

Q9(R1) QUALITY RISK MANAGEMENT

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For questions regarding this draft document contact (CDER) Rick Friedman, Rick.Friedman@fda.hhs.gov.

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**QUALITY RISK MANAGEMENT
Q9(R1)**

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ICH HARMONISED GUIDELINE
QUALITY RISK MANAGEMENT

Q9(R1)

ICH Consensus Guideline

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1 **1. INTRODUCTION**

2 *Risk management* principles are effectively utilized in many areas of business and government
3 including finance, insurance, occupational safety, public health, pharmacovigilance, and by
4 agencies regulating these industries. In the pharmaceutical sector, the principles and framework
5 of ICH Q9, coupled with the official ICH training material that supports this guideline, are
6 instrumental in enhancing the application of effective quality risk management by industry and
7 regulators. The importance of *quality systems* has been recognized in the pharmaceutical
8 industry, and it is evident that quality risk management is a valuable component of an effective
9 quality system.

10 It is commonly understood that *risk* is defined as the combination of the probability of
11 occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding
12 of the application of risk management among diverse *stakeholders* is difficult because each
13 stakeholder might perceive different potential harms, place a different probability on each harm
14 occurring and attribute different severities to each harm. In addition, subjectivity can directly
15 impact the effectiveness of risk management activities and the decisions made. In relation to
16 pharmaceuticals, although there are a variety of stakeholders, including patients and medical
17 practitioners as well as government and industry, the protection of the patient by managing the
18 risk to quality and availability, when availability risks arise from quality/manufacturing issues,
19 should be considered of prime importance.

20 The manufacturing and use of a drug product, including its components,
21 necessarily entail some degree of risk. The risk to its quality is just one component of the overall
22 risk. It is important to understand that product *quality* is assured based on appropriate risk-
23 based decision-making throughout the *product lifecycle*, such that the attributes that are
24 important to the quality of the drug product are maintained and the product remains
25 safe and effective.

26 An effective quality risk management approach can further ensure the high quality of the drug
27 (medicinal) product to the patient by providing a proactive means to identify and control
28 potential quality issues during development and manufacturing. A proactive approach to
29 quality risk management facilitates continual improvement and is of strategic importance in
30 achieving an effective pharmaceutical quality system. Additionally, use of quality risk
31 management can improve the decision making if a quality problem arises. In the development
32 phase, quality risk management is part of building knowledge and understanding risk

33 scenarios, so that appropriate risk control can be decided upon during technology transfer, for
34 use during the commercial manufacturing phase. In this context, knowledge is used to make
35 informed risk-based decisions, trigger re-evaluations and stimulate continual improvements.
36 Effective and proactive quality risk management can facilitate better, more informed and timely
37 decisions throughout the lifecycle. This can provide regulators with greater assurance of a
38 company's ability to deal with potential risks and avert problems, and can beneficially affect
39 the extent and level of direct regulatory oversight.

40 The application of digitalization and emerging technologies in the manufacture and control of
41 medicinal products can present certain challenges. The application of quality risk management
42 to the design, validation and technology transfer of advanced production processes and
43 analytical methods, advanced data analysis methods and computerized systems is important.

44 The purpose of this document is to offer a systematic approach to quality risk management for
45 better, more informed, and timely decisions. It serves as a foundation or resource document
46 that is independent of, yet supports, other ICH Quality documents and complements existing
47 quality practices, requirements, standards, and guidelines within the pharmaceutical industry
48 and regulatory environment. It specifically provides guidance on the principles and some of
49 the tools of quality risk management that can enable more effective and consistent risk based
50 decisions, both by regulators and industry, regarding the quality of drug substances and drug
51 (medicinal) products across the product lifecycle. It is not intended to create any new
52 expectations beyond the current regulatory requirements.

53 An understanding of formality in quality risk management (see Section 5 below) may lead to
54 resources being used more efficiently, where lower risk issues are dealt with via less formal
55 means, freeing up resources for managing higher risk issues and more complex problems that
56 may require increased levels of rigor and effort. An understanding of formality can also
57 support risk-based decision-making, where the level of formality that is applied reflects the
58 degree of importance of the decision, as well as the level of uncertainty, complexity and
59 criticality which may be present.

