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Submission of comments on 'Draft guideline on clinical development of medicinal products intended for the treatment of pain’ - EMA/CHMP/970057/2011

Comments from:

| Name of organisation or individual |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
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|  | The new draft guidelines are considered to describe acute pain more clearly and provide helpful guidance in the design of clinical programs. However some of the proposed study requirements for acute pain could be considered unnecessarily rigorous and some clarifications are needed. |  |
|  | The guidelines appear to dismiss the possibility of *pure* chronic nociceptive pain and suggest that examples of chronic pain may initially be nociceptive but evolve into mixed pain in time. The bar for chronic pain indication is then made impossible to achieve as therapies must have effect on both nociceptive and neuropathic pain. This risks excluding a large patient population that could potentially benefit from relief of an element of their mixed pain.Limitation of the indication to specific pain models that have been studied is reasonable but should be extended to subgroups of patients whose mixed pain condition e.g. CLBP is predominately nociceptive/neuropathic as appropriate to the therapeutic agent studied. |  |
|  | In this second draft guidance we apparently see a redefining of the distinction of chronic from acute pain, from duration of the pain disorder, to the presence of “maladaptive characteristics”, which over time have developed. In addition previously chronic pain conditions appear to have been reclassified as “long-standing” and in Section 6.2.3, Neuropathic Pain it is not clear if the term “chronic” is in any way now applicable. A reading of the guidance in the current draft suggests that only mixed pain disorders are now suitable to retain the chronic label. As stated in line 517-8, the contribution of nociceptive and neuropathic components in patients with chronic pain is not routinely evaluated in general clinical practice, and it is for this reason that we would strongly urge the committee to retain/clarify the link between persistence of a pain condition and the term chronic, to avoid confusion in the label for the physician, for whom the distinction between repeated acute insults (example in a “long-standing” nociceptive pain disorder), and a chronic pain condition (in which the initial pain of nociceptive origin has maladapted into an apparently mixed pain condition) is a moot point. |  |
|  | The second draft introduces to the guideline multiple concepts referred to as “maladaptive”: maladaptive pain (pain that is not useful as a signal of injury to the person), maladaptive functioning of a damaged pain processing system (i.e., the pathophysiology underlying a neuropathic lesion), and the maladaptive characteristics of “long-standing” nociceptive pain conditions. It is not clear if this latter concept (“maladaptive characteristics of…”) refers to neuropathy as narrowly defined (damage to neurons in pain sensory pathways) or to neural plasticity (e.g., central sensitisation), or to both. More detailed operational descriptions are needed to allow for a complete reading and understanding of the agency’s views.  |  |
|  | In Chapter 6 “*specific Considerations for clinical development*” it is proposed to discuss the specific cases of: - a new indication of know active substance, - a new pharmaceutical form, - a new route of administration.Specific paragraphs to cover these additional cases can be considered to be included in this Chapter. |  |
|  | It seems that EMA is calling ‘chronic mixed pain’ as ‘chronic pain’ in this guidance. Please describe why it is considered separate from pure neuropathic pain, nociceptive pain and cancer pain.  It appears that more specific and limited labels/ licences are encouraged, recognizing that every type of pain may not respond to a given mechanism. This is great a step forward vs. the “one size should fit all” generalisation. However, this also raises questions on requirements to show that a mechanism/compound works across pain types. This applies not only to CLBP but also very much to cancer related pain. For cancer pain- will one need to demonstrate all components of cancer pain or will they consider subtypes for labelling?  With respect to e.g. OA, but also CLBP, neuropathic pains (and FM), current evidence suggests that all types of pain that is long-lasting have a central component. However, it does not mean that you cannot block a component of that pain by a peripheral mechanism. (For reference e.g. Haroutounian S, et al. Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. Pain 2014;155:1272–1279. doi: 10.1016/j.pain.2014.03.022.). The draft guidance is eluding to this evolving science but this could be explained with a bit more clarity.  |  |
|  | In general the guidance in this draft has improved since draft 1. However, the section regarding Nociceptive Pain now appears to raise a number of important questions for developers which are not answered in this version of the guidance. While appreciating that the guidance may wish to raise some of the issues surrounding clinical studies in this area it would still be helpful to understand what type of clinical development pathways in nociceptive models could result in an indication either for broad chronic pain or indeed chronic nociceptive pain. This appears to be absent in this version.The following general comments are supplied in relation to the content regarding Nociceptive Pain, focussing on section 6.2.2. Maladaptive characteristics:* The only nociceptive pain model discussed is OA, and the requirement for maladaptive changes to be present is also stated. We consider that the presence of a centralised (maladaptive) component of the pain is not necessary to show that OA patients are suffering from chronic pain and therefore should not be a requirement to use OA, with associated structural damage at any stage, as a model of chronic nociceptive pain.
* In addition, this is not a requirement for development of medicinal products for the treatment of OA pain in the US for example and consequently this inclusion in the EU guideline could present problems in defining a global development plan.
* There is currently no guidance on how the maladaptive characteristics could be demonstrated in a clinical trial setting and the guidance itself indicates that in clinical practice it is difficult to characterise these different pathophysiological aspects in individual patients (line 544). If this requirement remains in the final guideline some additional guidance on this topic would be needed.

Support of chronic pain indication:* It is not clear from the draft guideline what would support an indication for chronic pain in the nociceptive component. For neuropathic pain, in section 6.2.3, this is made very clear, for example that both central and peripheral neuropathic pain should be studied or the indication restricted accordingly, and some examples of suitable models for both are given. Conversely, the only model discussed for chronic nociceptive pain is OA. In line 523, categories of somatic and visceral nociceptive pain are mentioned, but no further guidance is given on the expectation to study these types of pain. Is this intended to mean that studies in OA alone will support a claim for chronic nociceptive pain? And will this then support a broader chronic pain indication in conjunction with studies in neuropathic pain models? If OA alone is not sufficient to support an indication for chronic nociceptive pain and a model of visceral pain is required, we suggest that it would be useful to consider including some examples in the guideline. We consider that the following examples are likely to be considered for selection by companies: Interstitial Cystitis, pain due to Crohn’s disease.
 |  |
|  | In section 6.2.4 it is stated that CLBP typically begins as a nociceptive pain and then develops into a mixed pain due to maladaptive processes. Line 585 states that CLBP is an appropriate specific target population. While this clarification of the possibility of a specific CLBP indication is very welcome it is less clear whether this model would make a suitable model to support a broader chronic pain claim? It is also welcomed that a statement has been included that the inclusion of predominantly neuropathic CLBP would be supportive of a chronic neuropathic indication (line 575). However, it is our position that a predominantly nociceptive (early) CLBP population would be suitable to support a claim for chronic nociceptive pain and this is not made clear in the guidance.Additionally, it is our position that an indication for specifically nociceptive or neuropathic CLBP (where the population is predominantly one type) is an appropriate chronic pain target, as an improvement in one of two pain mechanisms would still lead to a benefit for the patients and is therefore valuable. We request that this is clarified in the guideline. **6.2.4. Mixed Pain**Mixed pain is common and CLBP is the example most commonly encountered in clinical practice. CLBP refractory to currently available treatments is a substantial healthcare problem and may therefore be considered as an appropriate specific target population. Multiple and complex factors are typically involved in the evolution of mixed pain, which in the case of CLBP generally starts as a primarily nociceptive pain condition with or without nerve compression in addition. Due to maladaptive processes further neuropathic characteristics develop over time. As the typical chronic mixed pain picture develops, the underlying structural damage correlates poorly with the pain experience. Appropriate studies of a mixed CLBP population would lead to a CLBP indication: however if the population studied consists of the predominantly nociceptive or neuropathic components of CLBP, then the indication could be restricted accordingly. |  |
|  | We would like to acknowledge the work of the CNS Working Party and other involved stakeholders that has considerably helped to advance the draft of the Guideline on the clinical development of medicinal products intended for the treatment of pain, while ensuring that new results in basic science and pharmaceutical research as well as current medical practice are much more adequately reflected as compared to the previous draft. The current guideline emphasizes the difficulties and limitations in categorizing pain, clearly acknowledging that for example the classification of pain based on the suspected underlying mechanism into nociceptive and neuropathic may make sense from a theoretical point of view, but that in practice many patients feature mixed pain including both nociceptive and neuropathic characteristics. This cannot be ignored when designing relevant clinical trials. Importantly, while a target indication of chronic mixed pain still is currently not encouraged because of unclear relevance to prescribers, studying mixed pain models is not explicitly discouraged any longer. Moreover we welcome the fact that cLBP, the most common example of mixed chronic pain is recognized as a major healthcare problem and therefore now considered as an appropriate specific target indication. The updated draft also allows for a more targeted development of drug candidates for particular subgroups of patients for whom the mechanism of action of the new medicine seems most suited, rather than focusing only on a concept of medicinal products with a very broad effectiveness which may be outdated. The updated draft, while providing a general framework for the development of medicinal products for the treatment of pain, encourages applicants to engage in specific, detailed discussions with national competent authorities or the EMA with respect to the specific requirements related to their development products, which is considered crucial for designing meaningful clinical development programs. |  |
|  | The guidance does not reflect the current medical body of evidence that identifies three pathophysiologies of chronic, non-cancer pain and must include all three.There are different ways to classify pain but the correct way to classify by pathophysiology is nocio, neuropthic and sensory hypersensitivity. Mixed pain is when nocio and neuropathic exist together and is not a separate pathophysiologic entity. Examples of sensory hypersensitivity pain is irritable bowel syndrome, interstitial cystitis. There is often a lot of overlap in patients and FM patients can have neuropathic pain but it is not a requirement for a diagnosis. |  |

1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Criticality\* of the comment: critical (C), important (I), editorial (E) *(FOR INTERNAL USE )* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- | --- |
| Line 56 |  | Comment: The guidance states “two categories of neuropathic and nociceptive” and does not reflect the current medical body of evidence that identifies three pathophysiologies of chronic, non-cancer pain and must include all three.For reference: e.g. Phillips K, Clauw DF. Best Pract Res Clin Rheumatol. 2011;25(2):141-154Proposed change (if any): “been divided into the **categories of neuropathic, nociceptive pain, and sensory hypersensitivity or “fibromyalgia-like” pain based on**….” |  |  |
| Lines 60-62 |  | Comment: It is helpful that CHMP recognize and clearly state the need for new medicinal products to treat chronic pain.Proposed change (if any): |  |  |
