implementation during that same time period of 2 major federal initiatives, including the Best Fed Beginnings Program, in which Louisiana (the authors' home state) participated. In 2016, 18.6% of US births occurred in Baby Friendly facilities, including 2 states with >85% Baby Friendly penetrance.[2] In contrast, in 2014, only 7.79 % of births occurred in Baby Friendly facilities, with the highest penetrance of 35.98% in a single state.[3] Therefore, we feel that using of that 2014 birth cohort for this analysis lacks construct validity. Of note, the breastfeeding initiation rates in 2014 and 2016 were quite similar (79.2% and 81.1%, respectively), and the outcomes that the authors noted may simply reflect the positive results of breastfeeding initiation, consistent with our conclusions.

The authors note that we did not use population weighting in our regression analysis but instead treated each state equally. Given the unique and heterogeneous characteristics of the individual states, including their demographics and coexisting programs for support of breastfeeding, weighting by population would erroneously diminish the impact of those important differences. The authors also performed a sensitivity analysis, excluding Delaware and Rhode Island, the 2 states with >85% Baby Friendly penetrance, treating these as outliers. We suggest that this is not appropriate, because these states, which are the least subject to the ecological fallacy and thus have the greatest relevance to the results, should be included for subgroup analysis, as we reported.

The authors also dismiss our use of an ecological design to address the relationships that we examined. We disagree, and note that this method is considered particularly applicable to the evaluation of public health strategies when obtaining individual data may be impractical.[4] There are many historical examples of important and unanticipated results that have come to light from such studies. We agree that the issue of the ecological fallacy is a limitation; however, there are accepted methods to diminish the impact of that limitation,[4] including multiple comparative regression analytics, subgroup analysis of groups with high factor penetrance, and contextual examples of alternate analyses and contemporary approaches, all of which we included to support our findings and confirm that Baby Friendly designation might not be the optimal approach to achieving the US Healthy People 2020 postdischarge breastfeeding objectives.

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Synthetic surfactant CHF5633 vs poractant alfa

To the Editor:

In a recent trial, Ramanathan et al claimed that the efficacy and safety of the new synthetic surfactant (CHF5633) were equivalent to that of poractant alfa.[1] However, closer analysis reveals that for several important clinical outcomes, the 95% CI indicates that there could be a significant benefit but also considerable harm from CHF5633 compared with poractant alfa.[2] For example, compared with poractant, the relative risk of death at 28 days of life with CHF5633 was 65% lower to 509% higher. Using absolute values, the results indicate that CHF5633 may reduce deaths by up to 7 deaths per 100 babies (best-case scenario) or increase deaths by up to 11 deaths per 100 babies (worst-case scenario). These results do not allow us to differentiate between the equivalence of the 2 surfactants or the noninferiority of CHF5633.[2]

The authors claim equivalence when there is a possible type II error. They did not calculate a sample size, stating that this was not required because this was an exploratory trial. If this was truly an exploratory trial, the authors firm conclusion that "CHF5633 is as effective and as safe as poractant alfa" is unjustified. Also, we are not aware of any reason, even in a phase II or exploratory trial,[3] to omit a sample size calculation, and not aim to recruit the optimal number of patients.[4] Without a sample size calculation, how did the authors decide to stop recruitment after enrolling 126 neonates?

We caution readers not to draw any definitive conclusions about the relative efficacy or harm of either surfactant from this trial. We hope that the authors will conduct a larger trial of these 2 surfactants designed to demonstrate superiority, noninferiority, or equivalence to draw some definitive conclusions.

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Reply

To the Editor:

We would like to clarify that no claims for equivalence or noninferiority were made in our article according to the exploratory design of our study. It is not an equivalence trial. Following a first-in-human clinical study,[1] the exploratory design of this phase II study was agreed and approved by Food and Drug Administration to gain additional information for designing further studies on the grounds of preliminary comparative data of the overall surfactant products' profiles. We referred to similarity between the results observed with the 2 surfactants with specific reference to the overall efficacy and safety profiles in line with the exploratory design of this study; accordingly, "Sixty-three randomized patients per treatment group (126 in total), in this vulnerable preterm population, were deemed reasonable to describe the efficacy and safety profile of CHF5633 compared with poractant alfa."

For this reason, we would like to point out that we did not decide to stop recruitment after enrolling 126 neonates and, as reported, a total of 297 infants were screened and 123 infants were randomized in this challenging study from December 2015 through February 2018 in 22 neonatal intensive care units in the US. "Similarity" is indeed mentioned with reference to the overall study endpoints.

Sample size calculations would have required a primary endpoint and a hypothesis, which is not in line with the aim of the present study. Therefore, our study could not be powered for any measured endpoint. In particular, an equivalence/noninferiority study on mortality would not have been feasible without enrolling a large number of neonates from this vulnerable very preterm population. Because of this, we think that these results on the relative risk of death at 28 days of life with CHF5633 or poractant alfa are absolutely by chance and were only reported, but not claimed as a standard outcome in preterm neonates with respiratory distress syndrome. However, and as reported in the discussion section, we acknowledge the need for further confirmatory and possibly statistically powered clinical trials to draw eventual conclusions on superiority, noninferiority, or equivalence between the 2 surfactants. We do not believe that there were any flaws in our conclusions or discussion.

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