewal), type II variation C.I.11 is a suitable route to assess a proposal for modification of

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		specific obligation needs to be modified, when and how the request for modification can be made.	timeframes. This is already addressed in the procedural guidance on variations on the EMA website.
368	12	Add: "a publicly available opinion…"	Starting in Q2 2016 the EMA will publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed).
370 - 371	2	The importance of sticking to an agreed shortest possible timeframe for submitting the full data set for confirmation of the B/R, and to avoid prolonged uncertainty, is underlined repeatedly in the document. It could be underlined that noncompliance with specific obligations would be the absence of provision of data, including possibly a deviation from the agreed time frame. Also writing that the positive benefit-risk balance is not confirmed, i.e. was pending confirmation, might be confusing and be mis-interpreted as an equivocal benefit-risk at the time of CA; it would be preferable to speak of whether the positive benefit-risk at the time of CA is maintained (e.g. in view of a the maintenance of the effect or of the long-term safety). Proposed changes. lines 371 and 372 "the marketing authorisation holders are reminded that specific obligations are imposed with an aim to confirm that the benefit-risk balance is positive, therefore in case of a non-compliance **with the agreed timeframe for submission of** specific obligations, the CHMP may consider that the positive benefit-risk balance is not	Not accepted. The situation described is not limited to non-compliance with timeframes of the obligation, but potentially also other aspects (e.g. the design of the study). Regulation (EC) No. 507/2006 refers to the benefit-risk balance being confirmed, therefore it is proposed to use 'confirmed' also in the corresponding CHMP guideline.

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		~~confirmed~~ **sustained (or maintained)** and recommend appropriate regulatory action.	
374 - 377	7	Comment: The intention of this paragraph could be made clearer. It is assumed that should (in probably rare cases) the renewal assessment procedure and/or the Commission decision steps take longer than expected; the conditional marketing authorisation will remain valid although it may have passed the deadline for its validity (for example; a conditional marketing authorisation is valid until 6 May 2015 and the renewal application was submitted on time i.e. 6 months prior to the expiry of the authorisation; if the Commission Decision is received on 10 May 2015 the marketing authorisation was still considered valid between the 6 and 10 May). In addition, the previous guidance mentioned that: "the renewal decision will refer to the expiry date of the preceding marketing authorisation so that the renewed authorisation will be valid for 1 year from the date of the previous expiry". It is suggested to re-introduce this information which is valuable for applicants and helps clarify the intention of the above paragraph. Proposed change: "In order to ensure that medicinal products are not removed from the market except for reasons related to public health, based on Article 6 (4) of Regulation (EC) 507/2006 the conditional marketing authorisation will	Not accepted. Renewal decisions are not issued by the EMA / CHMP therefore this guideline is not suitable to provide guidance on the content of those decisions. The guideline text has been updated to better explain this provision foreseen in Art. 6(4) of Regulation (EC) No 507/2006. The paragraph cited in the comment has been removed from the final guideline version, since it does not contain any additional guidance to the provisions of Regulation (EC) No 507/2006.

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		remain valid until the European Commission adopts a decision following the renewal assessment procedure, provided that the renewal application has been submitted on time. Following adoption of a positive opinion, the Commission decision on the renewal will refer to the expiry date of the preceding conditional marketing authorisation so that the renewed authorisation will be valid for 1 year from the date of the previous expiry."	
382 - 453 (Section 5.1)	7	Comment: The requirements and administrative burden for the annual renewal (Section 5.1) remain high while the value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD sequences/submissions, which are accessible to EMA and all CHMP members. Therefore EFPIA reiterates its request to reduce the requirements for an annual renewal and only include these items which have changed and are critical to assess that the MAH is fulfilling its commitments Proposed change: Section 5.1 on Renewal – proposal to reduce the list of requirements e.g. 5.1.1 Summary of product characteristics, Annex II, labelling and package leaflet if revised 5.1.2 Specific obligations; one interim report per obligation with the required details in order to allow the CHMP an evaluation of its progress. 5.1.3 Inclusion of information related to the fulfilment of a	Not accepted. The guideline does not foresee re-submission of data that have been submitted earlier. Annual renewal focuses on the compliance with specific obligations (hence the need for interim reports) and a re-assessment of benefit risk balance (as required on a yearly basis for these products with the data not yet being comprehensive). If the applicant proposes revisions to product information, the update proposal also has to be provided. Also, the applicants have been given possibility to include specific obligation data in the renewal submission, if the due dates coincide. This allows avoiding a separate submission of this data. If this data have been already submitted separately, they do not have to be re-submitted in the renewal application. Clarification on this is now included under bullet point e in section 5.1.1 of the guideline.