| 85-91 |  | Comment:Although acute/chronic pain are defined according to their duration, no quantification is provided. This seems inconsistent with the given indications for the duration of studies in acute and chronic pain. It is proposed to provide an estimation of the duration in line with other regulatory agencies.<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf> Proposed change:According to its duration pain can be described as acute or chronic. Acute pain is considered adaptive, meaning that pain has a warning function. It is of short duration**, requires treatment for no more than up to a few weeks** and declines with the healing of the underlying injury or disease (e.g. post-surgical pain). However, pain may persist beyond the expected healing period and various complex mechanisms (e.g. persistent inflammation, peripheral or central sensitization, neuroplastic events) may lead to a transition into chronic pain. Identifying a cut-off point for such a transition is challenging however. Chronic pain is generally regarded as maladaptive with lack of survival value to the organism. **Chronic pain is defined as either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months.** |  |  |
| Line 87 |  | Comment: Regarding “pain may persist beyond…”Proposed change (if any): Suggest we define chronic in this document as >=3mo. |  |  |
| Lines 90, 99, 126, 454, 541 |  | Comment: It appears that the term “maladaptive” is being used to discriminate acute pain from chronic pain. As there are multiple aspects of chronic pain that are maladaptive, suggest deleting this term (maladaptive) and refer to pain defined on duration and mechanism.Proposed change: Suggest deleting this term (maladaptive) and refer to pain defined on duration and mechanism. |  |  |
| 92-93 |  | Comment: Further examples of chronic pain disorders (in addition to CLBP) should be provided to aid the reader. As described in the general comments above, there is a lack of clarity as to the use of the term “chronic” in the context of a potential indication for treatment of neuropathic or nociceptive pain conditions. |  |  |
| 93-94 |  | Comment: The introduction lists frequently associated features of ‘chronic pain disorders’, such as anxiety, depression and fatigue (lines 93 and 94) that are difficult to measure and highly variable in expression across paediatric subsets. Similar to the text in regards to cancer pain in Line 99, features that children demonstrate associated with pain can be ‘more adaptive than maladaptive’ in particular as children mature. While this is hinted at in Section 8.1: Children (Lines 814 – 815), it should be better detailed (either here in the Introduction or in Section 8.1) by age subset in order to best relay the range of features that may require evaluation.  |  |  |
| 96-103 |  | Comment 1: in this document Cancer pain is considered as one category. This section would improve by refinement. The context of tumor related and pain due to tissue or organ destruction and Breakthrough pain related to the types of cancer related pain as aforementioned are both part of the same context and clinical trials in these areas are recognized as needing specific guidance. However, Breakthrough pain should have its own section, since the time course and therefore endpoints differ between breakthrough pain in other chronic pain conditions. Or consider breakthrough pain as a subsection in non-cancer related pain for improved clarity.Comment 2: Further, the population of cancer survivors is constantly increasing and thereby also the population with treatment related and/ or treatment induced pain, such as chemotherapy induced neuropathic pain. Suggest making a clear distinction into which category this group would fall. Proposed change to comment 2: clearly state that pain as a long term sequelae of chemotherapy, radiation and surgery should be treated as chronic pain due to non-cancer related causes, but protocol efficacy endpoints need to be open to handle cases of relapse. |  |  |
| 98 |  | Comment: It has been shown that cancer patients could develop chronic pain, which may results out of the given treatment, but there are also other effects leading to potential cancer caused chronic pain (e.g. bone metastases or mass effect from tumour growth). Proposed change (if any): Please delete “mostly treatment related” in the brackets |  |  |
| Lines 104-107, lines 528-529 and lines 582-589 |  | Comment: Given its very common presentation in clinical practice, it is helpful that CHMP clearly recognise CLBP as an acceptable pain model and indication. Proposed change (if any): |  |  |
| Lines 104-136Sections 6.2.2. and 6.2.3. |  | Comment: Nociceptive and neuropathic pains are described in the guideline, but it would be useful to provide a more detailed description of pain mechanism including pain signalling and the role of nerve growth factor (NGF). NGF is not mentioned in the guideline. A section on pain mechanism could be a good reference for NGF inhibitors. Proposed change: Introduction to section 6.2.2. Nociceptive painPathophysiology of Pain Signaling:Nociceptive Pain is related to damage of somatic or visceral tissue, due to trauma or inflammation, encoded by nociceptors. Tissue injury releases byproducts and mediators of inflammation (Prostaglandins, Serotonin, Cytokines, Substance P, Histamine, Bradykinin, Serotonin, Neurotrophins (Nerve Growth Factor), Reactive oxygen species, Inflammatory cytokines and chemokines). These mediators can bind to and activate and/or sensitize nociceptors on primary afferent neurons. The nociceptive pain signaling pathway transmits pain signals between the periphery and brain.Introduction to section 6.2.3.: Neuropathic painNeuropathic pain is defined as ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’. The spectrum of neuropathic pain covers a variety of disease states and presents in the clinic with a variety of symptoms. |  |  |
| Line 141 |  | Comment: Regarding “mild, moderate and severe pain”. Proposed change (if any): These should be defined – 0-3 mild, 4-6 moderate, 7-10 severe; and include Farrar citation: |  |  |
| 144 |  | Comment: Current text: *Fibromyalgia and other pain syndromes that have major elements other than nociceptive or neuropathic pain are outside of the scope of this guideline although some aspects may be applicable.* It is by the Europain experts that we do not have a clear idea of the cause of fibromyalgia pain. Thus, stating there are other major elements is not correct. The mechanisms involving alteration sin the central pain modulatory systems are validated from several groups and are similar to what is seen in other chronic pain conditions. In addition, there is current published data supporting a substantial neuropathic component to FM pain. In a study by J Serra et al, Ann Neurol 2014;75:196–208. In that study, microneurography was used to record C nociceptors of 30 female patients meeting criteria for fibromyalgia and compared with recordings from 17 female patients with small-fiber neuropathy and 9 female controls. In FM patients, many silent nociceptors exhibit hyperexcitability resembling that in small-fiber neuropathy, but high activity dependent slowing of conduction velocity was more common in fibromyalgia patients. Thus, abnormal peripheral C nociceptor ongoing activity and increased mechanical sensitivity could contribute to the pain and tenderness suffered by patients with fibromyalgia.Data published by Oaklander et al, in Pain 2013 (November ; 154(11): . doi:10.1016/j.pain.2013.06.001.) The latter paper investigated if some patients labeled with “fibromyalgia” have unrecognized small fiber neuropathy causing their illness symptoms. Twenty-seven FM patients were compared to 30 healthy controls. Endpoints were neuropathic pain questionnaires and PROs, ACR diagnostic criteria, skin biopsies and autonomic function testing. Results showed that all endpoints were significantly more represented in the FM patients than in controls (all P ≤ 0.001). Abnormal autonomic testing also suggested that fibromyalgia-associated SFPN is primarily somatic.Further, in a study by Doppler et al, Pain 2015;156(11):2319-2325, comparing patients with small fiber neuropathy, fibromyalgia and healthy controls with respect to QST, skin biopsies (proximal leg and finger) comparing intraepidermal nerve fiber density as well as electron microscopy measurement of nerve fiber diameter, investigating any morphological correlate to functional signs. Small fiber diameter was significantly lower in FM vs. small fiber neuropathy and controls, confirming a morphological neuropathic correlate to clinical findings. In conclusion, there is objective functional and structural evidence that pain due to fibromyalgia has a quantitative correlate not substantially different from peripheral small fiber neuropathy.Proposed change: ***Fibromyalgia is a chronic pain syndrome of unknown origin. However, pain due to fibromyalgia may fall within the scope of this guideline.*** |  |  |
| Lines 152 - 161 |  | Comment:**3. Scope**The term new medicinal product should be clarified. It should be specified that it covers both new and known active substances. It should also be specified that the scope of the guideline covers both systemic and topical forms.Proposed change (if any):“*The scope of the present document is to provide guidance on the clinical development of new medicinal products for systemic or topical use (including either new or registered active substances) intended for the treatment of nociceptive, neuropathic or mixed pain.”* |  |  |
| Line 153 |  | Comment: Mixed pain should not be listed as a distinct pathophysiology of pain since it is in principle a mixture of the three predominant types of chronic pain. Proposed change (if any): “The scope of the present document is to provide guidance on the clinical development of new medicinal products intended for the treatment of nociceptive, neuropathic or **sensory hypersensitivity pain**.” |  |  |
| Line 202 |  | Comment: While it is very important that pharmacokinetics (PK) be assessed in the target population during the clinical development of a drug for the reasons mentioned, in the post approval phase, when dosage, PK & PD relationships are known, testing of new formulations, delivery and interactions in healthy subjects (Phase I and IV study) are normally acceptable for regulatory agencies. Please clarify this point.Proposed change Add: For approval of new formulations, delivery system and DDI post-approval PK studies can be conducted in healthy volunteers. |  |  |
| 206-207 |  | Comment:It is not clear in which cases and at which stage the pharmacokinetics in the target patient population should be studied.In the particular case of acute pain these studies seems hardly feasible.In chronic pain, would population PK during a phase III study meet this requirement?  |  |  |
| Line 207 |  | Comment: Other than in migraine (Due to Gastric stasis) it is unclear what is driving the concern with respect to pain impact on absorption & perfusion. The suggestion is that we would need to understand absorption/perfusion in patients which would be highly impractical to do. Also PK is a surrogate and any delayed absorption would be manifested in delayed onset of efficacy which would be easily and practically measured.Propose change: Delete sentence 206 to 207 or provide significant literature detailing this to be a general issue that would not be detected via efficacy studies.Also this should have a statement that all general Clin Pharm guidelines apply with statements on lines 208 to 210 being the area where there may be some additional focus for pain products. |  |  |
| Line 215 |  | Comment: The focus is on pharmacogenetics and there is no mention of phenotype which is a bit out of keeping with the NeP/NcP characterisation being proposed elsewhere.Proposed change: “The development and validation of specific pain models and biomarkers characterising the different types of pain and exploration of pharmacogenomics **and phenotypic** aspects to identify patients…“  |  |  |
| Lines 226 - 270 |  | Comment:**5.2.1 Methods to assess efficacy**This section discusses various measures and tools for assessing efficacy, e.g. NPSI, PRO, HRQOl, etc. It would be interesting to add some guidance on how these parameters can be reflected in the product labelling. |  |  |
| 226-270802-851 |  | Comment: Section 5.2.1 discussed traditional pain related scales. These are fine in adults but may not be appropriate for some paediatric subsets. This is very briefly addressed in lines 815 and 816. Given the variety of expressions of pain that the pediatric subsets may display, it is our opinion that either Introduction or Section 8.1 could better elucidate features of pain that may be seen in these populations. In addition, while alternative scales specific to the pediatric subsets are partially included in Section 8.1, they could benefit from a clearer presentation of how they should be utilized in assessing pain, similar to what has been detailed in Section 5.2.1. |  |  |
| Line 234 |  | Comment: With regards to “VAS”.Proposed change (if any): It would be helpful to include a mention of the issues with using VAS, as NRS can be preferred.  |  |  |
| Lines 239-248 |  | Comment: The text describes the sing item pain intensity rating scales VAS, NRS and VRS, and then describes the shortcomings of this approach (that is not covering the range of pain qualities). If is not clear from the text if the additional multidimensional outcome measures (such as MPQ) can be used in place of a single item scale as the primary outcome measure, of if they only have a place as a key secondary measure of efficacy. Our view is that appropriately validated multidimensional tools are appropriate primary endpoints, particularly in the context of trials in chronic pain.Proposed change (if any): Line 240: “Therefore, in addition multidimensional outcome measures are recommended **as alternative primary endpoints,** especially for trials in chronic pain.” |  |  |
| Line 245 |  | Comment: With regards to “NPSI”.Proposed change (if any): Suggest including broader assessment and include DN4, painDETECT, ID Pain.  |  |  |
