

Table 6.2 Decreased Number of Critical Attributes with Risk Assessment Tools Using Three Factors

	CQA Risk Assessment	CPP Risk Assessment
Two factors	67%	53%
Three factors	50%	39%

Note: The values represent the percentage of critical attributes with respect to all attributes involved in the risk assessment. The threshold values for the selection of criticality are defined based on the rule of $T = (1/n)RN_{\max}$, where n is the number of factors.

failure mode and effects analysis, which is commonly used to assess the criticality of process parameters in manufacturing processes.

To demonstrate the effect of factor selection on the result of risk assessment, the ratio of critical attributes was calculated for the case of two or three factors. As shown in Table 6.2, the addition of a third factor decreased the ratio both in CQA and in CPP risk assessment. This observation suggests that the integration of additional knowledge with an appropriate factor in the risk assessment tool leads to the reduction of critical attributes and hence simplifies the experimental design for early process development. The lower number of critical attributes does not mean higher risk acceptance, but rather risk reduction by enhanced integration of prior knowledge into product development via efficient risk assessment tools.

6.3.3 Threshold definition for risk assessment

The criticality threshold expresses the level of risk that is accepted for a product or a process. As already stated earlier, its value has a great influence on the outcome of the risk assessment. The threshold value is always determined based on the acceptable level of risk. In the literature, threshold values around $0.2RN_{\max}$ are commonly reported, resulting in an average of 70% of critical attributes. However, applying a static formula for criticality threshold calculation leads to variable outcomes when the number of factors is changed in the risk assessment tool. Thus, general formulas should be developed in order to deliver comparable results when adjustments in the risk assessment tool are made (Table 6.3). Such a formula is $(1/n)RN_{\max}$, which calculates the criticality threshold based on the number of factors (n) involved in the risk assessment tool.

The final goal of criticality threshold selection in early-stage process development is to identify factors for the design of experiments along what is executable in the very strict development timeline of biosimilars. In this respect, the number of critical parameters is an important indicator of factor selection because it has a major effect on the experimental design. Table 6.3 shows how the threshold selection affects the number of critical attributes and demonstrates the need for threshold selection strategies that take the number of factors applied in the risk assessment