60 Appropriate use of quality risk management can facilitate but does not obviate industry's
61 obligation to comply with regulatory requirements and does not replace appropriate
62 communications between industry and regulators. Quality risk management should not be used
63 in a manner where decisions are made that justify a practice that would otherwise, in

64 accordance with legal requirements, be deemed unacceptable.

65

66 **2. SCOPE**

67 This guideline provides principles and examples of tools for quality risk management that can
68 be applied to different aspects of pharmaceutical quality. These aspects include development,
69 manufacturing, distribution, and the inspection and submission/review processes throughout
70 the lifecycle of drug substances, drug products, biological and biotechnological
71 products (including the use of raw materials, solvents, excipients, packaging and labeling
72 materials in drug products, biological and biotechnological products).

73

74 **3. PRINCIPLES OF QUALITY RISK MANAGEMENT**

75 Two primary principles of quality risk management are:

- 76 • The evaluations of the risk to quality should be based on scientific knowledge and
77 ultimately link to the protection of the patient. (Note: Risk to quality includes situations
78 where product availability may be impacted, leading to potential patient harm.)
- 79 • The level of effort, formality and documentation of the quality risk management process
80 should be commensurate with the level of risk.

81

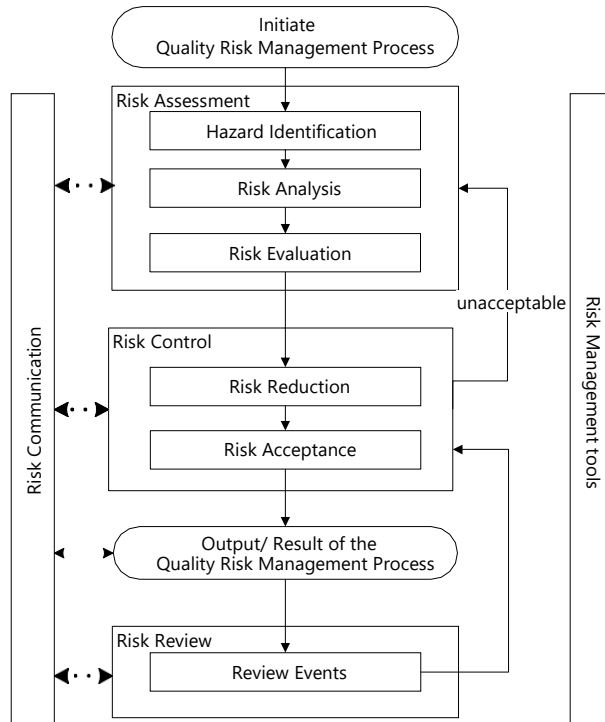
82 **4. GENERAL QUALITY RISK MANAGEMENT PROCESS**

83 Quality risk management is a systematic process for the assessment, control, communication
84 and review of risks to the quality of the drug product across the product lifecycle.

85 A model for quality risk management is outlined in the diagram (Figure 1). Other models could
86 be used. The emphasis on each component of the framework might differ from case to case but
87 a robust process will incorporate consideration of all the elements at a level of detail that is
88 commensurate with the specific risk.

89 Figure 1: Overview of a typical quality risk management process

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91 Decision nodes are not shown in the diagram above because decisions can occur at any point
92 in the process. These decisions might be to return to the previous step and seek further
93 information, to adjust the risk models or even to terminate the risk management process based
94 upon information that supports such a decision. Note: “unacceptable” in the flowchart does not
95 only refer to statutory, legislative or regulatory requirements, but also to indicate that the
96 risk assessment process should be revisited.-

97 4.1 Responsibilities

98 Quality risk management activities are usually, but not always, undertaken by interdisciplinary
99 teams. When teams are formed, they should include experts from the appropriate areas (e.g.,
100 quality unit, business development, engineering, regulatory affairs, production operations,
101 sales and marketing, supply chain, legal, statistics and clinical) in addition to individuals who
102 are knowledgeable about the quality risk management process.

103 Subjectivity can impact every stage of a quality risk management process, especially the
104 identification of hazards and estimates of their probabilities of occurrence, the estimation of
105 risk reduction and the effectiveness of decisions made from quality risk management activities.
106 Subjectivity can be introduced in quality risk management through differences in how risks are
107 assessed and in how hazards, harms and risks are perceived by different stakeholders.

108 Subjectivity can also be introduced through the use of tools with poorly designed risk scoring
109 scales. While subjectivity cannot be completely eliminated from quality risk management
110 activities, it can be controlled by addressing bias, the proper use of quality risk management
111 tools and maximizing the use of relevant data and sources of knowledge (see ICH Q10, Section
112 II.E.1).