| 247 & 252 |  | Comment: We propose that the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a self-administered questionnaire measuring both pain and function in OA (hip and knee), is a suitable addition to the examples of acceptable tools for assessment of effect on both pain and physical functioning. Proposed change (if any):Line 247: “… effects on neuropathic symptoms. **The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index has been developed and validated in the assessment of pain, and function, in the knee and hip of OA patients**.”Line 252: “Disease specific measures (e.g. Oswestry Disability Index for low back pain **and WOMAC osteoarthritis index**) have not been developed for many chronic pain conditions…” |  |  |
| 249-254 |  | Comment:It is agreed that there is a lack of tools to assess physical functioning in chronic pain. The Oswestry Disability Index (ODI) is well suited for its purpose but also points to that the functional assessment is in many parts linked to the part of the body affected and also the required functions of daily life. Any tool needs to be specifically developed to address these domains. We believe that also the western Ontario and McMaster Universities Arthritis Index (WOMAC), which is very well validated an qualified, perhaps even more so that ODI for CLBP, should be mentioned not only in the Osteoarthritis guideline but also in this guideline. Further, lately new specific functional PRO tools have been developed and validated for patients with chronic pain after thoracic surgery and breast surgery, respectively. For reference: Andersen KG, Christensen KB, Kehlet H, Bidstrup PE. The effect of pain on physical functioning after breast cancer treatment. Development and validation of an assessment tool. Clin J Pain 2015a; 31(9): 794-802. doi: 00002508-201509000-00006.Ringsted TK, Wildgaard K, Kreiner S, Kehlet H. Pain-related impairment of daily activities after thoracic surgery – a questionnaire validation. Clin J Pain 2013;29:791-9. doi: 10.1097/AJP.0b013e318278d4e2.Proposed change (if any): Add WOMAC to Line 252-253.Also add: New disease specific measures of physical function may be considered as valid endpoints if supportive independent validation is provided.  |  |  |
| Lines 249-259 |  | Comment: The Roland-Morris scale and EQ-5D should be included as examples of appropriate measures.Proposed change (if any):  |  |  |
| Line 252 |  | Comment: With regards to “Oswestry”.Proposed change (if any): It would be helpful to mention Roland-Morris Disability Questionnaire (RMDQ) as the Oswestry is more for severe patients. See attached paper that assess the best tools for assessing low back pain (LBP): |  |  |
| Lines 267-270 |  | Comment: Measurement of global improvement in pain is best assessed from the patient’s perspective, not a clinician’s. In addition, ratings of change are subject to recall bias. Current assessments of health status are therefore preferred e.g. Patient Global Assessment. Proposed change (if any): Patient Global Assessment of current health status, reported by the patient, is useful to support general indications and overall perceived benefit of treatment in chronic pain trials.  |  |  |
| 268-270 |  | Comment: it must be noted that physician determination of Global Improvement and satisfaction with treatment is a highly biased observer assessment. Physician’s Global Impression should be taken out since this is better covered by quantitative outcome measures rather than ratings of impressions. Proposed change: The Clinical Global Impression of Change (CGI-C)23 reported by the patient ~~or determined by the physician~~ ~~are~~ **may be a** useful supportive general indicator~~s~~ of the overall perceived benefit of treatment in chronic pain trials. |  |  |
| Line 268 |  | Comment: With regards to “reported by the patient”.Proposed change (if any): The patient measure is the Patients' Global Impression of Change (PGIC) scale. Both can be used, but the document should include PGIC as it’s the patient’s pain, not the clinician’s.  |  |  |
| 275-277 |  | Comment: present wording unclear. Does it mean that an opioid antagonist should be used as a comparator or as the IMP?Present wording: “To prevent healthy subjects from over-sedation or respiratory depression an opioid antagonist may be used in early studies of opioids”Proposed change: For clarification reword: “To prevent healthy subjects from over-sedation or respiratory depression an opioid antagonist may be used as an antidote in early studies of opioids” |  |  |
| Lines 278-280 & Line 286 |  | Comment: Lines 278-280 (Inclusion and exclusion) and line 286 (enrichment strategies) are a bit non-specific.Proposed change: If referring to phenotype, suggest editing line 280 to say “…might be predictive of the detection of a treatment effect **based on genotype or phenotype**.” |  |  |
| Line 284 |  | Comment: A cross-over design may not be appropriate in case of regular(ly) recurrent pain, the terminology is ambiguous. Please specify that this does not refer to intermittent pain or waxing and waning pain.Proposed change: A cross-over design maybe appropriate in case of stable pain symptomatology, where large variations can be excluded. |  |  |
| 290-1 |  | Comment: The draft guideline states that time to peak effect should be measured in dose-response studies. However there will be certain circumstances where this may not be appropriate, therefore we suggest adding “if appropriate” to qualify the statement. Proposed change (if any): Studies should be designed to inform the appropriate starting dose and titration schedule, and to provide information on time to onset of effect, time to peak-effect (if appropriate) and duration of effect. | Important |  |
| 290-291 |  | Comment:The guideline should include recommendations on how to measure onset of effect, time to peak-effect and duration of effect.Proposed change:It is necessary to characterize the dose-response and/or exposure-response profile of a new medicinal product. Studies should be designed to inform the appropriate starting dose and titration schedule, and to provide information on time to onset of effect, time to peak-effect and duration of effect. **Onset of effect is commonly evaluated using two stopwatches. The first measure corresponds to the Time to First Perceptible Relief, and the second measure to the Time to Meaningful Relief. A sensitive and reliable measure of onset of effect is the Time to Confirmed Perceptible Relief defined as the time to the first perceptible relief, but only if meaningful relief is eventually achieved. This derived measure has the advantage of eliminating a large proportion of placebo responders who experience minimal relief. Repeated measures of pain intensity and pain relief over the trial period should establish the time to peak-effect. The duration of analgesia generally is defined by the median time to a request for rescue or re-medication.**Depending on the active substance, identification of the highest tolerated dose might not always be possible as it may depend on pain intensity and/or duration of treatment (e.g. with opioids). Ceiling effects should be evaluated. |  |  |
| Line 294 |  | Comment: “Ceiling effects should be evaluated” is vague. Does this mean that dosing to emax in population or titration to maximum effect in an individual?Proposed change: Please clarify or remove.  |  |  |
| 295 |  | Comment: The draft guideline states that flexible dosing is insufficient for assessing dose response. We consider that the guideline should not rule out being able to make an argument for flexible dose-ranging in some circumstances.Proposed change (if any): Flexible dosing trials are generally insufficient to provide data on dose-response. | Important |  |
| Lines 295-298 |  | Comment: It does not tell you what would be acceptable in establishing dose response if you do need to titrate individuals (ref to dose response workshop).Proposed change: Conventional fixed dose-response studies are not always feasible, especially in the treatment of chronic pain with strong opioids, the dose has to be titrated to clinical response and may vary widely according to pain intensity and the development of tolerance. In such situation design and analysis of the exposure response using appropriate model based approaches is highly recommended.Also it would be much more useful if this section referred to the joint shared learnings from the recent joint EFPIA/EMA dose response workshop e.g.<http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/06/event_detail_000993.jsp&mid=WC0b01ac058004d5c3>Table 1 Key learnings Dose selection is a shared risk **D-E-R characterisation** is a key component of the development and evaluation of medicinal products. Especially for children, elderly and ethnic groups this is the mainstay of drug development. Failure to reproduce this information at the stage of MAA, misses the opportunity to mitigate regulatory uncertainties and may result in denial, delays in approval, and additional regulatory requirements in terms of post approval commitments. Traditional statistical **pairwise comparisons** in phase 2 trials to support dose selection, by testing for statistically significant differences between the groups **are not a regulatory requirement, and are suboptimal** in terms of dose selection. **Dose ranging studies** should be designed for estimating dose response characteristics. As many as 4-7 active doses across a >10-fold range (e.g. 0.1 - 1.0 of the maximum tolerated dose-MTD) might be targeted **adapting to the reality** of the specific drug and disease state. Mathematical, statistical and pharmacological **methodologies** to charactertise D-E-R and optimal dose selection are scientifically well developed, available for application and welcomed by regulators. These should be tailored to the specific development needs |  |  |
| Line 305 (Section 5.2.4) |  | Comment: Section 5.2.4 tried to provide general advice on comparator, add-on, trial population, rescue medication and concomitant etc. Some of this is repeated in 6.2.5 for Chronic pain studies. This is repetitive and confusing.Proposed change: Consider deleting 5.2.4 and having separate sections covering these items for acute and chronic pain trials in 6.1 and 6.2. Begin more specific for each situation would reduce duplication and confusion. |  |  |
| Lines 306-317 |  | Comment: It would be helpful if CHMP recognise and clearly state the need for placebo control.Proposed change (if any):  |  |  |
| Lines 307 - 309 |  | Comment:**5.2.4 – Choice of comparator (monotherapy trials)**The challenges related to the use of placebo in chronic pain studies should be mentioned in this section. For these studies and in accordance with Section 6.2.5 (*lines 652 – 659*), the possibility to investigate placebo response through run in periods should be specified.Proposed change (if any):*“Due to a high and variable placebo response rate in pain trials, placebo controlled superiority trials are in principle necessary. For chronic pain trials, run in periods can be considered for addressing the placebo response.”* |  |  |
| Lines 307-317 |  | Comment:There will be development programmes where inclusion of an active comparator as a 3rd arm is undesirable for ethical and practical reasons; for example when there is not an approved standard of care or approved medicinal product, or when the population in the clinical development program differs from that of the approved indication. In addition, patient variability in response to a medication often leads to heterogeneity of pain treatment and cycling of treatments which does not enable identification of a suitable active control. In some cases, a randomised withdrawal design can be an appropriate design to address the high and variable placebo response rate in pain trials and are likely to produce interpretable results without the need for reference to an active comparator. See additional comments on the randomised withdrawal design in the section on Lines 640 to 641 below. Proposed change (if any):‘In general a randomised controlled ~~parallel group~~ trial is the most appropriate design for confirmatory evidence of efficacy in pain trials. Due to a high and variable placebo response rate in pain trials, placebo controlled superiority trials are in principle necessary. ~~In most situations~~  Addressing variable placebo response rate should be considered in the design of clinical trials to assess pain. When appropriate, ~~it is advisable also to include~~ an active comparator of known effectiveness may be included to give context to the measured differences from placebo and to facilitate an evaluation of the clinical relevance of those differences…Posology, mode of action, time to onset of efficacy, duration of action and safety aspects should be taken into account. However, there are situations where including an active comparator may not be feasible, such as when there is not an approved medicinal product or standard of care. In addition, patient variability in response to a medication often leads to heterogeneity of pain treatment and cycling of treatments which does not enable identification of a suitable active control. A randomised withdrawal design may address the high and variable placebo response rate in pain trials without the need for reference to an active comparator It is not usually…’ |  |  |
| 311-313 |  | Comment:In our opinion the current sentence is not correct as puts together the comparison of active comparator vs new medical product and active comparator vs placebo. Regarding the first comparison we agree that no formal demonstration of non-inferiority is to be required. However, in the second case the confirmation of the superiority of the active comparator vs placebo, this is relevant in order to assess the sensitivity of the study and as a validation of the selected pain model.Proposed change:In most situations it is advisable also to include an active comparator of known effectiveness to give context to the measured differences from placebo and to facilitate an evaluation of the clinical relevance of those differences. **In such placebo controlled superiority studies including an active comparator, the demonstration of superiority of the active comparator versus placebo is required as a confirmation of the sensitivity of the model of pain.** It is not usually necessary formally to demonstrate non-inferiority to the active comparator but estimates of treatment effect differences between active comparator and new medicinal product, **~~as well as active comparator and placebo~~**, should be reported with confidence intervals. |  |  |
