AIM

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EMA suggestions on comparative clinical trials fall back behind ethical and scientific standards

A reflection paper from the European Medicines Agency (EMA) outlines proposals on clinical trials procedures that does not properly fulfil its duty to protect European citizen from inferior medicines. A broad coalition of AIM, ISDB and MiEF demands that the EMA adheres to agreed ethical and scientific standards and requests comparative evaluation of new medicines against standard treatment.

When new drugs are marketed, a key and simple question for patient and caregivers is: How does this drug compare with drugs which are already available? Unfortunately this very practical question is often not properly addressed in the dossier submitted by pharmaceutical companies to drug agencies for getting marketing approval. It is not addressed because it is not mandatory under current EU pharmaceutical legislation and agencies rules. It is not properly addressed because often the new drug is only compared to placebo or to a comparator which is not optimal, or because a non-inferiority trial has been used.

More and more patients and caregivers, as well as social protection systems, are requesting that comparison with relevant comparator should be documented in marketing approval dossier.

Against this historical trend the EMA has launched a consultation about "the need for active control" where the agency is very surprisingly proposing to request comparisons with an active comparator from the companies only in limited cases.(1)

The EMA proposal clearly shows that the European Medicines Agency does not have the interest of the patient and public health as primary objective. Although EMA states “Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold-standard and there are multiple reasons to support their use in drug development”; the EMA proposals will in many cases lead to a practice which is in contradiction with this scientific gold standard.

- EMA not only falls behind the scientific gold standard, but is also in contradiction with the World Medical Association’s "Declaration of Helsinki – Ethical principles for medical research involving human subjects" (2), which states:

“The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.”

The World Medical Association considers that the comparison of new medicines with "best current proven intervention" should be the ethical rule, and that the use of a placebo be the exception: “*Extreme care must be taken to avoid abuse of this option*”. We note that EMA reverses this ethical principle, considering that the use of a placebo is generally acceptable, unless in a limited number of cases.

- Finally, EMA even falls back behind ICH recommendations (which have been written by the regulators of United States, Europe and Japan in accord with the pharmaceutical industry). ICH guideline E10 states very clearly that: “*In most cases, evidence of efficacy is most convincingly demonstrated by showing superiority to a concurrent control treatment. If a superiority trial is not feasible or is inappropriate for ethical or practical reasons, and if a defined treatment effect of the active control is regularly seen (e.g., as it is for antibiotics in most situations), a non-inferiority or equivalence trial can be used and can be persuasive*.” (3)

There is a huge difference between this position and the one proposed by the EMA although the EMA reflection paper claims to refer to ICH guidelines!

MiEF, AIM and ISBD have refused to comment on the details of the proposals described in the EMA reflection paper as it moves away from the EMA’s acknowledged scientific gold standard, ethical rules of the World Medical Association, and even ICH guidelines. The EMA proposal is completely unacceptable and needs to be firmly rejected.

References

1- European Medicines Agency "Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available" Committee for Medicinal Products for Human Use - Draft November 2010 EMA/759784/2010. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/01/WC500100710.pdf

2- World Medical Association "Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" www.wma.net/en/30publications/10policies/b3/

3- International Conference on Harmonisation "ICH Topic E 10 - Choice of Control Group in Clinical Trials" www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf