Every process and product carries with it an associated risk that can range from totally unacceptable to acceptance in the context in which it is applied. Risk is the concept of the day in biotechnology, pushing continuous improvement, better quality management, and greater technology adoption. Criteria for addressing risk were developed for the civil aviation industry as far back as the late 1930s and continue to evolve, be updated (1), and get applied to diverse industries as well as to specific operations within industries.

The FDA risk-based GMP initiative for the 21st Century (announced in 2002) promulgates “a risk-based orientation” as one of its guiding principles (2). In essence, it requires that all sourcing and manufacturing operations measure up to a basic level of control, but quality assurance beyond that level is determined on the basis of potential impacts. FDA’s Strategic Action Plan: Protecting and Advancing America’s Health underscores the agency’s commitment to “provide high quality, cost-effective oversight of industry manufacturing, processing, and distribution to reduce risk.” Also highlighted is the need to “use emerging science and data analysis to target the highest risk areas” (3).

The clinical acceptability of biologicals and recombinant DNA-based (rDNA) products is concomitant with risk assessment and must be guided by risk-benefit analyses (4). Thus, for example, low levels of infectious virus in plasma products are prohibited, and virus-contaminated source material is immediately quarantined.

By contrast, in the biotechnology industry, cell lines such as Chinese hamster ovary (CHO) cells containing high levels of endogenous retrovirus (10^6–10^9 particles/mL, as visualized by electron microscopy), are deemed acceptable because the particles are noninfectious and pose primarily a theoretical safety concern.

**General Overview of a Quality Risk Management Process**

Figure 1 provides an overview of the quality risk management (QRM) process that can be applied to all aspects of pharmaceutical quality (5). These aspects include development, manufacturing, distribution, submission, and review processes throughout the lifecycle of a drug product and of biological and biotechnological products, including the use of raw materials, solvents, and excipients (ICH, Q9, draft consensus guideline; step two of the ICH process). Terms used in Figure 1 are defined in the “Glossary” box. Although the emphasis on any specific component varies case by case, a robust process incorporates consideration of the elements at appropriate levels of detail.

**Risk and Risk Assessment:** Risk is commonly defined as a combination of the probability of occurrence of harm and the severity of that harm. However, that is an oversimplification because it does not incorporate impact of value judgments or bias. The ICH-Q9 draft guideline on QRM cautions that involvement of diverse stakeholders (e.g., regulatory bodies, consumer groups, product manufacturers, and product users) makes achieving a shared understanding of the application of risk management difficult because each stakeholder might perceive different potential harms, place different probability on the occurrence of each harm, and attribute different severities to those harms.
Several approaches have been used to address risk. The ALARP (as low as is reasonably practicable) approach seeks to define a level below which risk is negligible (or at least tolerable) and an upper level beyond which risk is intolerable.

Often, public perception leans toward acceptance of risk associated with voluntary activities (e.g., skiing) even when they pose risk several orders of magnitude greater than medical interventions that provide the same (or greater) level of benefit. Professional assessments rely on technical experts in the ALARP approach. An alternative to professional, inductive, linear rules about risk is use of historical assessments, termed bootstrapping. Another approach is cost-benefit and decision analysis. In cost analysis, consequences are evaluated using a single common unit without a tie-in to interventions under study or the diseases they are intended to address (6).

Figure 2 summarizes risks associated with transfusions (7). Although risks associated with mistransfusion and undertransfusion are significantly higher than those associated with blood-borne virus transmission, public and political perception of the latter risk places an increasing burden of “zero risk” demonstration on manufacturers of biopharmaceuticals.

In a recent recommendation statement on “Screening for HIV,” the US Preventive Services Task Force (USPSTF) indicates that the dramatic reduction in the transmission of human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) by human blood and blood components is a result of several factors operating in concert. These include implementation of sensitive tests for viral antibodies, antigens (for HIV-1), and nucleic acids as well as the use of effective virus removal and inactivation methods for plasma derivatives (8). Both standard and FDA-approved rapid screening tests reportedly detect HIV infection with a sensitivity and specificity greater than 99%; false-positive test results are rare, even in low-risk settings.

Scientific risk assessment procedures are conducted within regulatory frameworks (FDA, EMEA) and by many national and international bodies (e.g., WHO, FAO, OIE, OECD). Risk assessment for plasma-derived biologicals and biopharmaceuticals includes consideration of factors such as potential virus input from the source material, extent of virus inactivation or removal achieved through manufacturing processes, and the potential level of infectious virus particles in a dose of final product.
Glossary (i)

Harm: Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: A potential source of harm (ISO/IEC Guide 51)

Product Lifecycle: All phases in the lifecycle from the initial development through pre- and postapproval until the product’s discontinuation.

Quality: Degree to which a set of inherent properties of a product, system, or process fulfills requirements.

Quality Risk Management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System: Formalized system that documents the structure, responsibilities, and procedures required to achieve effective quality management.

Requirements: Needs or expectations that are stated, generally implied, or obligatory by the patients or their surrogates (e.g., healthcare professionals, regulators and legislators).

Risk: Combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance: Decision to accept risk (ISO Guide 73).

Risk Analysis: The estimation of the risk associated with the identified hazards.

Risk Assessment: Systematic process of organizing information to support a risk decision to be made within a risk management process.

Risk Communication: Exchange or sharing of information about risk and risk management between the decision maker and other stakeholders.