| 318-320 |  | Comment:Also in this case the confirmation of the superiority of the active comparator vs placebo is relevant to assess the sensitivity of the study and as a validation of the selected pain model.Proposed change:Trials aiming to show superior efficacy to an active comparator are acceptable but even in this case it may be preferable to include a placebo arm in order to evaluate the absolute efficacy and safety profile of the new agent**, as well as to confirm the sensitivity of the selected model of pain.** |  |  |
| Lines 318 - 320 |  | Comment:**5.2.4 Confirmatory efficacy studies (acute and chronic pain)**Terms “new medicinal product” and “new agent are used in this section. A common wording should be used throughout the text.Proposed change (if any):*“Trials aiming to show superior efficacy to an active comparator are acceptable but even in this case it may be preferable to include a placebo arm in order to evaluate the absolute efficacy and safety profile of the new ~~agent~~ medicinal product.”* |  |  |
| Line 321 |  | Comment: With regards to “Add on treatments and combination treatments”. Proposed change (if any): Although mentioned later in the document, it may more appropriate to mention this here to discuss multi-modal treatment for pain. Non-pharmacological should be considered as well. |  |  |
| 321 |  | Comment: It would be helpful if this section could be further clarified to support the development of add-on therapies for the broad indications foreseen in the guidance (e.g. peripheral neuropathic pain).  |  |  |
| 324-326 |  | Comment: The new draft guidance contains information regarding confirmatory efficacy studies for add-on treatments. This section includes the following statement, “Patients should be randomised to receive either active test treatment or placebo in addition to a stable optimised dose regimen of open label background therapy.” It is suggested that this statement be modified to clarify that the open label background therapy may also include established treatments for neuropathic pain which are approved for indications other than pain conditions (e.g. anticonvulsants and antidepressants). This clarification would be consistent with Sec. 6.2.3 of the guidance which recognizes that a number of medicinal products with approved indications such as anticonvulsants and antidepressants (tricyclics) are established treatments for neuropathic pain. Additionally, we interpret this statement to mean that no active comparator is required. If this interpretation is accurate, it would be helpful if this is explicitly stated in the guideline.Proposed change (if any): “Patients should be randomised to receive either active test treatment or placebo in addition to a stable optimised dose regimen of open label background therapy. Open label background therapy may include established treatments for neuropathic pain which are approved for indications other than pain conditions (e.g. anticonvulsants and antidepressants).” |  |  |
| 329-332 |  | Comment: As the development of fixed combination products is out of the scope of the present guideline, just a sentence addressing the reader to the relevant guideline suffices. No additional comments are required.Proposed change:The development of fixed combination products for the treatment of pain should be conducted in accordance with the relevant guidelines. **~~The benefits of the combination over the single active substances and optimal dose regimen should be clearly demonstrated, considering both efficacy and safety.~~** |  |  |
| Line 333 |  | Comment: While screeners for NeP are mentioned later in the guidance, it would be helpful to include the Agency’s view on the use of patient-reported screening tools to identify an appropriate trial population in this section.Proposed change (if any): It would help if the Agency provides guidance on the acceptability and use of self-report screening tools to help identify (or exclude) an appropriate trial population. |  |  |
| Lines 334-342& L 594-595 |  | Comment: The need for distinct efficacy in subgroups of pain intensity (334-442) and 594-595 needs to be clarified by proving details on how these sub populations are identified. Also given that pain in many conditions is not static but changes over time and is dependent on how it is measured it is unclear when and how stratification would be appropriate. It would seem more appropriate to require that the sponsor provide “sufficient data to support the intended label” e.g. Mild to Mod or Mod to Severe. This would allow for sub-group analysis and covariate analysis to support the claims which would seem more appropriate given the variable nature of pain.Proposed change: Suggest removing need for stratification but request that sponsors provide sufficient evidence of effectiveness across the range of pain intensity that will be proposed in the submission. |  |  |
| 338-341 |  | Comment: To clarify that major categories of pain severity correspond to mild-to-moderate and moderate-to-severe in agreement with the pain models defined in the guideline. Pain categories (considered as mild, moderate and severe) are not so well defined and did not correspond to pain models described. In this sense stratification should be sufficient. Otherwise, in the case of a study in acute pain model of moderate to severe pain (e.g. major orthopaedic surgery) the requirement to power the study to show statistically significant efficacy for each subgroup (e.g. moderate or severe pain intensity) would require a considerably larger sample.In our opinion, in the cases where a confirmation of the efficacy in severe pain independent from data in less severe pain would be required, this could be provided by a pooled analysis of severe pain subgroups from various trials within the clinical development provided that study designs were similar enough. Proposed change:If more than a single pain model and/or major category of pain severity **(mild-to-moderate and moderate-to-severe)** are included, it is generally advised to power the trials to show statistically significant efficacy for each of these major subgroups.**~~In particular, efficacy in severe pain is likely to require confirmation independent from data in less severe pain.~~** Randomisation should be stratified accordingly. **In some cases, efficacy in severe pain is likely to require confirmation independent from data in less severe pain, this can be obtained from the pooled analysis of severe pain subgroups from various trials within the clinical development when study design are similar enough.** |  |  |
| 339 |  | Comment: In the section on trial population is it not clear whether the major categories of pain referred to are; mild-moderate and moderate-severe or mild, moderate and severe.Proposed change (if any): “If more than a single pain model and/or major category of pain severity **(mild to moderate or moderate to severe)** is included, it is generally advised to power the trials to show statistically significant efficacy for each of these major subgroups.” |  |  |
| 342-5 |  | Comment: The draft guideline states that patients with significant pain disorders other than the target disease should be excluded from the study. It also states that patients with depression or anxiety should be excluded if the drug is expected to have an effect on those conditions. While it is agreed that every effort should be made to exclude such patients, it may not be possible to do so because of the prevalence of some comorbidities with pain, without compromising the feasibility of conducting the study. It may also not be known whether the product will have a clinical effect on conditions like depression. In such circumstances it should be made clear that a review of the data by subgroups of other concomitant pain conditions and depression/anxiety status can be used to determine if the profile of the study drug is the same in these populations, rather than excluding them from trials. Proposed change: Patients with significant pain disorders other than the target disease or with disorders that could interfere with pain assessments should be excluded if feasible. Likewise, patients with anxiety or depression should in general be excluded if the tested drug is expected to have a significant effect on these conditions. If exclusion of certain subgroups of patients is considered inappropriate or infeasible then subgroup analyses may be undertaken to demonstrate that the comorbidities do not significantly change the effect of the study drug. | Critical |  |
| 349 |  | Comment: We are happy to see that the unbalanced randomisation is acceptable, since in fact may constitute a prerequisite in some pain indications. |  |  |
| 364 |  | Comment:In our opinion, it would be advisable to add the following clarification this paragraph:“It is currently recommended that patients who choose to take rescue medication are instructed to continue to participate fully for the remainder of the study period. This procedure is included to avoid potential patient bias because of treating participants differently (e.g., requesting rescue medication sooner if they perceive they will no longer be inconvenienced after taking the rescue medication).”[Reference: Cooper SA, Desjardins PJ, Turk DC et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain. 2016 Feb;157(2):288-301.] “Other approaches could be considered if adequately justified.”Proposed change:**It is currently recommended that patients who choose to take rescue medication are instructed to continue to participate fully for the remainder of the study period. This procedure is included to avoid potential patient bias because of treating participants differently (e.g., requesting rescue medication sooner if they perceive they will no longer be inconvenienced after taking the rescue medication). Other approaches could be considered if adequately justified.** |  |  |
| Line 365 |  | Comment: With regards to “concomitant therapy”.Proposed change (if any): Non-pharmacological is briefly mentioned here but it should be discussed earlier in the document. . |  |  |
| Lines 365-374 |  | Comment: It is helpful that CHMP recognise and clearly state the need for washout of concomitant treatmentsProposed changes (if any):  |  |  |
| 366-70 concomitant |  | Comment: The draft guideline states that concomitant treatments that might affect the patient’s perception of pain should not be permitted during the trial. This is to include not only medicinal products (OTC and prescription only), but also physical therapy, TENS and psychological support. These factors would be very difficult to measure and standardise in practice, particularly OTC medicines and non-medicinal treatments. While the use of stratification may be an option it is likely, particularly in the case of pain studies, that the list of possible concomitant medications would be significant in any single trial and it would therefore not be feasible to ensure formal stratification of even important concomitant therapies. We propose that in cases with multiple options for other treatments that subgroup analyses in the efficacy dataset would be more appropriate. Proposed change (if any): Treatments that might modulate the perception of pain or patients’ response to pain, either directly or by interacting with the investigational products should generally be avoided during the trial if possible. This includes not only medicinal products (including over the counter and alternative therapies), but also nondrug therapies such as physical techniques, transcutaneous electrical nerve stimulation (TENS), surgery or psychological / behavioural support. Where feasible, s~~S~~tudy designs should include appropriate washout periods of sufficient duration. Where unavoidable, concomitant treatments should be standardised and should remain stable for a defined period before and during the trial. It is acknowledged that this may be practically impossible given the difficulties curtailing use or standardising over the counter, alternative and non-drug therapies in such trials. Stratification for important concomitant therapies should be considered where necessary. In situations where exclusion from the trial or stratification is not appropriate, these factors should be assessed by subgroup analysis. The potential impact of the concomitant therapies on clinical efficacy measures must be evaluated. | Critical |  |
| 366-374 |  | Comment: the topic of avoiding physical therapy is controversial and must be controlled for. This comment alludes to physiotherapy that would be considered as “active” i.e. involving patients’ active participation, e.g. physical activity, with specific workouts, gym training, etc. led or instructed by a physiotherapist. There are several reasons for this: (a) For most patients with chronic musculoskeletal pain, especially chronic low back pain (irrespective of type of pain) and OA pain, physiotherapy in the sense of physical activity with specific workouts, gym training, etc. led or instructed by a physiotherapist, is first line therapy. It is neither feasible nor ethically defendable to for these patients to refrain from this type of physiotherapy during a 12-week or longer trial period. (b) it is also not clear for how long such a washout period would need to be and therefore also not clear for how long patients would need to refrain from any physiotherapy; ( c) patients would deteriorate in their pain if refraining from ongoing physiotherapy. This would negatively affect trial outcome and give false negative information on the efficacy of the drug and also not reflect actual use after possible launch.Proposed change: Patients on pre-defined concomitant non-pharmacological treatments, e.g. stable physiotherapy treatment, should remain on this stable intervention during the trail. The randomisation of the patient population should be stratified based on ongoing physiotherapy or other stable non-pharmacological treatment involving physical activity. Concomitant TENS or acupuncture should be washed out.  |  |  |