113 All participants involved with quality risk management activities should acknowledge,
114 anticipate, and address the potential for subjectivity.

115 *Decision makers* should

- 116 • take responsibility for coordinating quality risk management across various functions and
117 departments of their organization; and
- 118 • assure that a quality risk management process is defined, deployed and reviewed and that
119 adequate resources and knowledge are available;
- 120 • assure that subjectivity in quality risk management activities is controlled and minimized,
121 to facilitate scientifically robust risk-based decision making.

122 **4.2 Initiating a Quality Risk Management Process**

123 Quality risk management should include systematic processes designed to coordinate, facilitate
124 and improve science-based decision making with respect to risk. Possible steps used to initiate
125 and plan a quality risk management process might include the following:

- 126 • Define the problem and/or risk question, including pertinent assumptions identifying the
127 potential for risk;
- 128 • Assemble background information and/ or data on the potential hazard, harm or human
129 health impact relevant to the risk assessment;
- 130 • Identify a leader and necessary resources;
- 131 • Specify a timeline, deliverables and appropriate level of decision making for the risk
132 management process.

133 **4.3 Risk Assessment**

134 **Risk assessment** consists of the identification of hazards and the analysis and evaluation of
135 risks associated with exposure to those hazards (as defined below). Quality risk assessments
136 begin with a well-defined problem description or risk question. When the risk in question is
137 well defined, an appropriate risk management tool (see examples in Section 5) and the types
138 of information needed to address the risk question will be more readily identifiable. As an aid
139 to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are
140 often helpful:

1411. What might go wrong?

1422. What is the likelihood (probability) it will go wrong?

1433. What are the consequences (severity)?

144 **Hazard identification** is a systematic use of information to identify hazards referring to the risk
145 question or problem description. Information can include historical data, theoretical analysis,
146 informed opinions, and the concerns of stakeholders. Hazard identification addresses the “What
147 might go wrong?” question, including identifying the possible consequences. This provides the
148 basis for further steps in the quality risk management process.

149 **Risk analysis** is the estimation of the risk associated with the identified hazards. It is the
150 qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.
151 In some risk management tools, the ability to detect the harm (detectability) also factors in the
152 estimation of risk.

153 **Risk evaluation** compares the identified and analyzed risk against given risk criteria. Risk
154 evaluations consider the strength of evidence for all three of the fundamental questions.

155 In doing an effective risk assessment, the robustness of the data set is important because it
156 determines the quality of the output. Revealing assumptions and reasonable sources of
157 uncertainty will enhance confidence in this output and/or help identify its limitations.

158 Uncertainty is due to combination of incomplete knowledge about a process and its expected
159 or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in
160 pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a
161 process, sources of variability), and probability of detection of problems.

162 The output of a risk assessment is either a quantitative estimate of risk or a qualitative
163 description of a range of risk. When risk is expressed quantitatively, a numerical probability is
164 used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”,
165 “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a "risk
166 score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a
167 risk estimate provides the likelihood of a specific consequence, given a set of risk-generating
168 circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a
169 time. Alternatively, some risk management tools use a relative risk measure to combine
170 multiple levels of severity and probability into an overall estimate of relative risk. The
171 intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

172 **4.4 Risk Control**

173 **Risk control** includes decision making to reduce and/or accept risks. The purpose of risk
174 control is to reduce the risk to an acceptable level. The amount of effort used for risk control
175 should be proportional to the significance of the risk. Decision makers might use different
176 processes, including benefit-cost analysis, for understanding the optimal level of risk control.

177 Risk control might focus on the following questions:

- 178 • Is the risk above an acceptable level?
- 179 • What can be done to reduce or eliminate risks?
- 180 • What is the appropriate balance among benefits, risks and resources?
- 181 • Are new risks introduced as a result of the identified risks being controlled?

182 **Risk reduction** focuses on processes for mitigation or avoidance of quality risk when it exceeds
183 a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to
184 mitigate the severity and probability of harm. Processes that improve the detectability of
185 hazards and quality risks might also be used as part of a risk control strategy. The
186 implementation of risk reduction measures can introduce new risks into the system or increase
187 the significance of other existing risks. Hence, it might be appropriate to revisit the risk
188 assessment to identify and evaluate any possible change in risk after implementing a risk
189 reduction process.

