EFPIA comments - Guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010, Rev 3

1. General comments on the draft Guideline on clinical investigation of medicinal products in the treatment of depression

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	The update to the clinical guideline for depression is welcomed and appears to reflect recent advances in understanding in this therapeutic area. However, the guideline frequently references existing uncertainties in the context of recent developments which may evolve further in the next few years and quite quickly lead to this guideline becoming outdated in some areas. Given this, it would be helpful for the EMA to consider how to provide further updates to medicine developers in this therapeutic area once rev 3 is finalised. Perhaps considering a rapid update alongside the current guidance format may be useful.
2	EFPIA	The revision 2 guidance (section 4.1.1) explicitly calls out that "Three-arm trials including both a placebo and an active control are recommended." This is not present in the draft revision 3. Noting about one-third to two-third of the trials, in which an active control is used as a third arm, the effect of the active control could not be distinguished from that of placebo, the absence of active control/reference is welcomed in order to expedite trial conduct and reduce the risk of generation of ambiguous data, but please confirm the draft revision reflects EMA's current attitude.
3	EFPIA	The term placebo effect is used within the document. Placebo effect is a causal statement which cannot be assessed in clinical trials for new medicines. We would propose to replace 'placebo effect' with 'placebo response' throughout the document.
5	EFPIA	With the advent of precision psychiatry approaches (e.g. combined EEG/wearable/psychometric profiling) intending to identify subpopulations that may respond better to specific agents, please elaborate on EMA's attitudes to such technologies and expectations for supportive information.
6	EFPIA	Please elaborate on EMA's current expectations with regards to anhedonia in depression, notably preferred endpoints and population selection.

7	EFPIA	Given the specific attributes associated with post-partum depression and widespread use of the Edinburgh Postnatal Depression Scale (EPDS) as a peripartum screener for depressive symptoms, consider a recommendation for cut-off scores for inclusion based on EPDS in addition to more general depression assessments.
9	EFPIA	Noting current data on psychedelic agents (4.3.2.4) also suggests rapid action and that these and other agents in development do not follow a classic chronic dosing paradigm, consider expanding the foreseeable treatment situations to include single course or single dose-intermittent treatments to allow elaboration of expectations in these settings.
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(Add more rows as needed)

2. Specific comments on text

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
	111	EFPIA	Editorial comment: Major Depressive Disorder written out in full again, whereas already defined earlier in the guideline.	Proposed change (if any): *of patients with ~~major depressive disorder (~~MDD~~)~~ experience residual symptoms with first line standard*
	127-128	EFPIA	Comment/rationale: Providing examples of the instruments/scales would help the sponsors e.g., C-SSRS scale.	Proposed change (if any): *The need to monitor the degree of suicidal thoughts and behaviour and their change (improvement or worsening) with antidepressant therapy by use of validated instruments is confirmed **(e.g. C-SSRS scale, SIBAT, Sheehan-STS).***
	166	EFPIA	Editorial comment: The text references recent approval of a treatment for TRD. Inclusion of time references may rapidly become outdated and may cause confusion. Propose to remove the word 'recent'	Proposed change (if any): *not standardised. The ~~recent~~ approval of a treatment for TRD in an add-on setting with conventional….*
	172	EFPIA	Typographical comment: Include full stop and space after "guidelineNotwithstanding"	Proposed change (if any): "*guideline. Notwithstanding the availability of*