| 381 |  | Comment:In acute pain trials timing of pain assessments is of particular relevance. It is common that patients are included in the study only if they experience a certain pain intensity (i.e. inclusion criteria for the study). This confirmation triggers the patient randomization procedure which ideally should be very quick. Nevertheless, a time gap from pain intensity inclusion criterion to availability of the study drug for the patient is unavoidable. Then it is recommended to repeat pain intensity measurement immediately before study drug intake (baseline value). Considering that pain intensity is a subjective assessment, the repetition of the measurement is likely to result in a different value, which for some borderline results could be relevant. In our opinion this considerations should be included in the guideline, together with the recommendations to manage the potential discrepancies. That is, pain intensity value measured to verify inclusion criteria (randomization pain intensity) should be used to define study subgroups; and pain intensity measured immediately before study drug intake (baseline value) should be used for the study analyses. Proposed change:**In acute pain trials timing of pain assessments is of particular relevance. It is common that patients are included in the study only if they experience a certain pain intensity (i.e. inclusion criteria for the study). This confirmation triggers the patient randomization procedure which ideally should be very quick. Nevertheless, a time gap from pain intensity inclusion criterion to availability of the study drug for the patient is unavoidable. Then it is recommended to repeat pain intensity measurement immediately before study drug intake (baseline value). Considering that pain intensity is a subjective assessment, the repetition of the measurement is likely to result in a different value, which for some borderline results could be relevant. It is recommended that pain intensity value measured to verify inclusion criteria (randomization pain intensity) should be used to define study subgroups; and pain intensity measured immediately before study drug intake (baseline value) should be used for the study analyses.**  |  |  |
| 381-383 |  | Comment:The following sentence: “Depending on the clinical situation, pain measurements should be performed not only at rest but also on movement or after applying an appropriate stimulus. Pain on movement is very important for function, whereas pain at rest correlates more with comfort.” should be more appropriate to section 5.2.1 or alternatively to secondary endpoints description |  |  |
| 390-405 |  | **Comment:**Defining primary efficacy measures and estimands**Proposed change:**We suggest moving the examples for efficacy measures in acute pain as PID, SPID, TOTPAR to section 6. Specific considerations for clinical development, where one can also find a discussion on efficacy endpoints in chronic pain. |  |  |
| 391-397 |  | Comment:According to the current text (long-term studies excerpted): “Mean differences of pain intensity (PID) at specific time points are commonly used for analysis” and “Alternative approaches are based on the analysis of the area under the time-analgesic effect curve for pain intensity (SPID) or pain relief (TOTPAR). These summary measures reflect the cumulative response to the intervention, but do not provide information regarding onset or peak of analgesic effect.”In our opinion this is misleading, as it might be interpreted that “mean PID at specific time points” should be the primary variable and SPID is just an “alternative approach” of limited value as provides less information.It is agreed that primary efficacy measures should derive from pain scores, and that PID time-course is essential to determine the peak of analgesic effect and to assess the onset of analgesia (together with the stopwatches) and therefore it should be reported.However, either the comparison of mean PID at a single time point or the comparison of mean PID over a period of time (i.e. over specific time points) do not provide information regarding onset or peak of analgesic effect. In fact, the comparison of mean PID at a single time is of limited value as it depends only from baseline pain intensity and pain intensity at the considered time point without considering any intermediate values.The second case, comparison of mean PID over a period of time, implies averaging PID to our knowledge, there is no current consensus on the procedure to do so reliably.It is therefore surprising that the Sum of Pain Intensity Differences (SPID), is not considered as the primary efficacy variable recommended for short term studies. SPID is a time-effect variable derived from pain scores with a clear methodology and that has been extensively used over decades in analgesic studies. Proposed change:The exact way in which the primary efficacy measure is derived from the reported pain scores will depend on the clinical setting and must be justified and clearly pre-specified in the protocol. **In short term studies m~~M~~**ean differences of pain intensity (PID) at specific time points **should be provided, the Sum of Pain Intensity Differences (SPID), that is the analysis of the area under the time-analgesic effect curve for pain intensity, is recommended as the primary efficacy variable. ~~or i~~I**n long-term studies the weekly averages of the daily measurement compared to baseline**~~, are~~** **is** commonly used for analysis. A**n a**lternative approach **in short term studies can be~~es are~~** based on the analysis of the area under the time-analgesic effect curve for **~~pain intensity (SPID) or~~** pain relief (TOTPAR). **~~These summary measures reflect the cumulative response to the intervention, but do not provide information regarding onset or peak of analgesic effect.~~** |  |  |
| 399-403 |  | Comment:The description of these sensitivity analyses should be more precise and justified as the rationale for this “extremes” remains unclear. Considering that usually patients who choose to take rescue medication are requested to perform an additional assessment of their pain intensity immediately before rescue medication intake, and instructed to continue to participate fully for the remainder of the study period (and therefore assessing their pain intensity at scheduled time points). The meaning of “all data regardless of rescue medication” seems to refer to data from all scheduled time points, excluding assessment prior to rescue medication intake. Anyway, both considerations will unduly attribute the effect of the rescue medication to the study drug, therefore this cannot be considered as a sensitivity analysis.The proposed alternative of including data only in patients not requiring rescue medication seems too restrictive to be recommended as a sensitivity analysis, taking into account that in placebo controlled studies it is expected that a high number of patients use rescue medication and that the distribution is not expected to be homogeneous among the study arms.Finally, in our opinion, the alternative “up to first use of rescue” deserves to be further discussed considering alternative approaches reported in literature.Proposed change: This includes in particular the use of rescue medication, which will typically be different in the active and placebo groups. **Different approaches have typically been used to impute Pain Intensity and Relief scores occurring after rescue last observation carried forward (LOCF) baseline observation carried forward (BOCF), and worst observation carried forward (WOCF). The LOCF approach consists in measuring Pain Intensity and Relief just before rescue and using those scores for any subsequent planned assessments during the time the rescue is expected to work. The latter two approaches consist in carrying forward baseline value (or worst value during the period) regardless of the patient’s score immediately before the rescue medication. The approach selected for the primary analysis should be adequately justified.** It **~~may be appropriate to specify~~is recommended to include** alternative **approaches as** sensitivity analyses**. Additionally a sensitivity analysis~~between the extremes of including all data regardless of rescue medication (ITT), and~~** including data only in patients not requiring rescue medication **~~(or up to first use of rescue)~~may be considered, however this will be likely impaired by the high number of patients excluded (especially in placebo arm).** |  |  |
| Lines 404-405 |  | Comment: It is not specified how time to meaningful pain relief and duration should be measured.Proposed change: “Measures of the temporal aspects of the treatment of pain, such as time to onset of meaningful pain relief, **assessed using stopwatch methodology,** and its duration, **assessed using time to rescue medication use,**…” |  |  |
| 406 |  | Comment:It is not clear if the responder analysis is to be considered a primary, co-primary or secondary endpoint. |  |  |
| 406-415 |  | **Comment:**The guideline provides a general recommendation on how to handle patients who discontinue prematurely:“Patients who discontinue the trial prematurely or who require more than a pre-specified amount of rescue medication should generally be defined as non-responders.”The “EMA Guideline on Missing Data in Confirmatory Clinical Trials” differentiates between different reasons for discontinuation and between different trial objectives, see e.g. the following citations: “It may be appropriate to treat data missing for different reasons in different ways.”“If a patient prematurely withdraws from the study it would be normal to consider this patient as a treatment failure. However, the best way of categorisation will depend on the trial objective (e.g. superiority compared to non-inferiority).”**Proposed change:**A similar approach could be adopted in this guideline as well, we i.e. suggest to adapt to “Patients who discontinue the trial prematurely *due to treatment related reasons* or who require more than a pre-specified amount of rescue medication should generally be defined as non-responders.” |  |  |
| 431-433 |  | Comment:Since Lines 498-504 provide more detail as to when maintenance of effect data is required for products intended for short term use, this text should be moved from its present location a reference to be included here (or as a minimum a refence to lines 498-504 made). Proposed change:The requirement to establish maintenance of efficacy of a new medicine should not be restricted to medicinal products intended primarily for long term use but should also take into account the likelihood of prolonged and repeated use of medicinal products that are primarily intended for short term use. **Where such products have a well characterized mechanism of action (e.g. conventional NSAIDs or mu agonist opioids), the need to establish maintenance of efficacy will be determined on the basis of the likelihood of repeated use. For medicinal products primarily intended for short term use with a fully or partly novel mechanism of action, it is required to establish maintenance of efficacy, long-term trial(s) in an appropriate pain model (as described in 6.2.2 section) will be necessary.** |  |  |
| Lines 431-433 |  | Comment: It does not seem reasonable to expose patients to drug for longer than is clinically necessary. Therefore demonstration of maintenance of effect for drugs only intended for, and which have marketing authorisation for solely, acute use would seem difficult to justify ethically.Proposed change (if any): Remove lines 431-433. | Important |  |
| 441-3 |  | Comment: The intended meaning of the statement below regarding the inter-individual variability of pain scores and the consideration of the underlying medical condition in selecting a pain model is not clear. We request that the Agency rewrites this statement to make it clearer what scenario they consider to be (in)appropriate in this regard.Passage in the guidance proposed for rewriting: As pain scores always represent subjective categories of pain severity with a high inter-individual variability, the underlying medical condition is an essential consideration in selecting a pain model.  | Important |  |
| 462-464 |  | Comment:Acute pain is of short duration and declines with the healing of the underlying injury or disease. In most of acute pain models considering the average time to recovery is a useful indicator of the study duration. However, taking into account the inter-patient variability, it is advisable that the duration of the study treatment is slightly superior to the expected average duration of the pain (time to recovery), unless tolerability/safety concerns exist. This would increase the number of patients who receive treatment up to full recovery and expand safety data.Proposed change:Study duration may vary from hours to weeks in acute pain trials, depending on the pain model or clinical situation being studied. **In most** **acute pain models considering the average time to recovery is a useful indicator of the study duration. However, taking into account the inter-patient variability, it is advisable that the duration of the study treatment is slightly superior to the expected average duration of the pain (time to recovery), unless there are tolerability/safety concerns. This would increase the number of patients who receive treatment up to full recovery and increase safety data.** |  |  |
