July 31, 2014

Submission of comments on 'Guideline on the investigation of subgroups in 4 confirmatory clinical trials' (EMA/CHMP/539146/2013)

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

In a May 16, 2014 comment on the on the U.S. Federal Drug Administration (FDA) proposed subgroup regulations I challenged reliance of subgroup analyses on the assumption that absent such a subgroup effect as the concept is generally understood, an intervention will cause the same proportionate change in all baseline rates for experiencing an outcome. I pointed out both (a) that such an expectation is illogical given that a factor cannot cause equal proportionate changes in the rates of experiencing the outcome for groups with different baseline rates while at the same time causing equal proportion changes in the two groups' rates of experiencing the opposite outcome; and (b) that, according to the standard approach to subgroup analyses, a factor that affects the outcome rates for groups with different baseline rates will tend invariably to yield a subgroup effect either as to that outcome or as to the opposite outcome. I also explained that when a factor affects an outcome rate for two groups with different baseline rates, the factor will tend to cause a larger proportionate change in the outcome rate for the group with the lower baseline rate while causing a larger proportionate change in the opposite outcome for the other group. I incorporate that comment by reference. It can be found here: http://www.gpo.gov/fdsys/pkg/FR-2014-03-04/html/2014-04625.htm

I have since treated aspects of this matter further in the following article, which was cited as a forthcoming article as reference 1 in the FDA comment.

"Race and Mortality Revisited," Society (July/Aug. 2014)
http://jpscanlan.com/images/Race_and_Mortality_Revisited.pdf

Particularly relevant to the subgroup effect issues is the section titled "Illogical Expectations and Unfounded Inferences" at pages 12 to 14.

The European Medicines Agency's proposed guidelines raise an additional issue in that, at lines 300 to 316, the guidelines discuss subgroup analyses based on a relative scale and based on an absolute scale as if the two might be equally sound. The guidelines mainly advise that the assessor needs to be aware of the scale. That discussion fails to offer guidance as to what scale should be used in the common situation where the relative and absolute scales offer contrasting results as to the direction of a subgroup effect. It also fails to reflect an understanding there exists only one reality as to the quantification of an effect in a manner whereby the effect can be employed to estimate the absolute risk reduction and number need to treat in a situation involving baseline rates different from that at issue in a trial.

The problem with the acceptance that more than one measure of an effect can be correct with respect to a subgroup analyses even when the measures offer conflicting conclusions about subgroup effects (which is implied in lines 300 to 316 of the guidelines) is highlighted when one considers the instruction at lines 521 to 523 that interpretations should be informed by considerations of biological plausibility. For in the common circumstances where a study examines the effects of a factor on an uncommon outcome for two groups with different baseline rates (Group A with lower rate and Group B with the higher rate), the factor will tend to cause (a) the larger proportionate effect on the outcome rate for Group A, (b) the larger proportionate effect on the opposite outcome for Group B, and (c) the larger absolute effect (for both outcomes) for Group B. Yet, to the extent that biological factors are having any role in the differing effects, it would be same biological factors causing (a), (b) and (c). Compare the discussion of an analogous issue with respect to Table 5 in the recent article.

Subgroup effect analyses – as well as the appraisal of the biological plausibility of observed patterns – must be based on an analytical approach employing a measure that is unaffected by the baseline rates, such as that discussed in references 6 and 9 of the comment on the FDA proposed regulations.

2. 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')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.