190 **Risk acceptance** is a decision to accept risk. Risk acceptance can be a formal decision to accept
191 the residual risk or it can be a passive decision in which residual risks are not specified. For
192 some types of harms, even the best quality risk management practices might not entirely
193 eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk
194 management strategy has been applied and that quality risk is reduced to a specified
195 (acceptable) level. This (specified) acceptable level will depend on many parameters and
196 should be decided on a case-by-case basis.

197 **4.5 Risk Communication**

198 **Risk communication** is the sharing of information about risk and risk management between
199 the decision makers and others. Parties can communicate at any stage of the risk management
200 process (see Fig. 1: dashed arrows). The output/result of the quality risk management process
201 should be appropriately communicated and documented (see Fig. 1: solid arrows).
202 Communications might include those among interested parties; e.g., regulators and industry,
203 industry and the patient, within a company, industry or regulatory authority, etc. The included
204 information might relate to the existence, nature, form, probability, severity, acceptability,
205 control, treatment, detectability or other aspects of risks to quality. Communication need not
206 be carried out for each and every risk acceptance. Between the industry and regulatory
207 authorities, communication concerning quality risk management decisions might be effected
208 through existing channels as specified in regulations and guidances.

209 **4.6 Risk Review**

210 Risk management should be an ongoing part of the quality management process. A mechanism
211 to review or monitor events should be implemented.

212 The output/results of the risk management process should be reviewed to take into account new
213 knowledge and experience. Once a quality risk management process has been initiated, that
214 process should continue to be utilized for events that might impact the original quality risk
215 management decision, whether these events are planned (e.g., results of product review,
216 inspections, audits, change control) or unplanned (e.g., root cause from failure investigations,
217 recall). The frequency of any review should be based upon the level of risk. Risk review might
218 include reconsideration of risk acceptance decisions (section 4.4).

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220 5. RISK MANAGEMENT METHODOLOGY

221 Quality risk management supports a scientific and practical approach to decision-making. It
222 provides documented, transparent and reproducible methods to accomplish steps of the quality
223 risk management process based on current knowledge about assessing the probability, severity
224 and sometimes detectability of the risk.

225 Traditionally, risks to quality have been assessed and managed in a variety of informal ways
226 (empirical and/ or internal procedures) based on, for example, compilation of observations,
227 trends and other information. Such approaches continue to provide useful information that
228 might support topics such as handling of complaints, quality defects, deviations and allocation
229 of resources.

230 Additionally, the pharmaceutical industry and regulators can assess and manage risk using
231 recognized risk management tools and/ or internal procedures (e.g., standard operating
232 procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1
233 and chapter 8):

- 234 • Basic risk management facilitation methods
235 (flowcharts, check sheets etc.);
- 236 • Failure Mode Effects Analysis (FMEA);
- 237 • Failure Mode, Effects and Criticality Analysis (FMECA);
- 238 • Fault Tree Analysis (FTA);
- 239 • Hazard Analysis and Critical Control Points (HACCP);
- 240 • Hazard Operability Analysis (HAZOP);
- 241 • Preliminary Hazard Analysis (PHA);
- 242 • Risk ranking and filtering;
- 243 • Supporting statistical tools.

244 It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance
245 and drug product quality. Quality risk management methods and the supporting

246 statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined
247 use provides flexibility that can facilitate the application of quality risk management principles.

248 The degree of rigor and formality of quality risk management should reflect available
249 knowledge and be commensurate with the complexity and/ or criticality of the issue to be
250 addressed.

251 **5.1 Formality in Quality Risk Management**

252 Formality in quality risk management is not a binary concept (i.e. formal/informal); varying
253 degrees of formality can be applied during quality risk management activities, including when
254 making risk-based decisions. In this way, formality can be considered a continuum (or
255 spectrum), ranging from low to high.

256 When determining how much formality to apply to a given quality risk management activity,
257 certain factors can be considered. These can include, for example, the following:

258 • **Uncertainty:** The term “uncertainty” in quality risk management means lack of knowledge
259 about risks. The level of uncertainty that is associated with the area being risk assessed
260 informs how much formality may be required to manage potential risks. Systematic
261 approaches for acquiring, analyzing, storing and disseminating scientific information are
262 essential for generating knowledge, which in turn informs all quality risk management
263 activities. Uncertainty may be reduced via effective knowledge management, which enables
264 accumulated and new information (both internal and external) to be used to support risk-
265 based decisions throughout the lifecycle.