| Insert in lines 479-480 |  | Comment: In the case of new formulations of existing active substances, for example faster -acting or longer lasting formulations, it should not be necessary to evaluate the new formulation in both somatic and visceral pain to obtain a general pain indication if efficacy of the active substance in both types of pain has already been demonstrated. Demonstration of efficacy in one or the other should be adequate.Proposed change: In the case of new formulations of existing active substances, for example formulations designed to be faster acting or longer lasting, demonstration of efficacy in either somatic or visceral pain would be adequate to obtain a general pain indication, if efficacy of the active substance in both types of pain has previously been demonstrated.  | Important |  |
| Insert after Line 475 |  | Comment: With regard to the examples of pain models in Line 486 Table 1 it is considered appropriate if efficacy in demonstrated in moderate to severe pain to extrapolated these results to mild to moderate pain in the same model. For pain models to be sensitive (including extraction of impacted third molars and dysmenorrhea), it is often necessary to have baseline pain greater than 6 on the NRS or 60 mm on a VAS, which is categorized as moderate to severe pain in the table.Proposed change: Efficacy demonstrated in moderate to severe pain can be extrapolated to mild to moderate pain, in the same model. | Important |  |
| Lines 490-491 |  | Comment: It is not clear why a 4-way crossover design is necessary in dysmenorrhea? The longer duration studies make subject retention challenging, and require a larger sample size. A 3-way crossover should be adequate, especially if only three treatments are being evaluated (e.g., Investigational drug, active control, and placebo). Proposed change: “…a crossover design with at least **3** treatment periods is recommended.”  | Important |  |
| 498-504 |  | Comment:This paragraph seems to be more relevant and useful in Lines 431-433. It is proposed that this should be relocated to section 5.2.5 as detailed above.Proposed change:**~~If a new active substance intended for use in acute pain can potentially also be used for longer term treatment, data on the development of tolerance and maintenance of efficacy are required. If the mechanism of action is fully or partly novel, long-term trial(s) in an appropriate pain model will be necessary. If the mechanism of action is well characterized (e.g. conventional NSAIDs or mu agonist opioids) extrapolation of data from products in the same class can be accepted on a case by case basis. In the case of new formulations of existing active substances, additional data on tolerance and maintenance of efficacy could potentially be required if these are not already well characterised.~~** |  |  |
| Line 506 |  | Comment: Previous draft guidance contained a table showing type of pain and examples of models to study and this type of information is included for acute and neuropathic pain. Proposed change (if any): Additional information would be welcomed either in tabular or other format, but including acceptable models to study. | Important |  |
| Lines 528-531 |  | Comment: While requirements for 3 types of indication are provided. The concept of drug development for a phenotypically optimised population across pain models is not covered. Proposed change: Introduce this fourth scenario and provide guidelines on the data package that would be required. |  |  |
| Lines 511-512 |  | Comment:It is important to demonstrate homogeneity within patient populations studies for pain conditions. Homogeneity may include verifiable similarities within the pain condition of interest, but could alternatively include patients with a pain condition with the same pathophysiology occurring in different clinical settings. The pathophysiology could be shown to be the same using an objective and reproducible test. Proposed change (if any): '…may have additional impact. It is important to demonstrate homogeneity within patient populations studies for pain conditions. Homogeneity may include verifiable similarities within the pain condition of interest, but could alternatively include patients with a pain condition with the same pathophysiology occurring in different clinical settings. The pathophysiology could be shown to be the same using an objective and reproducible test. Better characterisation… ' | Important |  |
| Line 522-524 |  | Comment: “Chronic pain” (line 519) is the preferred target indication by the guideline, but in the next section it says that “it is recognised that in the past the term “chronic pain” included conditions we now recognise as chronic mixed pain….”. This suggests that this chronic pain description is rather a past term Therefore could the guidelines be clear that the current interpretation of the term “chronic pain” is still mixed pain, nociceptive pain, etc. Proposed change: Line 522-524The term chronic pain includes chronic mixed pain, as well as long-standing nociceptive pain (somatic and visceral), neuropathic pain conditions, and to a certain extent cancer pain. Therapy should be tailored based on the predominant type of pain. | Important |  |
| 520-1 |  | Comment: We consider that the statement regarding disease specific indications should be made more definitive as it is already caveated by the inclusion of ‘where appropriate’ in the sentence. It also seems to be at odds with other sections of the guidance which make clear that disease specific indications are possible e.g. line 528-529 Proposed change: Disease specific indications will ~~may also~~ be possible where appropriate data are provided. | Important |  |
| 528-531 |  | Comment:This section is not very clear and raises a number of important questions. To use the present example in the guidance:Is CLBP considered “a single model” and at the same time two models? i.e. it appears it would it be required to separate the two components? If a nociceptive–only or a neuropathic-only population is studied, how does this affect the label for a specific condition? Do both components need to be documented separately within a study or would the pain intensity endpoint be considered at an overall level? Will it be possible to get a CLBP indication if both neuropathic and nociceptive components are not addressed separately within the study/ program? Proposed change: Better guidance as to differentiation is requested. | Important |  |
| Lines 528-531 |  | Comment: In the case of “mixed” pain models, it would be helpful to clarify whether recruitment of (and adequately characterising at baseline) subjects with predominantly/exclusively nociceptive or neuropathic pain from a “mixed” model population would be an acceptable pivotal study to support chronic nociceptive or neuropathic pain indications (as appears to be suggested in lines 574-576 for neuropathic pain).Proposed change (if any): The recruitment of (and adequate characterization of) subjects with predominantly/exclusively nociceptive or neuropathic pain from a “mixed” model population would be an acceptable pivotal study to support either chronic nociceptive or neuropathic pain indications. | Important |  |
| 528-531 |  | Comment: In the description of a need to demonstrate an effect on both nociceptive and neuropathic components in a mixed pain model, it is unclear what endpoint could be used to demonstrate an effect.Proposed change (if any):A single (composite) endpoint that satisfies both components or co-primary endpoints are acceptable to demonstrate the effects. | Important |  |
| Line 530, line 533 |  | Comment: In the event that it is mechanistically unrealistic to require that a single pain medication has an action on both nociceptive and neuropathic pain in a mixed pain model, it should be clear that it may still offer an acceptable therapeutic options for patients with the mixed pain condition Proposed change (if any): Suggest revising the text on line 530 to say “mixed it ideally the drug should demonstrate an effect on both nociceptive and neuropathic components but the demonstration of a meaningful impact on the predominant pain component and functional improvement could still be useful.” | Important |  |
| 532 |  | Comment: The draft guideline states that if models of just neuropathic pain are studied, the indication will be restricted accordingly. There is no mention of the equivalent indication for nociceptive pain. We consider that, as with neuropathic pain, if models of nociceptive pain only are studied, then an indication for nociceptive pain should be possible. Proposed change: If models of just neuropathic or just nociceptive pain are studied, the indication will be restricted accordingly.  | Critical |  |
| 533-4 |  | Comment: We appreciate the guidance stated here with regard to the need to make a judgement on the extent of the data needed for a chronic pain indication. However, we consider that guidance over the number of studies (and number of models) expected to achieve a chronic pain indication would be beneficial to the implementation of guidance. It is not considered possible or indeed desirable to provide a prescriptive proposal which will cover all possibilities, but developers would find it helpful to understand if there is a generally accepted minimum (e.g. one model for each type of pain – predominately neuropathic and nociceptive) or a worked (hypothetical) example showing a pathway to a chronic pain indication. With this guidance and the statements provided in lines 534-538 the developer could then take into account the specific molecule.Passage of guidance for extension with the information proposed above: To justify a general indication for the treatment of chronic pain, compelling evidence of efficacy in both neuropathic and nociceptive pain components has to be provided.  | Important |  |
| Line 534 |  | Comment: It would help to clarify if the broad indication of chronic pain which includes studies in models of neuropathic and nociceptive pain other than CLBP would therefore automatically cover a mixed pain such as CLBP? Proposed change if any: Insert after Line 533 - A general indication of chronic pain which requires compelling evidence of efficacy would also include use in a chronic mixed pain indication such as CLBP. | Important |  |
| 536-8 |  | Comment: The draft guideline indicates that the acceptability of extrapolation of efficacy data across pain models will depend on the known properties of the drug. It is unclear what known properties will be key to determining the acceptability of extrapolation and we request that further details be included to clarify what would need to be demonstrated about a drug in order to permit extrapolation to broader indications.Passage from guidance: The extent to which efficacy data can be extrapolated across pain models will depend on the known properties of the drug and others in its class and needs to be considered on a case by case basis. Such properties would include… | Important |  |
| 538-9  |  | Comment: If no further example pain models are included in Section 6.2.2, we suggest deleting the statement referring to descriptions of the different models as these are not discussed in the sections indicated.Proposed changes: ~~Examples for suitable pain models in the different categories of pain of long duration are discussed in the following.~~  | Editorial |  |
| 541-546 |  | Comment: For the reasons given in the general comments section above, it is considered that this section will need to provide further guidance and clarity on the requirements for studying chronic nociceptive pain. The difficulties of studying and characterising patients in clinical trials according to their pathophysiological aspects are acknowledged here (line 544) but are apparently still required. As stated above a clinical development pathway to a chronic nociceptive pain model that can reasonable be achieved is needed (and preferably one in line with those for other regulatory regions where the presence of maladaptive changes are not necessary to describe chronic pain) in this section.  | Critical |  |
| 545-546 |  | Comment:It is not clear whether osteoarthritis of the hip and/or knee clearly featuring maladaptative characteristics would be an adequate pain model to support a chronic pain indication.And, if this is the case it should be considered a nociceptive or a mixed pain model? |  |  |
| Line 550 |  | Comment: A similar statement to that included in Lines 574-576 for neuropathic pain should be included for nociceptive pain.Proposed change:Demonstration of efficacy in chronic mixed pain models with predominantly nociceptive symptoms could provide supportive evidence (e.g. some cancer pain, predominantly nociceptive CLBP). The nociceptive component should be reliably documented. | Important |  |
| 541-546 |  | Comment: If the term maladaptive is used in this section and throughout the draft guideline. It is our view that within the industry this is open to considerable differences in interpretation; therefore confirmation is needed of the definition of this term as used in this guidancePassage from guidance: Long-standing nociceptive pain conditions such as osteoarthritis of the hip and/or knee do not always feature maladaptive characteristics. Maladaptive characteristics refer to … | Critical |  |
| 547-550 |  | Comment: We fundamentally disagree with the guideline assertion that data from trials in patients with osteoarthritis of hip and/or knee are unsuitable for support of chronic pain indications, unless “maladaptive characteristics” are shown. Line 517 & 518 of the guidance state that “the contribution of nociceptive and neuropathic components in patients with chronic pain is not routinely evaluated in general clinical practice”, therefore there seems to be no clear rationale for the guideline distinction between OA patient populations in trials (+/- maladaptive features) resulting in apparent differences in labeling (chronic pain or long-standing pain), which are of limited value to the physician.  | Critical |  |