Risk Evaluation: Compares the estimated risk against given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification: Systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management: Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling and communicating risk.

Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review: Step in the risk management process for taking account of new knowledge and experiences.

Severity: Measure of the possible consequences of a hazard.

Stakeholder: Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patients, healthcare professionals, regulatory authorities, and industry.

Potential Virus Input: For plasma-derived products, the potential virus burden in a manufacturing pool is based on the number of viraemic donations, the volume of individual donations, and the titer of a viraemic donation that might escape detection in a virus assay (9). Note that regardless of whether testing is conducted on a single donation or a minipool, the “potential virus input” in the manufacturing pool is an extrapolation based on estimates of the titer and on the number of undetected viraemic donations.

Although donor selection and exclusion criteria (as well as inventory hold measures) have contributed significantly to a decrease in the number of viraemic donations, sources of risk remain. Examples include marker-negative “window period” donations (made during the period when a donor is infected with a virus not yet detectable by current tests), donors infected with immunovariant viral strains, persistent antibody-negative (immunosilent) carriers, and presence of virus-specific antibodies in a plasma pool.

Establishment of comprehensive frameworks for monitoring blood donations and infectious disease markers is key to monitoring blood safety. The Retrovirus Epidemiology Donor Study Allogeneic Donor and Recipient (RADAR) repository (10) is a contemporary donor–recipient repository that can be accessed to study the transfusion transmissibility of emerging agents.

Source materials for rDNA products are required to be well characterized (e.g., through a tiered system of cell banking), and raw material characterization and control are required per GMPs. This is combined with the three methods below to ensure viral clearance.

Virus Inactivation/Removal Capacity: Several incidents of viral transmission due to insufficient effectiveness of virus inactivation or reduction methods have occurred in the past. Examples include HIV transmission by chemically-inactivated prothrombin complex concentrates, HCV transmission by IVIg manufactured by Cohn fractionation, and HAV transmission by Factor VIII products inactivated by solvent-detergent treatment. To date, no case of iatrogenic virus transmission by rDNA-based biopharmaceutical products has been reported. This is, however, no cause for complacency; instead, it is evidence that our current approach appears to be adequate and provides reasonable assurance that the risk will not increase from its present level.

Data from viral clearance evaluation (validation) studies must be interpreted carefully and in the
appropriate context. Study limitations include the validity of summing-up logarithmic reduction numbers from single steps, the relevance of viruses used in validation studies (model viruses or specific laboratory strains from the same species), and experimental limitations on the levels of inactivation/removal that can be measured. Reliability of virus validation data must be addressed through scaled-down experiments, and virus reduction factors must be addressed with respect to variations of manufacturing process parameters (4).

**Estimation of Virus Particles in a Finished Product:** As a general principle, for a safe product the virus inactivation or removal capacity should clearly exceed the potential virus burden. An adequate safety margin of 4–6 logs above the estimated virus load in a dose of finished product has become an industry-accepted practice. Because virus safety reduction requirements are subject to various qualitative aspects of interpretation, and the potential number of viral particles per vial of product, it is impossible to assign specific numerical values to them. The estimated number of viral particles per vial can be calculated from the product of a worst-case virus concentration in the starting material and the plasma volume required to produce one vial, divided by the viral reduction factor obtained from validation studies:

\[ N = c \times V \div R \]

where \( N \) is the potential number of viral particles per vial of product, \( c \) is the potential virus concentration in the plasma pool, \( V \) is the volume of plasma required to produce one vial of product, and \( R \) is the viral reduction factor obtained from validation studies (9).

**Clinical Experience and Pharmacovigilance:** Absence of reported viral transmission during clinical trials does not offer conclusive proof of viral safety of a product because data from clinical experience related to the number of investigated patients is usually too low to detect infections, and only a limited number of batches are used.

Plasma-derived products and biopharmaceuticals require a different pharmacovigilance strategy than that used for chemical drugs. A unique feature of biologic products is that virus transmission can occur after years or even decades of safe use. Factors implicated in iatrogenic virus transmission include antibody depletion in the final product (due to decreased antibody prevalence in a donor population), changes in the production process and purification, virus inactivation methods of marginal effectiveness, or even GMP failure.

**How Much Risk Is Acceptable?**

Causality assessment and management approaches for plasma-derived products differ from those of their drug counterparts. For a conventional drug, benefit-risk assessment usually entails investigating the problem and collating a body of data to determine conclusive evidence beyond reasonable doubt for attributing the adverse event to the drug. For biopharmaceuticals, every single reported case of suspected virus transmission must be considered as a potential indicator of an infectious batch, with the inherent risk of transmitting the disease to hundreds or thousands of patients (11). Additionally, suspected iatrogenic transmission of viruses (HIV, HAV, HBV, HCV) requires causality assessment because viruses can also be further transmitted through other exposures (e.g., sexual transmission).

With biologicals and biopharmaceuticals, how much risk is acceptable, and who decides what constitutes ALARP? On one hand, Farrugia questions whether the so-called “safety tripod” (appropriate sourcing, demonstrating viral clearance capacity through the manufacturing process, and in-process controls) for virus safety assurance is relevant today (12). On the other hand, the number of putative risks from new and emerging blood-borne virus infections continues to increase, creating a growing burden to demonstrate zero risk.

In the final analysis, although different numeric constructs have their place in estimating and ranking risk, protecting patients is paramount and should be the ultimate deciding factor in any risk management paradigm.

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