266 • **Importance:** The more important a risk-based decision is, the higher the level of formality
267 that should be applied, and the greater the need to reduce the level of uncertainty associated
268 with it.

269 • **Complexity:** The more complex a process or subject area is to a quality risk management
270 activity, the higher the level of formality that should be applied to assure product quality.

271 In general, higher levels of uncertainty, importance or complexity require more formal quality
272 risk management approaches to manage potential risks and to support effective risk-based
273 decision making.

274 The overall approach for determining how much formality to apply during quality risk

275 management activities should be described within the quality system. Resource constraints
276 should not be used to justify the use of lower levels of formality in the quality risk management
277 process. Regardless of how much formality is applied, the robust management of risk is the
278 goal of the process. This should be based on evidence, science and knowledge, where risk
279 scores, ratings or assessments are supported by data or by an appropriate justification or
280 rationale.

281 *The following may be characteristics of higher levels of formality:*

- 282 • All parts of the quality risk management process (Risk Assessment, Risk Control, Risk
283 Review and Risk Communication) are explicitly performed, and stand-alone quality risk
284 management reports (or related documents) which address all aspects of the process may be
285 generated and are documented (e.g., within the quality system).
- 286 • Recognized or other quality risk management tools are used in some or all parts of the
287 process.
- 288 • A cross-functional team is assembled for the quality risk management activity. Use of a
289 trained quality risk management facilitator may be integral to a higher formality process.

290 *The following may be characteristics of lower levels of formality:*

- 291 • One or more parts of the quality risk management process are not performed as stand-alone
292 activities but are addressed within other elements of the quality system which may have risk
293 assessment and risk control activities embedded within them.
- 294 • Recognized or other quality risk management tools might not be used in some or all parts
295 of the process. A cross functional team might not be necessary.
- 296 • Stand-alone quality risk management reports might not be generated. The outcome of the
297 quality risk management process is usually documented in the relevant parts of the quality
298 system.

299 Note: Degrees of formality between the above higher and lower levels also exist and can be
300 used.

301 5.2 Risk-based Decision Making

302 Risk-based decision making is inherent in all quality risk management activities; it provides an
303 essential foundation for decision makers in an organization. Effective risk-based decision

304 making begins with determining the level of effort, formality and documentation that should
305 be applied during the quality risk management process. The outputs of quality risk management
306 activities include decisions in relation to what hazards exist, the risks associated with those
307 hazards, the risk controls required, the acceptability of the residual risk after risk controls, the
308 communication and review of quality risk management activities and outputs.

309 Approaches to risk-based decision-making are beneficial, because they address uncertainty
310 through the use of knowledge, facilitating informed decisions by regulators and the
311 pharmaceutical industry in a multitude of areas, including when allocating resources. They also
312 help recognize where uncertainty remains, so that appropriate risk controls (including
313 improved detectability) can be identified to enhance understanding of those variables and
314 further reduce the level of uncertainty.

315 As all decision making relies on the use of knowledge, see ICH Q10 for guidance in relation
316 to Knowledge Management. It is important also to ensure the integrity of the data that are used
317 for risk-based decision making.

318 *Approaches to risk-based decision-making:*

319 There are different processes that can be used to make risk-based decisions; these are directly
320 related to the level of formality that is applied during the quality risk management process.
321 (See Section 5.1 above for guidance on what constitutes formality in quality risk management.)
322 In general, higher levels of formality in quality risk management call for higher levels of
323 structure in relation to risk-based decision making. There can be varying degrees of structure
324 with regard to approaches for risk-based decision making. These degrees of structure can be
325 considered to be on a continuum (or spectrum). Below are descriptions for highly structured
326 vs. less structured processes, and for rule-based processes when making risk-based decisions:

- 327 • Some risk-based decision making processes are highly structured and can involve a formal
328 analysis of the available options that exist before making a decision. They involve an in-
329 depth consideration of relevant factors associated with the available options. Such processes
330 might be used when there is a high degree of importance associated with the decision, and
331 when the level of uncertainty and/or complexity is high.

