of APC [2] in the currently indicated high-risk population [3].

This EMEA opinion, on the most rational way to proceed, reflects results of the trials requested by the FDA. The PROWESS follow-up trial showed no significant difference in the number of patients discharged home between APC and placebo groups [4]. The authors suggest that ENHANCE confirmed drug efficacy and safety. However, this has been seriously questioned: as a non-randomized, uncontrolled trial it was not designed to assess efficacy; compared with PROWESS the serious bleeding rates were greatly increased in ENHANCE (a NNT of 16 for a serious bleed) [5]. As the authors indicate, ADDRESS did not help APC and the drug's failure to demonstrate efficacy and safety in paediatric sepsis [6] raised further doubts around APC having any beneficial effect, even in adults [7].

It may be a particular concern that the authors' data included a relatively high proportion of surgical patients (50%) vs. PROWESS (455/1690: 27%). Original Phase II and PROWESS trial data showed a higher mortality in the surgical patients randomized to APC [8]. A later retrospective reclassification of PROWESS patients may be difficult to interpret [9]. With treated surgical patients in ADDRESS also having a higher mortality, there is a consistent trend towards poorer outcome, with APC administration, in almost 1500 surgical patients enrolled to all three placebo controlled trials in adults. It may be hazardous to imply that APC has an acceptable benefit/risk profile in this group of patients.

Finally, data from a small number of hospitals in 2002–2005 may not reflect current UK practice. Following recent trial results use may now be very low as in other countries: recent French data (2006) showed that APC was not used in 14 of the 15 ICUs surveyed [10]. Low usage will probably persist unless new trials demonstrate clear benefit in easily identifiable patient groups.

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Reply

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EDITOR:

Thank you for the opportunity to respond to Dr Mackenzie. Dr Mackenzie is wrong to assert that we 'considered it more rational to use *our* cited approach rather than have further formal drug appraisal'. At the time of writing up our collective experience as the five largest UK users of drotrecogin alfa in severe sepsis [1], very little was known about the use of drotrecogin alfa in routine clinical practice. Moreover, it was far from clear that it was ethically justifiable to perform a further trial, given that the drug has been licensed since 2002 and is currently used in high risk cases around the world. The majority of intensive care units in the UK, and many intensivists now have some experience of using the drug. Use of the drug in the UK has remained constant

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since early 2006 in spite of the announcement of the new trial (Eli Lilly, personal communication).

In his letter, Dr Mackenzie restates the well-documented views questioning the efficacy of the drug. Many of these arguments have been answered on numerous occasions to the satisfaction of the majority of clinicians, but we accept not all [2]. However, the fact remains that in appropriately selected cases of severe sepsis at high risk of death [3], drotrecogin alfa reduces mortality, which is why both the FDA and EMEA have decided not to withdraw the drug from the market.

Over the last few years there have been an increasing number of audits and registries of the use of drotrecogin alfa in clinical practice which are remarkably consistent, and confirm the results of the original trial [4–6]. In the UK the ICNARC registry of 1245 drotrecogin alfa-treated patients, which used several different ways to match cases (historic admissions, contemporaneous admissions from the same unit, contemporaneous admissions from units that never used drotrecogin alfa, or contemporaneous admissions from units prior to first use), there was not even the remotest signal to harm; in fact, the results were very consistent with the mortality reduction seen in PROWESS [7]. An Italian registry also showed a reduction in mortality but also clearly demonstrated that the drug must be prescribed according to the Summary of Product Characteristics [8].

The very low usage that Dr Mackenzie highlights in France [9] may have more to do with the very cumbersome remuneration mechanism in that country, rather than the view of the clinicians that the drug is not safe.

In summary, we believe the audit we conducted of our earliest use of drotrecogin alfa was valid and responsible, and shows that when used according to the licensed indications is safe and effective in patients with septic shock. We are saddened that Dr Mackenzie feels it is necessary to continue attacking the drug [10–12] rather than adopting a more open-minded and balanced perspective, which might include a description of his own experience with the drug.

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