Appendix 1

When sponsors have uncertainty about the effect sizes, and either study/indication is possible to succeed at the 0.000625 level, one cannot prespecify which is to succeed at the 0.000625 level. Intuitively, if the multiplicity issue is ignored, one would argue that both indications can be approved if either study/indication succeeds at the 0.000625 significance level and the other study/indication succeeds at the 0.025 significance level. To adjust for multiplicity, one reasonable approach could be to 'raise the bar' for the less stringent condition, i.e. 0.025, in one indication, (while keeping the 0.000625 significance level for the other). Specifically, both indications can be approved if either study/indication succeeds at 0.000625 level and the other succeeds at the 0.0128 level, because the overall type I error rate allowed is

$$0.000625 \times 0.0128 \times 2 - 0.000625 \times 0.000625 = 1.56 \times 10^{-5},$$

which is the combined-indications significance level that is required for two indications if developed sequentially. The specification for this 'simultaneous approval of two indications without pre-specified order' is as follows.

$$\{p_1 \le 0.000625, p_2 \le 0.0128\} \bigcup \{p_1 \le 0.0128, p_2 \le 0.000625\}.$$

Appendix 2

In addition to the requirement on the combined-studies evidence of two indications, one can further require the p values of individual studies/indications to meet certain criteria, e.g. $p_i \le 0.025$, for $i = 1, 2$. With this restriction, the combined-studies evidence can be relaxed to a less stringent level than 1.56×10^{-5}. Let us use Stouffer's Z-score method to explain. Assume the test statistics from the individual studies, Z_1 and Z_2, are

asymptotically standard normal. For simplicity, let us consider two equally-sized balanced studies with 1:1 randomization to compare the test and control treatments. So the individual Z_i 's have equal weight in the aggregated Z-score, i.e. $Z_a = (Z_1 + Z_2)/\sqrt{2}$. Similar to the argument by Maca et al [1], a bound of 0.025 for individual p values corresponds to a bound $Z_{0.025} = 1.96$ on the test statistics Z_i; then the bound for the aggregated statistic, Z_C, can be derived by solving the following equation (4), and the adjusted combined-indications significance level, $\alpha_c = p(Z > Z_C)$, where Z is a standard normal random variable.

$$\Pr\{Z_1 > 1.96, Z_2 > 1.96, Z_a > Z_C\} = 1.56 \times 10^{-5}. \quad (4)$$

From Monte Carlo simulation (of 140,000,000 runs with random seed of 2018), the solution for (4) is that the combined-studies evidence needs to be $\leq 1.81 \times 10^{-5}$ for two indications, if we require the largest individual p value to be ≤ 0.025, i.e.

$$\{p_1 \leq 0.025, p_2 \leq 0.025, p_a \leq 1.81 \times 10^{-5}\}.$$

Appendix 3

For simultaneous development of more than 2 indications, it is straightforward to still use 0.025 as the upper bound for the individual studies/indications. As the p value distribution is skewed and can be highly variable, it could be inefficient to require each individual p value to be less than 0.025 [1]. A more efficient approach may be to require that the largest p value from individual studies be less than α_s which is larger than 0.025, e.g. $\alpha_s = 0.05$, and the combined-studies evidence to be less than α_c, the adjusted combined-indications significance level, such as to maintain the target significance level

of $\alpha_p = 0.025^{k+1}$. Similar to the descriptions in Section 3.2, Z_C in (5) is solved to derive α_c.

$$\Pr\{Z_1 > Z_{\alpha_s}, \cdots, Z_k > Z_{\alpha_s}, Z_a > Z_C\} = 0.025^{k+1}, \qquad (5)$$

where $Z_a = \sum_{i=1}^{k} Z_i / \sqrt{k}$, α_s is a bound for individual p values which corresponds to a bound Z_{α_s} on the test statistics Z_i. The adjusted combined-indications significance level is $\alpha_c = p(Z > Z_C)$, where Z is a standard normal random variable. Table 3 shows the adjusted combined-indications significance level for different scenarios.

Table 3. Adjusted combined-indications significance levels α_c to enable $\alpha_p = 0.025^{k+1}$

Number of indications, k	Single study p value bound, α_s	Adjusted combined-indications significance level, α_c
2	none	1.56×10^{-5}
	0.05	1.64×10^{-5}
	0.025	1.81×10^{-5}
3	none	3.91×10^{-7}
	0.05	4.11×10^{-7}
	0.025	4.67×10^{-7}