- 332 • Other risk-based decision making processes are less structured; here, simpler approaches
333 are used to arrive at decisions, and they primarily make use of existing knowledge to support
334 an assessment of hazards, risks and any required risk controls. Such processes might still be
335 used when there is a high degree of importance associated with the decision, but the degree
336 of uncertainty and/or complexity is lower.
- 337 • Decisions might also be made using rule-based (or standardized) approaches, which do not
338 require a new risk assessment to make such decisions. This is where there are SOPs, policies
339 or well understood requirements in place which determine what decisions must be made.
340 Here, rules (or limits) may be in place which govern such decisions; these can be based on
341 a previously obtained understanding of the relevant risks and they usually lead to
342 predetermined actions or expected outcomes.

343

344 **6. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND**
345 **REGULATORY OPERATIONS**

346 Quality risk management is a process that supports science-based and practical decisions when
347 integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use
348 of quality risk management does not obviate industry's obligation to comply with regulatory
349 requirements. However, effective quality risk management can facilitate better and more
350 informed decisions, can provide regulators with greater assurance of a company's ability to
351 deal with potential risks, and might affect the extent and level of direct regulatory oversight. In
352 addition, quality risk management can facilitate better use of resources by all parties.

353 Training of both industry and regulatory personnel in quality risk management processes
354 provides for greater understanding of decision-making processes and builds confidence in
355 quality risk management outcomes.

356 Quality risk management should be integrated into existing operations and documented
357 appropriately. While manufacturing and supply chain diversity can be enablers of product
358 availability, increasingly complex supply chains lead to interdependencies that can introduce
359 systemic quality/manufacturing risks impacting supply chain robustness. Application of quality
360 risk management can proactively mitigate these risks. Preventive measures supporting product
361 availability may be identified through quality risk management activities.

362 Annex II provides examples of situations in which the use of the quality risk management
363 process might provide information that could then be used in a variety of pharmaceutical
364 operations. These examples are provided for illustrative purposes only and should not be
365 considered a definitive or exhaustive list. These examples are not intended to create any new
366 expectations beyond the requirements laid out in the current regulations.

367 Examples for industry and regulatory operations (see Annex II):

- 368 • Quality management.

369 Examples for industry operations and activities (see Annex II):

- 370 • Development;
- 371 • Facility, equipment and utilities;
- 372 • Materials management;
- 373 • Production;
- 374 • Laboratory control and stability testing;
- 375 • Packaging and labeling;
- 376 • Supply Chain Control.

377 Examples for regulatory operations (see Annex II):

- 378 • Inspection and assessment activities.

379 While regulatory decisions will continue to be taken on a regional basis, a common
380 understanding and application of quality risk management principles could facilitate mutual
381 confidence and promote more consistent decisions among regulators on the basis of the same
382 information. This collaboration could be important in the development of policies and
383 guidelines that integrate and support quality risk management practices.

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386 The role of Quality Risk Management in addressing Product Availability Risks

387 Quality/manufacturing issues, including non-compliance with Good Manufacturing Practice
388 (GMP), are a frequent cause of product availability issues (e.g., product shortages). The
389 interests of patients are served by risk-based drug shortage prevention and mitigation activities
390 that help to proactively manage supply chain complexities and ensure availability of needed
391 medicines. An effective pharmaceutical quality system drives both supply chain robustness and
392 sustainable GMP compliance. It also uses quality risk management and knowledge
393 management to provide an early warning system that supports effective oversight and response
394 to evolving quality/manufacturing risks from the pharmaceutical company or its external
395 partners. The level of formality applied to risk-based drug shortage prevention and mitigation
396 activities may vary (see Chapter 5). Factors that can affect supply reliability, and hence product
397 availability, include the following:

398 *Manufacturing Process Variation and State of Control (internal and external):*

399 Processes that exhibit excessive variability (e.g., process drift, non-uniformity) have capability
400 gaps that can result in unpredictable outputs and may adversely impact quality, timeliness,
401 yield, and consequently product availability. Quality risk management can help design
402 monitoring systems that are capable of detecting departures from a state of control and
403 deficiencies in manufacturing processes, so they can be investigated to address root causes.

404 *Manufacturing Facilities:*

405 A robust facility infrastructure can facilitate reliable supply; it includes suitable equipment and
406 well-designed facilities for manufacturing and packaging. Robustness can be affected by
407 multiple factors, such as an aging facility, insufficient maintenance or an operational design
408 that is vulnerable to human error. Risks to supply can be reduced by addressing these factors,
409 as well as through use of modern technology, such as digitalization, automation, isolation
410 technology, amongst others.

