Table 6.1 Overview of the Risk Assessment Tools for CQA and CPP Selection

	CQA Risk Assessment	CPP Risk Assessment
Linkage	CQAs–QTPP specification	CPPs–CQA ranges
Risk question	How critical is the effect of a possible deviation from the innovator's quality profile with respect to safety and efficacy?	How critical is the effect of the process parameter or process variable on CQAs?
Risk assessment tool	RN = severity × uncertainty × deviation	RN = severity × uncertainty × complexity
Scores for the third factor	Deviation (from the quality profile of the reference material): 1. No deviation in the quality profile 2. The low deviation in the quality profile or robust purification method deviation, limited purification efficiency 3. The severe deviation in the quality profile limited purification efficiency 4. The severe deviation in the quality profile, a variant cannot be purified	Complexity (of the mechanism responsible for the CPP–CQA effect): 1. The mechanism described by physical law 2. Simple mechanism with well-known characteristics 3. Complex mechanism with previously reported quantitative interactions 4. Complex mechanism without quantified characteristics 5. Very complex mechanism

originator product's quality profile. Quality attributes with minor importance would receive a low deviation score, indicating a higher acceptable deviation. Thus, this factor helps to prioritize the quality attributes for product development based on their effect on biosimilarity. However, as communicated by regulatory bodies, the effect of a deviation from the originator in attributes with low relevance has to be justified as well in biological assays. The factor deviation can also contain information about the purification capacity of downstream process steps if the risk assessment is conducted for the determination of CQAs in upstream process development (see Table 6.1).

Another example to incorporate additional information into the risk assessment in this study was, considering the complexity of the mechanisms, how process parameters can affect the investigated quality attributes. Accordingly, besides the factors severity and uncertainty, a third factor called complexity was added to the risk assessment tool of CPP selection. This factor quantifies as to which extent the mechanism of the CPP–CQA interaction can be described by a scientifically developed formula (Table 6.1). The higher the score, the more complex the mechanism and the less information available for its quantification. As the lack of reliable information on CPP–CQA interactions raises the uncertainty score of almost each process parameters and variables in early-stage process development, including complexity as a third factor, helped to differentiate CPP candidates based on scientific considerations. Introducing this factor also emphasizes the scope of CPP risk assessment at this stage of process development, which is not to select critical parameters for a finalized manufacturing process but rather to rank parameters in order to prioritize experiments for process development. These considerations justify the development of novel tools as described earlier instead of