| 556-561 |  | Comment: Current wording is partly not updated as to current labels and evidence and partly inaccurate. SSRIs and topical capsaicin cream are mentioned but are not recommended due to lack of efficacy and should then not be included. It would be inconsistent if the current guideline is contradictory to current evidence and international guidelines. For reference see:Finnerup NB, Attal N, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet 2015. [http://dx.doi.org/10.1016/S1474-4422(14)70329-1](http://dx.doi.org/10.1016/S1474-4422%2814%2970329-1). Proposed change (if any): Neuropathic pain is frequently resistant to treatment and if an effect is observed may be transient. Non-steroidal anti-inflammatory drugs are generally ineffective. A number of medicinal products have the approved indications, including anticonvulsants (gabapentinoids), carbazepines (for the treatment of trigeminal neuralgia only), tricyclic antidepressants (tricyclics), SNRIs, topically applied lidocaine patches and capsaicin patches: these are all established treatments for neuropathic pain but have variable efficacy.  | Important |  |
| 567-569 |  | Comment: It is not clear how many different pain models are required for the expansion of an indication from a specific condition to a more general indication. Proposed change (if any): “To justify a general indication for the treatment of neuropathic pain, efficacy needs to be demonstrated independently **both** in **a** model of central and **a model of** peripheral neuropathic pain.” | Important |  |
| 568-569 |  | Comment: The statement “If models of just central neuropathic pain or of just peripheral neuropathic pain are studied, the indication will normally be restricted accordingly.” The previous draft guidance indicated that for the broader claim of peripheral neuropathic pain, the efficacy of the tested drug should be shown separately in more than one clinical situation of peripheral pain (e.g. post-herpetic neuralgia and painful diabetic neuropathy). It would be helpful to indicate in the current draft guidance that more than one clinical situations would need to be studied to obtain the broad indications of central and peripheral neuropathic pain if this is the expectationProposed change (if any): Insert for Line 569 - More than one clinical situations would need to be studied to obtain the broad indications of central and peripheral neuropathic pain. | Important |  |
| 570-572 |  | Comment: It is recognized that DPN and PHN are well studied models of peripheral neuropathic pain. However, the PHN incidence is declining and the prevalence limited. However, there are other neuropathic pain models that are also well characterized, such as idiopathic small fiber polyneuropathy, a group significantly larger than PHN. Also the prevalence of Chemotherapy induced neuropathic pain (CINP) and antiretroviral therapy induced neuropathy is increasing.  Proposed change (if any): Suitable peripheral neuropathic models include post herpetic neuralgia, diabetic painful neuropathy, trigeminal neuralgia, idiopathic small fiber polyneuropathy, antiretroviral therapy induced neuropathy and chemotherapy induced neuropathic pain. | Important |  |
| 577-581 |  | Comment: This text is seems to be unclear or perhaps there is a misunderstanding. - With the proposed text, does the guidance address treatments only intended for the treatment of evoked pain, or neuropathic pain in patients characterized by irritable nociceptors/ hyperphenomena, as characterized by e.g. QST? The former seems obsolete, while the latter is highly relevant. Current text (1): ”*Treatments intended to have an effect on stimulus evoked pain (allodynia or hyperalgesia)…* “ – is this really what is meant to be addressed in this paragraph? In most patients with neuropathic pain who receive an efficacious treatment this will also have a reduction in supranormal response to evoked stimuli if present at initiation of treatment. Current text (2): “… *should be studied in a suitable defined target population*” – this is a bit confusing since the population would be defined already by the previous part of the sentence.Current text (3): “*Depending on the mechanism of action of the new treatment and the anticipated claims this could be either in a specific trial or within a larger mode general trial population. In the latter case stratification according to stimulus evoked pain should be considered*.” – what would be the more general population of evoked pain stimuli?In summary, there seems to be a confusion of neuropathic pain (intensity of perceived spontaneous pain, e.g. 12-hour recall, assessed by a pain intensity scale) in patients who present also with allodynia and hyperalgesia and possibly occurring patient populations presenting with allodynia and hyperalgesia but without spontaneous pain. This latter group does not really seem to be within the scope of this guideline. Patients with spontaneous pain due to neuropathy **with** allodynia and hyperalgesia may have a differentiated treatment response compared to patients with spontaneous pain due to neuropathy **without** allodynia and hyperalgesia, based on mechanism of action of the drug.Please see for reference: Demant et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study. Pain. 155(11):2263-2273, 2014. doi: 10.1097/j.pain.0000000000000266 EMA/CHMP/SAWP/604202/2015 Procedure No.: EMEA/H/SAB/066/1/QA/2015/SME Product Development Scientific Support Department  | Important |  |
| 582-589 |  | Comment: As discussed in the general comments section above, it is our position that a predominantly nociceptive (early) CLBP population would be suitable to support a claim for chronic nociceptive pain and that a mixed CLBP population is a suitable model to support a broader chronic pain claim, which is not made clear in the guidance.**6.2.4. Mixed Pain**Mixed pain is common and CLBP is the example most commonly encountered in clinical practice. CLBP refractory to currently available treatments is a substantial healthcare problem and may therefore be considered as an appropriate specific target population. Multiple and complex factors are typically involved in the evolution of mixed pain, which in the case of CLBP generally starts as a primarily nociceptive pain condition with or without nerve compression in addition. Due to maladaptive processes further neuropathic characteristics develop over time. As the typical chronic mixed pain picture develops, the underlying structural damage correlates poorly with the pain experience. Appropriate studies of a mixed CLBP population would lead to a CLBP indication: however if the population studied consists of the predominantly nociceptive or neuropathic components of CLBP, then the indication could be restricted accordingly. | Critical |  |
| 594-595608-609 |  | Comment: It is unclear in the description of a suitable patient population if “at least moderate to severe pain (typically VAS >= 40 mm or NRS ≥=4)” refers to baseline pain prior to, or after washout of background therapy.The text in lines 608-609 seems to indicate that baseline pain severity categories refers to pain categorization after washout.Proposed change (if any):Line 594: “It is generally recommended to include patients with at least moderate to severe pain, (typicallyVAS >= 40 mm or NRS ≥=4 **in the pre-washout period**). | Important |  |
| 602-9 |  | Comment: The guideline mentions the need for more complex methods for categorising pain severity than baseline pain scores in patients when a wash-out period is not appropriate. Please provide more detail on the methods that are recommended Trial design examples where this issue has been managed would be helpful.Passage from guidance: The washout of prior non-trial medications may raise particular issues in chronic pain trials. A potential effect not only on pain perception but also on mood may need to be considered when withdrawing treatments such as tricyclics or anticonvulsants. Patients with severe chronic pain are likely to be receiving partially effective analgesic treatment before entering a clinical trial and withdrawing that treatment before commencing randomised trial medication can be problematic. In such cases a pre-study wash-out period in order to assess pain intensity without treatment might not be feasible. Baseline pain scores might not therefore be a reliable way of selecting patients with more severe pain and more complex methods for categorising patients according to pain severity may be required. An example of a possible trial design which would achieve this is… | Important |  |
| Lines 602-638 |  | Comment: This text appears to relate predominantly to neuropathic pain. For reasons of clarity it may be helpful to separate out the nociceptive and neuropathic considerations in separate sections rather than combining all under section 6.2.5Proposed change (if any): Please consider re-writing this section - for reasons of clarity it may be helpful to separate out the nociceptive and neuropathic considerations in separate sections rather than combining all under section 6.2.5. | Important |  |
| 637-638 |  | Comment: Electrophysiological variables are useful to detect if the pain is of peripheral neuropathic origin, and what sensory fiber types have a functional ailment, but it cannot specifically distinguish the etiology behind the neuropathic pain. Proposed change (if any): Electrophysiological variables may be useful to clarify pain as being of neuropathic aetiology and to demonstrate proof of mechanism, but does not correlate sufficiently with pain intensity to be considered as surrogate efficacy endpoints |  |  |
| Lines 640 to 641 |  | Comment: Guidance should also give examples and details of potentially suitable alternatives. This includes enrichment strategies, which may improve homogeneity of the trial population, increasing the trial’s change of success, in line with the approach described in section titled Trial Population (lines 333-348).A randomised withdrawal study may also be appropriate to demonstrate efficacy and this option should be discussed in the context of pivotal clinical trial design. The randomized withdrawal design provides a way to establish effectiveness of drugs for chronic pain indications in which use of a placebo under a parallel control study design would not be acceptable leading to ethical considerations or could otherwise make it difficult to recruit patients into a study. Additionally, drop-out rates with placebo use are often high, posing difficult analysis problems. A randomised withdrawal study design also allows a patient to be removed from the study after reaching a pre-specified endpoint thus avoiding long-term exposure to an ineffective treatment. A pivotal study using a randomized withdrawal design in which all patients are on treatment for a specified duration followed and then randomized to remain on investigational drug or to placebo in a blinded phase could provide evidence of effectiveness with only brief exposure to placebo while addressing the challenge of placebo use in studies in pain indications.Proposed change (if any):In general a randomised controlled parallel group trial is the most appropriate design for confirmatory evidence of efficacy in pain trials. Variations on the randomized, placebo-controlled parallel study, such as population enrichment strategies (e.g., placebo non-responders or test agent responders) may be acceptable. A randomized withdrawal design may also be appropriate to establish effectiveness of drugs for chronic pain indications in which use of a placebo under a parallel control study design would not be acceptable.’ | Important |  |
| Lines 642-643 |  | Comment: It is proposed that 8 weeks be acceptable for specific appropriate pain models e.g. PHN?Proposed change (if any): Insert at Line 643 - For PHN an 8 weeks treatment period is acceptable.  | Important |  |
| 644-645 |  | Comment: There is a difference in approach around dose response provided in sections 5.2.3 and 6. Lines 299-301 state “Pivotal clinical trials might incorporate more than one fixed dosage arm to provide additional dose-response information…” but lines 644-645 (describing pivotal trial design) state “Study medication should in general be titrated to (optimal) effect according to a clearly pre-specified algorithm in line with the expected clinical use of the product.”We propose that the text be expanded to clarify that consideration of drug Mode of Action, potential for tolerability and potential side effects associated with increasing doses be taken into account in decisions around titration, and that a titration regimen would eliminate the need to gather additional data from the additional of more than one fixed dosage arm into a pivotal study. Proposed change (if any): “…pre-specified algorithmtaking into account the Mechanism of Action of the drug, potential for tolerability concerns and expected safety at higher doses, in line with the expected clinical use of the product. ” | Important |  |
| 406-415 |  | **Comment:**The guideline provides a general recommendation on how to handle patients who discontinue prematurely:“Patients who discontinue the trial prematurely or who require more than a pre-specified amount of rescue medication should generally be defined as non-responders.”The “EMA Guideline on Missing Data in Confirmatory Clinical Trials” differentiates between different reasons for discontinuation and between different trial objectives, see e.g. the following citations: “It may be appropriate to treat data missing for different reasons in different ways.”“If a patient prematurely withdraws from the study it would be normal to consider this patient as a treatment failure. However, the best way of categorisation will depend on the trial objective (e.g. superiority compared to non-inferiority).” A similar approach could be adopted in this guideline as well.**Proposed change:** “Patients who discontinue the trial prematurely *due to treatment related reasons* or who require more than a pre-specified amount of rescue medication should generally be defined as non-responders.” | Important |  |
