OPEN LETTER

European regulatory agencies should employ full time statisticians

We would like to draw attention to what we believe is a major deficiency in European regulatory agencies that are responsible for reviewing applications to market new medicines across the whole of the European Union. Only agencies in the UK, Germany, Sweden, and Austria employ several full time statisticians, and a few others employ a single statistician. Some agencies that have a major role in the European regulatory process, such as those of Italy and Spain, do not employ any full time statisticians—instead they rely on external consultants.

Statistics is central to the design of clinical trials and to the interpretation of their results. Key regulatory guidelines such as ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) E3, E9, and E10 carry this clear message, as do numerous disease specific, clinical guidelines from CHMP (Committee for Medicinal Products for Human Use). The clinical trial component of regulatory submissions can be made up of the accumulated data from several thousand patients enrolled in several clinical trials. Evaluation of the data requires consideration of the impact of complex statistical issues relating to design of the trial and analysis of the data, such as bias in trial design, use of multiple end points, missing data, interim analysis, subgroup analyses, analytical technique, and selection of statistical model.

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Decisions to approve or deny potentially important new medicines will be based on the assessment of these dossiers. Unless the design and statistical analysis of a trial are appropriate, results cannot be considered reliable and no confidence can be placed in the subsequent clinical interpretation. These issues have been recognised by major medical journals, which routinely provide a statistical review of submitted papers.

Another important role of regulatory agencies is to provide scientific advice on proposed clinical development programmes and general guidance on statistical issues. Companies seeking regulatory advice want to be confident that the advice they receive is based on considerable experience of regulatory work and knowledge of acceptable methodology. Without permanent statisticians, agencies are at risk of giving incomplete advice. In particular, innovation may be stifled if novel methods that are presented are methodologically sound but are disregarded because they are poorly understood by regulatory advisers.

Statistical review should be conducted by those who are professionally expert in the area, not by medical assessors with some knowledge of statistics. Part time academic consultants, regardless of their level of expertise and experience, are unlikely to be able to devote the time required to carry out a thorough assessment of a regulatory dossier and of the individual clinical trials contained in it. Work of this nature must be carried out in an organised and timely fashion by experts interacting regularly and in detail with experts from other disciplines. Knowledge and experience must be carried over from assessment to assessment. When necessary, assessors must be able to devote sufficient time to an assessment to allow them to explore issues concerning statistical methods and data in real depth.

We believe the current situation is unacceptable. These same concerns were raised in the 1990s by a working party from the Royal Statistical Society (*J Royal Stat Soc (A)* 1991;154:413-9) and were subsequently addressed by the UK regulatory agency. All agencies who undertake review of applications should employ full time statisticians to enable competent licensing and labelling decisions. We call on the heads of the regulatory agencies in the EU that do not have full time statisticians in their organisations to rectify this as a matter of urgency.

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Responses to this letter are invited via the *BMJ* or via email to chair@psiweb.org