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		specific obligation within the yearly CMA renewal application where the due date for submission coincides with the renewal application.	
395	7	Comment: Please update reference Proposed change: "… (see also section ***5.1.2. ~~3.2~~***)."	Accepted.
396	11	To document on the benefit-risk of the product on the basis of data generated in Specific Obligations and taking into account any other safety (including PSUR) or efficacy data accumulated since the granting of the marketing authorisation, the guidance could advise the applicant to consult with patients' organisations. Patients' expertise could be part of the "clinical expert statement". Here, technics to elicite patients' preferences and weighting the benefit/risk as developed by the IMI PROTECT WP5 and WP6 could be used. Proposed changes: d. A clinical expert statement addressing the current benefit-risk of the product on the basis of data generated in Specific Obligations and taking into account any other safety (including PSUR) or efficacy data accumulated since the granting of the marketing authorisation. *Eliciting patients' views on the benefit/risk by consultation with patients or by using methods developed to generate the views of groups of patients in this respect is encouraged to complete the clinical expert opinion.*	Not accepted. The importance of involvement of patients in the decision making process is recognised and reflected in various documents, e.g. the CHMP work plan. In the context of conditional marketing authorisation it is felt that involvement of patient representatives should not be specific to preparation of renewal submission by the marketing authorisation holders, but could be even more important for the review of the initial and post-authorisation applications by the CHMP. The scope of the guideline, however, does not cover the organisational aspects of all the various situations when patient consultation could be valuable, therefore Guideline text is not amended. The consultation with patient representatives can continue to be conducted on a case by case basis, as needed.

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		In exceptional cases, a non-clinical or quality expert statement may also be required.	
396	12	Add: "a clinical expert statement (to be made public)…"	Not accepted. The renewal submissions are not currently within the scope of activities in the framework of EMA policy on proactive publication of clinical data. Nevertheless, any documents in the possession of the Agency can be requested through an access to documents requests. In addition, starting in Q2 2016 the EMA will publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed).
396 and 464	7	Comment: "… clinical expert statement … " In line with the request for simplification of the requirements and administrative burden, EFPIA assumes that a revised Module 2.5 together with an updated signature of the clinical expert would be considered sufficient to fulfil this requirement.	It is expected that the expert statement is provided as an addendum to the clinical overview.
401 - 402	7	Comment: EFPIA would like to better understand this bullet point. What is meant with "data related to specific obligations" and what would be the scope of submission of such data on top of the interim report. Also, in situations when specific obligations are linked to clinical studies and no protocol specified interim analysis has been performed within the reporting timeframe for the	Data related to specific obligations refers to any data that is generated during fulfilment of specific obligations and needs to be submitted to the EMA. MAHs have been given opportunity to include it, when applicable, in renewal application, in order to avoid a separate submission. The periodicity of interim reports, if such are required, would be specified on a case by case basis (e.g. in the Risk Management Plan).

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		renewal, the timing of data cut to be used for the interim report should be indicated.	
405 - 406	7	Comment: For clarity, we would recommend specifying that the other submissions should relate to the medicinal product in scope. Proposed change: "Data included in other submissions <u>for the medicinal product</u>, but relevant to the benefit-risk balance of the product should be taken into account in preparation of the renewal application."	Not agreed. Any data at the disposal of the MAH should be taken into account.
413	12	This interim report should be publicly available, as per regulation 1049/2001. Add this provision.	Not necessary. All documents held by the EMA can be subject to a request for access to documents and it is not specific to conditional marketing authorisations. Application of provisions of Regulation (EC) No 1049/2001 is further elaborated in the respective EMA Rules for the implementation and the Policy on access to documents. In addition, starting in Q2 2016 the EMA will publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed).
420-422	19	Comment: It would be useful to add clarification of which assessment procedure is referred to. Proposed change (if any): Agreement on the key elements of these reports on fulfilment of specific obligations should be sought during	Not accepted. The reference was intended to the initial MAA procedure. The Guideline text has been updated.

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		the **renewal** assessment procedure.	
446 (Section 5.1.2)	7	Comment: In line with our comments on EMA Policy 70, we requests that the results of interim clinical study analysis are exempted from publication until the study has been finalised. This is important to retain the scientific integrity of the study and avoid statistical bias.	Proactive publication of clinical data by the EMA is outside the scope of this guideline, although they can be requested through an access to documents request. It has to be noted that starting in Q2 2016 the EMA will publish more information in the EPAR on progress with and completion of specific obligations (i.e. assessment reports for annual renewals and other procedures where specific obligations are being completed). Redaction of interim clinical data will be considered, on a case-by-case basis, during the consultation with the MAH in preparation for the publication of reports or release of documents.
462 - 465	7	Comment: The requirements and administrative burden for granting full approval (Section 6) remain high while the value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD sequences/submissions which are accessible to EMA and all CHMP members. Therefore, EFPIA continues to request to reduce the requirements for an annual renewal and only include these items which have changed and are critical to assess that the MAH is fulfilling its commitments (see lines 339-342). Proposed change: EFPIA would welcome further simplification of this process since the completion of all specific obligations and the related assessments are available for the CHMP.	Not accepted. Re-submission of previously provided data is not required. Update on specific obligations is to be provided as it is regarded necessary for assessing compliance and obtaining up-to-date information on the benefit-risk balance of the product.