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Dear Colleagues,

Please find below some views on the issues raised by the EMA Senior Medical Officer's '*Reflections on the legal basis for EMA/CHMP opinions*'.

Although a drug does have intrinsic ('absolute') properties, it is obvious that we can *only* form a – cognitive – *judgment on the clinical value* of these properties through (a) comparison(s) with (an)other therapeutic option(s), be it against the therapeutic abstention or against another possible treatment ('comparison' here being used in the cognitive sense, putting aside all practical and methodological issues). Every judgment of value comes from at least one comparison to another therapeutic option, and the statement that a drug has a favourable benefit-risk balance is, by itself, a judgment on the value of this drug. Hence, it is a conceptual mistake to consider that the comparison to placebo implies "*an absolute regulatory standard*". There is nothing 'absolute' in this, it is as fundamentally comparative as any other comparison, and it merely implies that among all possibilities, the decision is made (for good or poor reasons) of comparing the new drug to therapeutic abstention in order to judge the drug (in the sense that placebo is the closest representation in clinical experimentation of therapeutic abstention in clinical practice).

However, it is obvious that in clinical practice, therapeutic abstention is fortunately not always the sole available option. It is also no less obvious that physicians providing health care to patients take into consideration the existence of alternative drugs, where such exist in the therapeutic situation, in order to determine whether the benefit-risk balance of a particular drug is 'favourable' or not. In fact, because there is often at least one other active drug to be proposed to the patients, the comparison to therapeutic abstention is actually, very often, the least useful comparison a physician makes before he reaches his own conclusion on whether a specific drug has or not a 'favourable' B/R balance. Indeed, once a physician deems that a drug is better than therapeutic abstention, this is by comparing the qualities of this drug to the qualities he attributes to the other drugs he could prescribe, that he can form his own conclusion regarding the B/R balance of this drug.

Therefore, deciding that the placebo should be the unique comparison by which we, as EU regulators, should judge that a benefit-risk balance is favourable would therefore make it that we would assess the benefit-risk balance in a drastically different way than do usually physicians 'of the real world'. This would severely undermine the confidence EU citizens put into their drug regulatory system.

Hence the crux of the issue is whether or not a conclusion of 'favourableness' for the B/R balance should, in the drug regulatory context, only be reached through the comparison to placebo. This is not at all obvious since from such comparison one can formally only conclude that a drug is more or less favourable than therapeutic abstention, and this addresses only a small part of the problem.

With regard to this question, the SMO's paper simply *posits* that the conclusion that a drug has a positive benefit-risk balance is only to be reached through the comparison to placebo. In our view, this is nothing more than an opinion, as it is nowhere clearly stated in the legislation that "*greater than placebo*" should be equated with "*favourable B/R balance*".
On the contrary, the legislation simply asserts that the B/R should be considered as 'favourable' (or 'positive') and that the properties of the drug must be taken into account in order to assess whether the assessment of the benefit-risk balance can be considered as 'favourable'. This is rather vague and, apart from stating the obvious, this does not say anything on the cognitive process by which regulators should reach a conclusion on the question of whether a benefit-risk balance is 'favourable' or not. In particular this does not imply that superiority to placebo should be the only basis of the conclusion of favourableness of the B/R balance, all the more that '*established medicinal product of proven therapeutic value'* are also cited in the legislation as having some part to play in the assessment of the B/R, even though in non explicit terms. One can argue that, should the 'Lawmaker' had the willingness that only the comparison to placebo should be the basis of a regulatory marketing authorization, he certainly would not have mentioned active controls at all in regulatory texts.

Hence, although it must be acknowledged that the legislation is rather vague, this vagueness of the legislation should very logically be interpreted as implying that the 'Lawmaker' has (and reasonably so) left to the 'Regulator' the responsibility to ascertain on a case by case basis, the most scientifically reasonable, consistent and ethically adequate process by which the conclusion of 'favourableness' is to be drawn.
It follows that, although the SMO predicates that only the comparison to placebo should dictate the conclusion to the question of whether the benefit-risk balance is positive, this is in no way mandated by the legislation, and we have therefore to evaluate whether this approach would be reasonable, consistent and ethical.