| 680-684 |  | **Comment:** The guideline recommends including only opioid-experienced patients into the cancer pain trials, aiming at improvement of assay sensitivity. Such limitation in patient population appears unjustified for several reasons:1. There is ample evidence that a substantial number of patients with cancer suffer from cancer pain of moderate intensity (e.g. Grond et al. 1996, Breivik et al. 2009) when they are referred for pain treatment. These patients have not yet been treated with opioids and would also benefit from new treatment options. Therefore excluding these patients from participation in trials does not appear to be justified. 2. Patients with cancer develop more severe pain in advanced/end stage of their disease. At this stage patients’ overall condition and pain intensity may worsen rapidly. At this stage Increasing pain levels will require round the clock opioid analgesia. It is highly unlikely, that patients in this stage of their disease would develop relevant placebo effects irrespective of whether they have been treated previously with opioids or not. 3. Patients with cancer suffering from chronic cancer related pain, and already treated with opioids are in progressed, or end phase of their disease and have limited survival time. Their overall condition and disease progression do not allow for adequate assessment of safety and efficacy of a novel treatment, e.g. due to high number of adverse events and drop-outs. High number of missing data (i.e. due to drop-outs) puts the trial at high risk of failure. 4. For new analgesics mild/moderate cancer related pain may be a more appropriate target indication. Therefore there should be an option to also include opioid naïve patients into cancer clinical trials. **Proposed change:**~~“Opioid naïve patients are not suitable for trials in cancer pain as this would increase concerns over placebo response, assay sensitivity and the relevance of the data to a severe pain indication.~~ In patients requiring opioids there can be reasonable confidence that a relatively ineffective treatment would be seen to be inferior to an appropriate active comparator on the basis of pain scores, rescue medication requirements or both.” |  |  |
| 689-693 |  | Comment: The draft guideline gives the example of a 3 arm study with 2 doses of study drug to overcome concerns over assay sensitivity in active comparator trials. We would welcome discussion of study designs to address this concern that have been used successfully as the practical feasibility of a 3 arm study in these populations is challenging due to the low number of patients.Passage from guidance: However, non-inferiority trials with only an active comparator are inherently susceptible to concerns over assay sensitivity. Including two doses of trial medication could in principle provide information on assay sensitivity if superiority of high dose over low dose is shown but this would not be suitable for drugs such as opioids that are individually titrated to clinical response and excessive reliance on rescue medication could again be an ethical problem. However it is recognised that the population for such conditions is relatively small and therefore if a 3 arm study is not appropriate then other design options could be considered. | Important |  |
| Lines 702-703 |  | Comment: The current proposal relates to studies designed to show that adding on another treatment enhances efficacy. Given the concerns related to development of opioid tolerance, dependence, and misuse, studies for demonstrating an opioid-sparing effect should also be mentioned.Proposed change: Studies designed to decrease the need for opioids, while maintaining adequate levels of analgesia, should also be considered. | Important |  |
| Line 707 |  | Comment: According to the literature there are many causes of breakthrough pain from chronic non-malignant pain conditions (e.g. lower back pain).Proposed change : Breakthrough pain is a term usually associated with management of cancer pain, although there are other non-malignant pain conditions that are also associated with breakthrough pain | Editorial |  |
| Line 711 |  | Comment: Background scheduled analgesia, for the underlying pain condition, does not necessarily consist of opioids. Proposed change: “it should be ensured that **scheduled background analgesia (around-the-clock medication)** is optimised in order to keep baseline pain **as tolerable as possible**.” | Important |  |
| Lines 718-719 |  | Comment: Is it not clear what this statement regarding general pain models means. Does this mean other than cancer pain? If so, please change to indicate this.Proposed change: “In the case of breakthrough pain clinical data from more general pain models **other than cancer pain will be appropriate for this purpose**.” | Editorial |  |
| Lines 721-740 |  | Comment: It is helpful that this guideline clearly recognises FMS. It would also be helpful if this section could make clear if pain due to fibromyalgia can be considered as a separate label indication. Proposed change: Ideally insert at Line 740 - Pain associated with FMS is an acceptable indication, which is distinct to the indication, treatment of FMS. |  |  |
| 726-727 |  | Comment: It is proposed to substitute the term Irritable bladder syndrome with Bladder Pain Syndrome which is more precise.https://uroweb.org/guideline/chronic-pelvic-pain/ Proposed change:Associations with conditions such as irritable bowel syndrome or **~~irritable~~** bladder **pain** syndrome are described. |  |  |
| 727-729 |  | Since any statements such as ”functional (or dysfunctional)” are stigmatizing and should not be: changes to this section are proposed.Proposed Change: Replace Lines 727-729 by - There is some evidence for alterations in CNS pain processing as signs of altered peripheral neural function. | Important |  |
| 752 |  | Comment:The current guideline on nociceptive pain (CPMP/EWP/612/00) included this statement: “When a pain variable is assessed as an efficacy endpoint the same variable does not need to be captured as an adverse event when worsened”We propose to include this statement or similar in the new guidelineProposed change:**When a pain variable is assessed as an efficacy endpoint the same variable does not need to be captured as an adverse event when worsened.** |  |  |
| 767 - 771 |  | Comment: For centrally acting drugs respiratory depression is considered to be a topic of concern. The draft guidance seems to promote to use of polysomnography to gather valuable data. We question the value of this data, especially in light of the potential confounding factor of the underlying disorder and considering an acute or chronic administration. Not only for opioids, but also for other centrally acting analgesics, such a recommendation would put an immense burden on the development of these compounds. Such a procedure would be a source of additional stress for the patients in the trials, including children in the case where a PIP is required. Lines 767 to 769 already state that appropriate tools should be used for measurement of effects on alertness or respiratory depression.The explicit mentioning of polysomnography is perceived as too prominent and should be deleted. **Proposed change:**~~Polysomnography data might be of considerable value.~~ | Important |  |
| 826 |  | Comment:It has been shown that parental behaviour plays a powerful role in children´s response to pain (McMurtry et al, Pain 2010;150:52–58). Parental discourse that focusses on child pain is associated with higher levels of child pain and distress, whereas the reverse is true for discourse not focused on child pain (McMurty et al, J Pediatr 2006;148:560–1 and Walker et al, Pain 2006;122:43–52). When anxiety is assessed for a single procedure, this assessment is of very limited value given that it depends largely on previous experiences and/or the parents’ behaviour. Similarly, the same bias can be introduced in the case of cross-over designs. We therefore suggest removing the suggested measurement of anxiety in the assessment of pain in children.Proposed change**:**~~It may also be necessary to measure anxiety in the assessment of procedural pain.~~  | Important |  |
| 842 |  | Comment:The introduction of the paediatric section describes that a separation between acute and chronic pain is difficult. Nevertheless, the duration continues to be mentioned as a criterion for chronic pain in children, although especially in this population this is not really applicable. In our opinion in a pediatric population chronic pain should rather be defined as long lasting pain. In most children even long lasting pain will have a shorter duration than 12 weeks. A search of the website Clinicaltrials.gov for paediatric interventional trials in chronic pain produced approximately 78 entries of ongoing, completed or terminated trials. Of the trials assessing a treatment with an analgesic (total number=11), none planned for a treatment period of 12 weeks. Instead, the minority (n=3) were set up to evaluate a treatment period of max 4 weeks, whereas the majority of trials (n=8) was designed for a treatment duration of 2 weeks or less.Therefore the requirement to have 12 weeks of study duration in this population is not appropriate and does not reflect the need in the pediatric population. **Proposed change:**If it is considered necessary to perform separate paediatric trials in children with long lasting pain, such trials will require alternative trial designs with a shorter duration than those in adults.  | Important |  |
| 831-41 |  | Comment: the current draft states that there are no validated diagnostic tools for the assessment of neuropathic pain in children. This is not correct. Further, prevalence is very low, but incidence is likely to increase due to treatment induced neuropathies, e.g. CINP.In analogy with trials with adults, sensory testing can be recommended also in trials with children with neuropathic pain. This on the one hand as basis for stratification and as secondary endpoint for quantifying evoked pain, as it is shown to be feasible in children older than 6 y (e.g. Blankenburg et al. Diabet Med. 2012;29(11):1425-32; Cornelissen L, et al. Pediatr Rheumatol Online J. 2014;12:39. eCollection) and reference data have been published (Blankenburg et al. Pain. 2010;149(1):76-88.).Proposed change: insert text that neuropathic pain is diagnosed similarly in children as in adults, including QST which is also validated in children from age 6. |  |  |
| 843-844 |  | **Comment:** There are only very few validated tools to assess functionality or emotion in paediatric pain conditions; if they are, they cover only a limited age range. **Proposed change: Tools that are validated to asses functionality and emotion may only be useful in** school children and adolescents where a reasonable outcome can be expected.  | Important |  |
| 850-851 |  | **Comment**: Although at first glance it might seem reasonable to follow up on the neurodevelopment for CNS active drugs in practice this might not provide relevant information. When newborns are in need of a CNS active substance this is then undoubtedly linked to a severe underlying disease that, as a consequence, will most likely have an influence on the neurodevelopment by itself. This would be a major confounding factor in any follow up of these newborns. Moreover the neurodevelopment is influenced by multiple additional factors such as the environmental conditions, the use of other CNS active substances etc. and as a result this assessment would be hard to interpret. **Proposed change:** We suggest to delete this requirement due to its limited value. |  |  |
| Lines 863-865 |  | Comment: This sentence may imply that specific DDI studies in the elderly are necessary. However, it would seem valuable to point out that valuable information can also be obtained from the clinical trial patient data. Proposed change:“The need for specific PK or drug-drug interaction studies in the elderly patients should be based on the knowledge of the product characteristics, the expected clinical use in this **population and following consideration of the information to be gained from patient efficacy / safety trials**.”Also both section 8.1. and 8.2 should be updated in terms of content and considerations based on the planned extrapolation workshop ( link to this output from this workshop in the final guideline would be appropriate).<http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/10/event_detail_001230.jsp&mid=WC0b01ac058004d5c3> |  |  |
|  Lines 824 – 827 |  | Comment: Similar to the text in regards to cancer pain in Line 99, features that children demonstrate associated with pain can be ‘more adaptive than maladaptive’ in particular as children mature. Along these lines, assessing efficacy of a therapy via response to immunization in young children may not be capturing relief of pain. In young children, the anticipation of pain may lead to screaming, crying, trying to move away from an immunization needle, which is unchanged after the immunization is completed even in children pre-treated with topical anaesthetic agent. Therefore, observational pain scales require expert application in order to accurately convey a response to treatment. This section should seek to provide clearer insights on how to apply these tools by paediatric subset in order to achieve a more meaningful research outcome.  |  |  |
| 883-884 |  | Comment: To make homogeneous the denomination of the scale along the document. Proposed change:NRS, **~~VDS (verbal descriptor scales)~~VRS** and the MPQ have been reported to be appropriate measurement tools in the elderly |  |  |