				many compounds with established efficacy and safety there"
	221-237	EFPIA	Comment/rationale: Under section 4.1 (Clinical Pharmacology studies), it will be helpful to add 3 more sub-headings as below: 4.1.4. Safety studies like tQT (section 4.6.1.7), driving and human abuse liability potential assessments 4.1.5. Biopharmaceutical studies including relative BA, BE studies, and assessment of impact of acid reducing agents on the investigational drug e.g., proton pump inhibitor drug and antacids. 4.1.6. ADME studies which include absolute bioavailability and mass balance assessments.	Proposed change (if any): Additional text to include in line 232: …….*tolerability profile of the proposed product.* ***In addition, safety profiling should include studies providing data informing the probability of adverse events to be monitored as described in 4.6.***
	231	EFPIA	Editorial comment: MOA is not defined in abbreviation list and later in the section 'mechanism of action' is written out in full.	Proposed change (if any): …*should be considered based on pharmacological profile/****mechanism of action (****MOA****)*** *and evolving…..*
	241	EFPIA	Comment/rationale: Clarification is sought to highlight that responses include both efficacy and safety.	Proposed change (if any):...*exposure and response* ***(including efficacy and safety).***
	243	EFPIA	Comment/rationale: Sponsors would benefit from the ability to use PBPK modelling approaches to inform the trial design (inclusion/exclusion), and assess dosing recommendations, as appropriate.	Proposed change (if any): ….*pharmacokinetics of the drug.* ***PBPK modelling may be used to inform study design in combination with PK/PD or Population PK analysis.***
	247	EFPIA	Comment/rationale: CNS drugs may interact with the investigational agent due to either PK-mediated interactions, and/or PD	Proposed change (if any): ….*Interactions with alcohol and other relevant CNS active compounds should be*

			interactions (e.g., serotonin syndrome exaggeration; decrease the threshold for seizures etc.). Therefore, further clarification is proposed regarding interaction studies.	*investigated* ***which may include pharmacokinetic as well as pharmacodynamic interactions.***
	271-272	EFPIA	Editorial comment: The sentence on the final benefit risk assessment may be moved to the end of section *4.2 Assessment of Therapeutic Efficacy*	Proposed change (if any): move the text in lines 271-272 ("*For final benefit-risk assessment the whole data package of a development program will be taken into consideration")* to the end of section 4.2 after line 280.
	Section 4.2 Assessment of Therapeutic Efficacy Line 260 and section 4.2.3.	EFPIA	Comment/rationale: The draft guideline states that a relapse prevention study should be conducted. In view of the near consistent success of this type of study, could it be considered sufficient to either waive these trials, or to allow them to be conducted as a post-marketing commitment (similar to the FDA approach)?	Proposed change (if any): "…..*usually at least two pivotal short-term studies are expected. A relapse prevention study should also be* ~~*conducted*~~ ***considered***, *(section 4.2.3)*"
	Section 4.2 Lines 274-276	EFPIA	Comment/rationale: It is unclear whether multiplicity adjustment for response/remission is needed and whether significance or specific numeric advantages are required. The word 'addressed' is very broad.	Proposed change (if any): *"When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool,* ~~*this effect has to be addressed also as rates of responders and remitters*~~ ***response and remission rates should also be provided***~~*of responders and remitters*~~*."*
	Section 4.2.1 Lines 289-292	EFPIA	Comment/rationale: Propose to clarify and strengthen the wording in the following text:…"treatment of acute symptoms in current (index) episode, maintenance of effect during current episode (relapse prevention)	Proposed change (if any): treatment of acute symptoms in current (index) episode, ~~maintenance of effect during current episode~~ **long-term efficacy** (relapse**/recurrence**

			and prevention of new episodes (recurrence prevention) with long-term treatment (see also section 4.2.3.)."	prevention) ~~and prevention of new episodes (recurrence prevention) with long-term treatment~~ (see also section 4.2.3.). **All estimands should be clearly aligned with the scientific question of interest.**
	Section 4.2.1 Lines 304-306	EFPIA	Comment/rationale: A decision must be made as to whether or not the investigational product on its own is effective and to what extent. If other antidepressants are taken after treatment discontinuation effects of these products should not be included in the assessment of the effects of the investigational product.	Proposed change (if any): ~~Handling~~ **T**he use of alternative anti-depressants that are not considered part of the treatment regimen of interest (i.e. therapies that could not be co-administered with the investigational treatment) ~~is challenging and discussions on the most appropriate estimand are still ongoing~~ **are not part of the treatment *effect* of interest (i.e. the effects of the investigational product)**. A treatment policy strategy ~~could~~ **would not** be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, might be more relevant. ~~Still, the downside of this hypothetical strategy is that a theoretical treatment effect – not existing in the real world - is estimated, as alternative treatments are available in real life. Furthermore, t~~**The** use of …
	Section 4.2.2 Lines 336-338	EFPIA	Comment/rationale: We respectfully disagree with the statement that enrichment strategies with placebo run-in would not be acceptable for Phase 3 studies. With appropriate blinding these strategies can be effective in mitigating	Proposed change (if any): delete lines 336-338 ~~*Enrichment strategies with a placebo run-in are only acceptable in phase 2 but not for phase 3 studies, since the clinical validity of the studies*~~