Given that a conclusion on whether the benefit-risk balance is favourable can only be reached through a comparison of its properties to the properties of an alternative, there are, in principle, 3 distinct possibilities among which one is to be chosen:

- *Option 1*: only the superiority to therapeutic abstention (demonstrated through superiority to placebo in a clinical trial) should determine that a drug has a favourable benefit-risk balance;

- *Option 2*: only the superiority to existing drugs should determine that a drug has a favourable benefit-risk balance;

- *Option 3:* a drug should be considered as having a favourable benefit-risk balance when its benefit-risk balance is superior to therapeutic abstention, and when it can also reasonably be considered as not substantially worsened as compared to the benefit-risk balance of existing drugs.

The SMO considers that *Option 1* should be the regulatory standard. However, it raises some serious objections:

- this is nowhere to be unequivocally found in the legislation;
- as discussed above, this view is fully disconnected from the way ordinary physicians reach the conclusion that a particular drug has a favourable benefit/risk balance;
- this would be inconsistent with the requirement of clinical non-inferiority expressed in numerous CHMP scientific advices, as well as in existing EMEA guidance documents;
- this view would allow, as well illustrated by the SMO's extreme example, a drug to be licenced even though its use could lead to a large increase of the mortality among the unfortunate patients who would actually receive this drug instead of the alternative, this corresponding to a ‘major risk to public health’, a common ground for referring controversial procedures to the CHMP;
- it would be illogical in the sense that it would make an artificial distinction between (1) a mortality difference generated by some differential efficacy and (2) a mortality difference from safety causes (here we make the assumption that everybody would agree that a drug which would kill 40% of treated patients through adverse effects would not be tolerated to be/stay on the EU market);
- this view is blatantly unethical with regard to all recognized standards, to the point that it could even lead to the paradoxical situation where a drug which would be prohibited in clinical research on ethical grounds, may still be authorised by EU regulators for use in standard clinical practice. Indeed, in the example given by the SMO, the knowledge of the drug properties (notably characterized by a five-fold mortality increase as compared to the established drug) would make its use in clinical research to be in violation with the following articles (among others) of the Declaration of Helsinki (revision of 2008, emphasis added):

> Article 4 - The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
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> Article 10 - Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
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> Article 10 - It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
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> Article 31 - The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Option 2, although it has some proponents, would be ultimately deleterious to the interests of patients since it would lead to the monopoly of only one drug, until this drug would be in turn replaced by a single better one. Such approach would not take into consideration the fact that, in a therapeutic field, drugs with different characteristics can have a largely similar benefit-risk balance, in the sense that some decreased tolerance can well be counterbalanced by some improved efficacy (and *vice versa*), and it is very often not known a priori which patients will benefit most from a drug rather than from another. Indeed between relatively similar drugs, some patients may, unpredictably, show better benefit or better safety with one drug, whereas another drug may appear better suited to some other patients.

The latter *Option 3*, using for marketing authorization standard a double requirement (1) of superiority to placebo added to (2) a conclusion of the absence of substantial worsening of its benefit-risk balance as compared to existing drugs, so that it can be a priori considered that the basic health interests of the patients should not be substantially harmed by this drug, has several distinct advantages:

- it is protective of the patients' interests;
- it is in coherence with the way professional health care providers reach the conclusion that a therapeutic approach has, or not, a favourable benefit-risk balance;

- it is in coherence with the fact that a clinical judgment on the value of drugs is, by essence, comparative;
- it is in coherence with the practice of requiring non-inferiority trials to ascertain that new drugs are not associated with a substantially worsened benefit-risk balance as compared to reference drugs;
- it is the approach by which our fellow EU citizens expect us to deal with drug authorization (and probably think we do);
- it has the potential to increase the confidence of EU citizens toward the institutions specifically founded to protect them;
- it provides a way by which EU drug regulation can comply with the ethical principles set forth by the World Medical Association in the Declaration of Helsinki;
- it is reasonable because it gives the flexibility to adapt to each therapeutic situation the threshold above which a new drug can be considered as having a benefit-risk balance which is not substantially degraded as compared to existing drugs;
- it naturally allows drug assessment to evolve over time, with the evolution of clinical practices, and the discovery and availability of new drugs.

We believe that *Option 3* is fully compatible with both the letter and the spirit of the EU legislation, which simply gives to the drug regulation system the responsibility to authorize drugs for which the benefit-risk balance is 'favourable', and leaves to the Regulator the responsibility to define what 'favourable' should mean in each practical situation.
Finally, we strongly believe that if the EU legislation were eventually considered to be incompatible with this interpretation, as it is suggested in the SMO's note, we, as European Regulators, would have the duty to promote the promulgation of a new regulation in order to provide a more coherent and protective regulatory framework for EU citizens.

Best regards,

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