processes. Although the complex physiology of mammalian cells (e.g., CHO) has been investigated in many studies, little is known about how this information can be coupled to product quality. Therefore, physiological parameters such as specific rates have to be defined to support the extraction of scalable and science-based information on physiology–product quality interactions in bioprocess development. The identification of such physiological parameters in early-stage development has to be facilitated by structured risk assessment approaches.

Ishikawa diagrams and risk questions support the proper understanding of linkages targeted by risk assessments. With the help of these tools, interdisciplinary team members can come to an agreement on the scope of risk assessments. Due to the high complexity of targeted bioprocesses, the approach depicts a promising tool for more efficient process development, especially in its early stages.

6.3.2 Development of tailored risk assessment tools

Risk assessment tools convert subject knowledge into quantitative information in order to assess criticality. The outcome is the risk number (RN), which is calculated by multiplying two or more factors. Although the ICH Q9 guideline lists a variety of risk assessment tools, it does not provide a clear definition as how to select the most appropriate one for the specific purpose. Some studies have reported the use of these tools during biopharmaceutical product development, but they did not provide extensive information on the reasons for selection. As already discussed, the factor severity is always included in the risk assessment tool to express the potential harm to pharmaceutical quality as the basis for the determination of criticality. Additional factors are used to improve the risk assessment tool by breaking up the risk into multiple components. For example, uncertainty is often used as a second factor besides severity to include the quality of input data as a possible source of risk. This is especially relevant in early-stage process development, where scientific knowledge is often lacking to fully understand the linkage between product- and process-related parameters. The two factors severity and uncertainty are included in both CQA and CPP risk assessment tools within this study.

If additional information is available that can increase the selectivity of the risk assessment, the tool has to be appended to process all the information at hand. An example is the original product's quality profile for biosimilars. Biosimilar guidelines in the EU and the United States put emphasis on analytical comparability with the original product. Consequently, the quality profile of biosimilars is highly determined by the originator product. In order to involve this additional information in biosimilar development, a third factor called deviation was added to the here-described risk assessment tool for CQA selection (Table 6.1). This factor incorporates the extent of acceptable deviations from the