- Histograms;
- Pareto Charts;
- Process Capability Analysis.

## ANNEX II: QUALITY RISK MANAGEMENT AS PART OF INTEGRATED QUALITY MANAGEMENT

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

### II.1 Quality Risk Management as Part of Integrated Quality Management

**Documentation**

To review current interpretations and application of regulatory expectations;

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

**Training and education**

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness);

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

**Quality defects**

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc;

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

**Auditing/Inspection**

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements;
- Overall compliance status and history of the company or facility;
- Robustness of a company's quality risk management activities;
- Complexity of the site;
- Complexity of the manufacturing process;
- Complexity of the product and its therapeutic significance;
- Number and significance of quality defects (e.g., recall);
- Results of previous audits/inspections;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches);
- Test results of official control laboratories.

**Periodic review**

To select, evaluate and interpret trend results of data within the product quality review;

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

**Change management / change control**

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing;

To evaluate the impact of the changes on the availability of the final product;

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers;

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

**Continual improvement**

To facilitate continual improvement in processes throughout the product lifecycle.

## II.2 Quality Risk Management as Part of Regulatory Operations

**Inspection and assessment activities**

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" Section in Annex II.1);

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings;

To determine the appropriateness and type of post-inspection regulatory follow-up;

To evaluate information submitted by industry including pharmaceutical development information;

To evaluate impact of proposed variations or changes;

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

## II.3 Quality Risk Management as Part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:

- reduce product and material defects;
- reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;

To make use of the "design space" concept (see ICH Q8).

### II.4 Quality Risk Management for Facilities, Equipment and Utilities

**Design of facility / equipment**

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel;
- minimize contamination;
- pest control measures;
- prevention of mix-ups;
- open versus closed equipment;
- clean rooms versus isolator technologies;

- dedicated or segregated facilities / equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

**Hygiene aspects in facilities**

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns);

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

**Qualification of facility/equipment/utilities**

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

**Cleaning of equipment and environmental control**

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production);

To determine acceptable (specified) cleaning validation limits.

**Calibration/preventive maintenance**

To set appropriate calibration and maintenance schedules.

**Computer systems and computer controlled equipment**

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);

To determine the extent of validation, e.g.,

- identification of critical performance parameters;

- selection of the requirements and design;
- code review;
- the extent of testing and test methods;
- reliability of electronic records and signatures.

### II.5 Quality Risk Management as Part of Materials Management

**Assessment and evaluation of suppliers and contract manufacturers**

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

**Starting material**

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

**Use of materials**

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);

To determine appropriateness of reprocessing, reworking, use of returned goods.

**Storage, logistics and distribution conditions**

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

## II.6 Quality Risk Management as Part of Production

### Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods;

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation);

To distinguish between critical and non-critical process steps to facilitate design of a validation study.

### In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

### Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

## II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

### Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

### Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

## II.8 Quality Risk Management as Part of Packaging and Labelling

### Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

**Selection of container closure system**

To determine the critical parameters of the container closure system.

**Label controls**

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

### II.9 Quality Risk Management as Part of Supply Chain Control

With regard to product availability risks related to quality/manufacturing issues, lifecycle oversight of the supply chain includes maintaining current knowledge of quality/manufacturing hazards and prioritizing efforts to manage such risks. Understanding hazards to quality/manufacturing is critical to maintaining supply predictability. When risks are well understood and minimized, a higher confidence in product availability can be attained.

**Manufacturing Process Variation and State of Control**

To decrease variability in the manufacturing process (e.g., process drift, non-uniformity) and associated capability gaps that can result in unpredictable outputs, adversely impact quality and consequently timeliness, yield and product availability;

To design monitoring systems that are capable of detecting departures from a state of control and deficiencies in manufacturing processes, so they can be appropriately investigated to determine root causes and any required risk mitigations.

**Manufacturing Facilities**

To ensure that facility infrastructure and equipment are suitable and well-designed for manufacturing and packaging;

To establish equipment and facility maintenance programmes that assure reliable facility and equipment performance;

To ensure that the operational design of equipment is not vulnerable to human error;

To obtain efficiency gains (e.g. speed, throughput, supply timeliness, etc.) from investing in quality through the utilization of digitalization, automation, isolation technology, and other innovations.

## Supplier Oversight and Relationships

To enhance review and monitoring activities (see Section 2.7 of ICH Q10) when substantial variability is identified in the quality and safety of supplied materials or in the services provided.

To manage external product availability risks relating to quality/manufacturing, (e.g. from raw material suppliers, contracted organizations, service providers, etc.)