			exaggerated placebo-response. As acknowledged in the text of the guideline, mitigation of placebo response is important, even more in larger Phase 3 trials than Phase 2 trials. Clinical trials can only provide effects of medicinal products in the sample studied under the conditions of the trial. Therefore, observed effects will never be representative for actual treatment effects in individual patients in clinical practice.	~~*may be affected (section 4.3.2). For such studies, further discussion on the relevant estimand may be required.*~~
	Section 4.2.3 Lines 359-365	EFPIA	Comment/rationale: Reference is made to definitions of relapse prevention and recurrence prevention, but these are not given. In addition, it is suggested that symptomatic improvement occurs before resolution of pathology. As the pathology of MDD is not clear these suggestions are hypothetical. It is unclear how recurrence prevention should be addressed in terms of clinical trial design.	Proposed change (if any): Delete lines 359-363 ~~The definitions of relapse prevention and recurrence prevention assume that symptomatic 359 improvement occurs before resolution of the underlying pathophysiology and that the risk of relapse 360 only decreases as the pathophysiology continues to resolve. In practice, the prevention of relapse is 361 usually seen in the context of short-term treatment (and within the current depressive episode), whilst 362 the prevention of recurrence is seen in the frame of indefinite continuation.~~ Revise lines 364-365; **Whether long-term efficacy** ~~For authorisation it~~ should be shown **prior to authorisation or can be deferred to after authorisation will depend on the type of program and should be discussed** ~~-it that a short-term effect can be maintained during~~

				~~the current (index) episode (relapse prevention)~~ (section 4.3.2.)
	Section 4.2.3 Lines 366-371	EFPIA	Comment/rationale: It is not clear which data are expected to be provided to determine the frequency of episodes and how the duration of the trial treatment should be established. It is also not clear how relapse and recurrence rates would be recognized retrospectively in candidate subjects for a trial.	Proposed change (if any): ~~Prevention of the next episode(s) or recurrence prevention is a worthwhile treatment goal. It is 366 encouraged to evaluate this in specific studies (section 1.1.). Patients in full remission should be 367 randomized to test product or placebo. Study duration will be dependent on the frequency of episodes 368 in the study population and should be justified accordingly. Recurrence should be prespecified as a 369 depressive episode that fulfils current DSM-5 criteria and a certain degree of severity on a validated 370 rating scale. In non-bipolar patients, definitive comparisons of the test substance should be performed 371 versus a placebo. For prevention in bipolar patients, the relevant guideline should be consulted.~~
	378	EFPIA	Editorial comment: Major Depressive Disorder written out in full again, whereas already defined earlier in the guideline.	Proposed change (if any): *~~"Major depressive disorder (MDD)~~ should be classified according to an internationally acknowledged"*
	424	EFPIA	Comment/rationale: With the widespread application of central rating approaches (site-independent raters, centralised over-read of site ratings, technologies contrasting rater vs patient outcomes etc) please clarify EMA's attitude to implementation of these services	Proposed change (if any): Lines 424-427 It would be useful to add guidance regarding central and/or independent site-based raters to this section. There is a brief reference in lines 534-