411 *Oversight of Outsourced Activities and Suppliers:*

412 Quality system governance includes assuring the acceptability of supply chain partners over
413 the product lifecycle. Approval and oversight of outsourced activities and material suppliers is
414 informed by risk assessments, effective knowledge management, and an effective monitoring

415 strategy for supply chain partner performance. A successful manufacturing partnership is
416 strengthened by appropriate communication and collaboration mechanisms. When substantial
417 variability is identified in the quality and safety of supplied materials or in the services
418 provided, enhanced review and monitoring activities are justified (See Section 2.7 of ICH
419 Q10). In some cases, it may be necessary to identify a new supply chain entity (e.g. a pre-
420 qualified backup option) to perform a function.

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422 7. DEFINITIONS

423 **Decision Maker(s):**

424 Person(s) with the competence and authority to make appropriate and timely quality risk
425 management decisions.

426 **Detectability:**

427 The ability to discover or determine the existence, presence, or fact of a hazard.

428 **Harm:**

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

431 **Hazard:**

432 The potential source of harm (ISO/IEC Guide 51).

433 **Hazard Identification:**

434 The systematic use of information to identify potential sources of harm (hazards) referring to
435 the risk question or problem description.

436 **Product Lifecycle:**

437 All phases in the life of the product from the initial development through marketing until the
438 product's discontinuation.

439 **Quality:**

440 The degree to which a set of inherent properties of a product, system or process fulfills
441 requirements (see ICH Q6A definition specifically for "quality" of drug substance and drug
442 (medicinal) products.)

443 Quality Risk Management:

444 A systematic process for the assessment, control, communication and review of risks to the
445 quality of the drug product across the product lifecycle.

446 Quality System:

447 The sum of all aspects of a system that implements quality policy and ensures that quality
448 objectives are met.

449 Requirements:

450 The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health
451 care professionals, regulators and legislators). In this document, "requirements" refers not only
452 to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

453 Risk:

454 The combination of the probability of occurrence of harm and the severity of that harm
455 (ISO/IEC Guide 51).

456 Risk Acceptance:

457 The decision to accept risk (ISO Guide 73).

458 Risk Analysis:

459 The estimation of the risk associated with the identified hazards.

460 Risk Assessment:

461 A systematic process of organizing information to support a risk decision to be made within a
462 risk management process. It consists of the identification of hazards and the analysis and
463 evaluation of risks associated with exposure to those hazards.

464 Risk-based Decision Making:

465 An approach or process that considers knowledge about risks relevant to the decision and
466 whether risks are at an acceptable level.

467 Risk Communication:

468 The sharing of information about risk and risk management between the decision maker and
469 other stakeholders.

470 Risk Control:

471 Actions implementing risk management decisions (ISO Guide 73).

472 Risk Evaluation:

473 The comparison of the estimated risk to given risk criteria using a quantitative or qualitative
474 scale to determine the significance of the risk.

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Reduction:

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

Risk Review:

Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity:

A 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 patient, healthcare professional, regulatory authority, and industry.

Trend:

A statistical term referring to the direction or rate of change of a variable(s).

475

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512

513 ANNEX I: QUALITY RISK MANAGEMENT METHODS AND TOOLS

514 The purpose of this annex is to provide a general overview of and references for some of the
515 primary tools that might be used in quality risk management by industry and regulators. The
516 references are included as an aid to gain more knowledge and detail about the particular tool.
517 This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable
518 to every situation in which a quality risk management procedure is used.

519 It is neither always appropriate nor always necessary to use highly formal quality risk
520 management methods and tools. The use of less formal quality risk management methods and
521 tools can also be considered acceptable. See Chapter 5 for guidance on what constitutes
522 formality in quality risk management.

523 I.1 Basic Risk Management Facilitation Methods

524 Some of the simple techniques that are commonly used to structure risk management by
525 organizing data and facilitating decision-making are:

- 526 • Flowcharts;
- 527 • Check Sheets;
- 528 • Process Mapping;
- 529 • Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

530 I.2 Failure Mode Effects Analysis (FMEA)

531 FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and
532 their likely effect on outcomes and/or product performance. Once failure modes are
533 established, risk reduction can be used to eliminate, contain, reduce or control the potential
534 failures. FMEA relies on product and process understanding. FMEA methodically breaks down
535 the analysis of complex processes into manageable steps. It is a powerful tool for summarizing
536 the important modes of failure, factors causing these failures and the likely effects of these
537 failures.

