biological activity per milligram of product), which is also highly method-dependent. Consequently, the purity of the DS and DP is assessed by a combination of analytical procedures.

Owing to the unique biosynthetic production process and molecular characteristics of biotechnological and biological products, the DS can include several molecular entities or variants. When these molecular entities are derived from anticipated PTM, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and/or storage and have properties comparable with the desired product, they are considered product-related substances and not impurities.

Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.

For the purpose of lot release, an appropriate subset of methods should be selected and justified to determine purity.

9.9.9.2 Impurities

In addition to the evaluation of the purity of the DS and DP, which may be composed of the desired product and multiple product-related substances, the manufacturer should also assess the impurities, which may be present. Impurities may be either process- or product-related. They may be of known structure, partially characterized, or unidentified. When adequate quantities of impurities can be generated, these materials should be characterized to the extent possible, and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, that is, cell substrates (e.g., host cell proteins and host cell DNA), cell culture (e.g., inducers, antibiotics, and media components), and downstream processing. Product-related impurities (e.g., precursors and certain degradation products) are molecular variants arising during manufacture and/or storage that do not have properties comparable with those of the desired product with respect to activity, efficacy, and safety.

Further, the acceptance criteria for impurities should be based on the data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.

Individual and/or collective acceptance criteria for impurities (product-related and process-related) should be set, as appropriate. Under certain circumstances, acceptance criteria for some selected impurities may not be necessary.

9.9.9.3 Contaminants

Contaminants in a product include all adventitiously introduced materials that are not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases) and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for DS or DP specifications. For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in the ICH Guidances *Q5A Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* and *Q5D Quality*