			and any expectations with regards to use for primary or secondary endpoints. Some commentary on this approach is already noted in section 4.3.2.4 in terms of assessment of psychedelic compounds but has widespread applicability for other agents beyond psychedelics.	536, but the wording could be expanded within lines 424-427.
	Section 4.3.2 Line 442-445	EFPIA	Comment/rationale: The guidance text describes issues associated with placebo lead-in periods when used to select subjects for a subsequent randomised period. There are study designs where placebo lead-in periods are used for reasons other than subject inclusion - this guidance should differentiate between these two uses and provide guidance on each.	Proposed change (if any): Use of a placebo run-in period (single- or double-blind) and potential subsequent patient selection **should be discussed in Scientific Advice prior to the conduct of the trial(s).** ~~is considered problematic with regard to the~~ **G**eneralisability of the results to the population treated in clinical practice **should be considered.**, ~~since patients included in the trials may not correspond to the target population.~~ With respect to placebo response reference is made to section 4.2.2.
	504	EFPIA	Editorial comment: The sentence seems to be missing two words.	Proposed change (if any): *where the rapid acting antidepressant is administered alone **in patients** initiating therapy or replacing a conventional antidepressant….*
	539	EFPIA	Comment/rationale: Proposed text is considered potentially limiting and could exclude the need for individualised dosing for reasons other than those listed.	Proposed change (if any): *In particular, the relationship between characteristics of the acute psychedelic experience and clinical improvement, as well as the need **for dose adjustment** ~~individualised dosing due to inter-individual variability~~*

				~~in drug metabolism, age, sex, or personality~~ should be investigated
	610-612	EFPIA	Comment/rationale: Patients who have failed only one antidepressant treatment do not meet the regulatory definition of TRD and fall far short of what psychiatrists consider in actual clinical practice to be treatment-resistant depression. Including them in these studies would provide interesting information but may make it too easy to obtain an indication for TRD. In case their inclusion is finally accepted, it would have to be defined in what proportion they can be included vs. the total sample of patients, and this proportion should be minimal.	Proposed change (if any): Delete lines 610 – 612 as follows:- ~~Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials, the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded.~~
	648-657	EFPIA	Comment/rationale: Regarding maintenance of effect: The relapse rate under known ADT + placebo may be lower than pure placebo despite TRD. This may have to be taken into account in establishing the duration of follow-up during the randomized period.	Proposed change (if any): Suggest adding at the end of the paragraph after line 657: **As the relapse rate under the known antidepressant plus placebo may be different than under placebo alone, the duration of the randomized observation period should be considered.**
	663-666	EFPIA	Comment/rationale: The current wording suggests that it is established that the pathophysiology for the claimed mechanism of action to treat a specific symptom (sleep disturbance, cognitive dysfunction, anhedonia) is specific to a condition (e.g. depression or schizophrenia). However, if a	Proposed change (if any): ~~The efficacy in the targeted (cluster of) symptoms should be specific for depression and not applicable to the same (clustered) symptoms in other conditions. Thus, a pathophysiological justification for the claimed mechanism~~

			drug is effective for a symptom cluster (for example, insomnia/anhedonia/decreased concentration, anxiety) in depression, it cannot be ruled out that it may be applicable to the same symptom cluster in other neuropsychiatric conditions. Indeed, biomarkers/neural activity/genetics may be used in the future to identify common pathological mechanisms in transdiagnostic populations that share symptom clusters. A drug that targets that common pathological mechanism could be used to treat the same symptoms across diagnoses. As such it is recommended that the relevant text be deleted.	~~of action to treat specific symptoms will be required.~~
	668-671	EFPIA	Comment/rationale: Utilizing specific symptoms and domains within MDD can be used in drug development in 2 ways: 1. Measuring the improvement in the specific symptom/domain using clinically meaningful endpoints. 2. Using the specific symptom/domain to select patients who respond better to treatment (predictive enrichment). In the first scenario, measurement of the effect of an antidepressant on depressive	Proposed change (if any): ~~The effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.~~

			symptoms and the specific symptom/domain would be required. However, in the second scenario, using the specific symptom/domain for predictive enrichment should not necessitate demonstration of an effect on the specific symptom/domain. This is in alignment with ICH E8 (R1) that states that a study population may be narrowly defined to reduce the risk to study participants or to maximise the sensitivity of the study for detecting a certain effect. In this case, a study population could be narrowly defined with the specific symptom/domain to maximise the sensitivity of the study for detecting improvement in depression. This patient selection/enrichment approach is accepted and utilized across a number of diseases including cardiovascular, oncology, pulmonary disorders (among others) for upfront selection of patients in confirmatory studies or as clinical trial endpoints through a strong understanding of the at-risk population, disease biology and mechanism of action of the drug. These development approaches are supported by EMA guidelines in other diseases (i.e., Clinical Evaluation of Anticancer Medicinal Products) as well as FDA guidance (i.e., Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biologic Products).	

