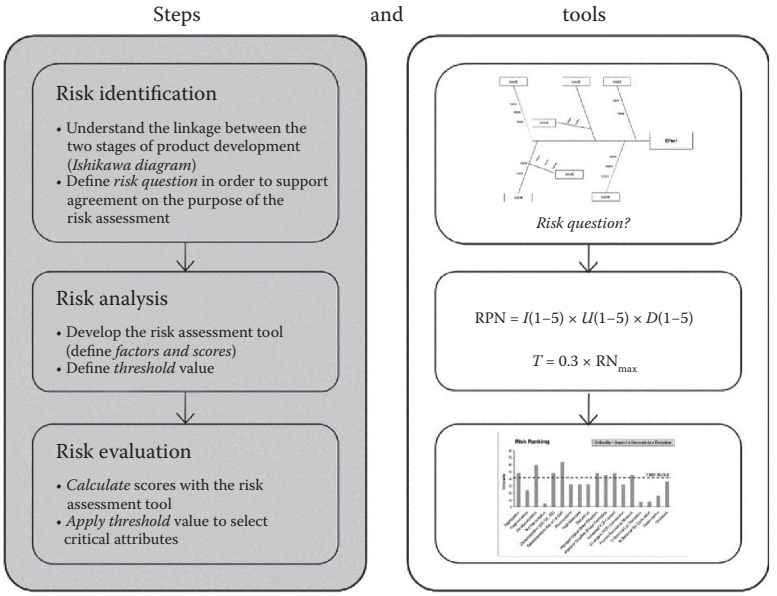

Figure 6.5 The general risk assessment process. The box on the left traces the three steps of risk assessment as described in ICH Q9, whereas the box on the right represents essential tools supporting the risk assessment process. (From Zalai, D. et al., *PDA J Pharm Sci Tech*, 67, 2013. With permission.)

all attributes by categories for the risk analysis, decision tools such as an Ishikawa diagram can be used. Afterward, the risk question—a clearly formulated sentence referring to the goal of the risk assessment—is defined. Risk question formulation supports the process to obtain an agreement on the purpose of the risk assessment. The progress of risk question formulation might be a challenging task due to the complex nature of biologics and the diverse concerns of interdisciplinary risk assessment teams.

The second step focuses on the assessment of criticality with the help of risk analysis tools. According to the ICH Q9 guidance, the risk is always defined as a function of the severity of potential harm. Consequently, a risk assessment tool always contains a factor that represents this severity. Additional factors can be chosen to optimize the tool for the exact purpose. After defining the score ranges for each factor, the maximal risk score can be calculated and subsequently the criticality threshold can be set. Although the threshold value has a great influence on the outcome of the risk assessment, there is no best practice reported for defining its value.

The last step of risk assessments is the calculation of risk scores and the subsequent ranking of the attributes. Finally, attributes receiving higher risk scores as the criticality threshold are designated as critical.