	701-705	EFPIA	Comment/rationale: Additional guidance is sought regarding assessing the co-occurrence of depressive and anxious symptoms in MDD beyond merely the anxious distress specifier. This should include information on diagnostic instruments that are recommended for assessing co-occurrence of depressive and anxious symptoms in MDD.	Proposed change (if any): *From a regulatory perspective the population in which benefit/risk is demonstrated will be described in the label.* ***The Structured Clinical Interview for DSM Disorders (SCID) and the Mini-International Neuropsychiatric Interview (MINI)are examples of suitable diagnostic instruments for assessing co-occurrence of depressive and anxious symptoms in MDD.***
	723-724	EFPIA	Comment/rationale: It would be beneficial for sponsors to have further guidance regarding extrapolation of dosing in elderly patients.	Proposed change (if any): *Moreover, extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the older people for the pharmacodynamics of the product.* ***Potential different sensitivities to pharmacological targets in the elderly, compared to adults, need to be considered to drug response as appropriate.***
	726	EFPIA	Comment/rationale: Pharmacokinetic studies may support the choice of the dose and should be conducted. The guideline should allow the possibility of the alternative approach of using population pharmacokinetics.	Proposed change (if any): *Pharmacokinetic* ***studies or population pharmacokinetics*** *may support the choice of the dose.* ~~***and. and should be conducted***~~

	747-787	EFPIA	Comment/rationale: As seen in recent years the requested paediatric development programmes make it very difficult to obtain informative data, proving efficacy. Hence several potential efficacious treatments are not made available to the paediatric population, where there is an unmet need. Given this, it is not clear why the guidance advocates for additional studies rather than utilising other approaches, such as extrapolation.	Proposed change (if any): Consider including extrapolation of acute treatment effects from adults and utilising an appropriate study design to demonstrate maintenance of effect in the paediatric population (and generate the short- and long-term safety data in the paediatric population).
	748-750	EFPIA	Comment/rationale: ICH E11 and CHMP guidelines (EMEA/CHMP/EWP/147013/2004) give the following age ranges: - children 2-11, adolescents 12-17. Line 748 notes depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. The age groups should be aligned to ICH guidance.	Proposed change (if any): *Depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. Hence, the relevant age groups for juvenile depression are children* ***(~~7-12~~ 7-11 years of age)*** *and adolescents* ***(~~13-17~~ 12-17 years of age).***
	770	EFPIA	Comment/rationale: Further guidance on the dose selection in adolescents is requested:	Proposed change (if any): *…wherever possible.* ***The PK in adolescents is often similar to the PK in adults, hence the doses for the adolescent population derived using adult data or population pharmacokinetics and scaling approaches with limited confirmatory PK data could be considered sufficient for the characterization in this age-group (EMA guidance EMEA/CHMP/EWP/147013/004***

				Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population). The initial dose selection to inform adolescent dosing can be based on allometric scaling without the need to conduct a dedicated Pk study and based on allometric scaling of adult PK data to match target adult exposures.
	823-828	EFPIA	Comment/rationale: The text states cognitive rating scales should be used, but should this be done for all trials/compounds? This will increase the number of scales to be applied and may increase the placebo effect (see below). Suggest using scales only if an effect has been identified in early trials or is clearly related to the MoA. "Guico-Pabia et al. [49] in an analysis of 31 MDD studies found that placebo response tended to increase, and drug– placebo effect size tended to decrease, with more assessments per visit. However, confounding of design features limits causal interpretation as both placebo response and number of assessments per visits has increased over time. Therefore, it is unclear whether increased assessment drives the increased placebo response or is simply an artifact of having more assessments in later trials where 58 W. Z. Potter et al. placebo response was greater. Nevertheless, this finding is	Proposed change (if any):

			consistent with the findings of Posternak and Zimmerman [48] in that more interaction with caregivers was associated with increased placebo response. " From Potter, W. Z., et al. (2014). "Controlling Placebo Response in Drug Development: Lessons Learned from Psychopharmacology." Pharmaceutical Medicine **28**(2): 53-65.	

(Add more rows as needed)