538 Potential Areas of Use(s)

539 FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

540 FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing
541 operation and its effect on product or process. It identifies elements/operations within the
542 system that render it vulnerable. The output/ results of FMEA can be used as a basis for design
543 or further analysis or to guide resource deployment.

544 I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

545 FMEA might be extended to incorporate an investigation of the degree of severity of the
546 consequences, their respective probabilities of occurrence, and their detectability, thereby
547 becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order
548 for such an analysis to be performed, the product or process specifications should be
549 established. FMECA can identify places where additional preventive actions might be
550 appropriate to minimize risks.

551 Potential Areas of Use(s)

552 FMECA application in the pharmaceutical industry should mostly be utilized for failures and
553 risks associated with manufacturing processes; however, it is not limited to this application.
554 The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank
555 the modes on a relative risk basis.

556 I.4 Fault Tree Analysis (FTA)

557 The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a
558 product or process. This tool evaluates system (or sub-system) failures one at a time but can
559 combine multiple causes of failure by identifying causal chains. The results are represented
560 pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault
561 modes are described with logical operators (AND, OR, etc.). FTA relies on the experts’ process
562 understanding to identify causal factors.

563 Potential Areas of Use(s)

564 FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to
565 investigate complaints or deviations in order to fully understand their root cause and to ensure
566 that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve
567 one problem yet cause a different problem). FTA is an effective tool for
568 evaluating how multiple factors affect a given issue. The output of an FTA includes a visual

569 representation of failure modes. It is useful both for risk assessment and in developing
570 monitoring programs.

571 I.5 Hazard Analysis and Critical Control Points (HACCP)

572 HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability,
573 and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured
574 approach that applies technical and scientific principles to analyze, evaluate, prevent, and
575 control the risk or adverse consequence(s) of hazard(s) due to the design, development,
576 production, and use of products.

577 HACCP consists of the following seven steps:

- 578 (1) conduct a hazard analysis and identify preventive measures for each step of the process;
- 579 (2) determine the critical control points;
- 580 (3) establish critical limits;
- 581 (4) establish a system to monitor the critical control points;
- 582 (5) establish the corrective action to be taken when monitoring indicates that the critical
583 control points are not in a state of control;
- 584 (6) establish system to verify that the HACCP system is working effectively;
- 585 (7) establish a record-keeping system.

586 Potential Areas of Use(s)

587 HACCP might be used to identify and manage risks associated with physical, chemical and
588 biological hazards (including microbiological contamination). HACCP is most useful when
589 product and process understanding is sufficiently comprehensive to support identification of
590 critical control points. The output of a HACCP analysis is risk management information that
591 facilitates monitoring of critical points not only in the manufacturing process but also in other
592 life cycle phases.

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594 I.6 Hazard Operability Analysis (HAZOP)

595 HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by
596 deviations from the design or operating intentions. It is a systematic brainstorming technique
597 for identifying hazards using so-called “guide-words”. “Guide-words” (e.g., No, More, Other
598 Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help
599 identify potential deviations from normal use or design intentions. It often uses a team of people
600 with expertise covering the design of the process or product and its application.

601 Potential Areas of Use(s)

602 HAZOP can be applied to manufacturing processes, including outsourced production and 603
formulation as well as the upstream suppliers, equipment and facilities for drug substances and 604
drug products. It has also been used primarily in the pharmaceutical industry for 605 evaluating
process safety hazards. As is the case with HACCP, the output of a HAZOP analysis 606 is a list of
critical operations for risk management. This facilitates regular monitoring of critical 607 points in the
manufacturing process.

608 I.7 Preliminary Hazard Analysis (PHA)

609 PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or 610
failure to identify future hazards, hazardous situations and events that might cause harm, as 611 well
as to estimate their probability of occurrence for a given activity, facility, product or 612 system.
The tool consists of: 1) the identification of the possibilities that the risk event happens, 613 2) the
qualitative evaluation of the extent of possible injury or damage to health that could 614 result, 3) a
relative ranking of the hazard using a combination of severity and likelihood of 615 occurrence, and
4) the identification of possible remedial measures.

616 Potential Areas of Use(s)

617 PHA might be useful when analyzing existing systems or prioritizing hazards where 618
circumstances prevent a more extensive technique from being used. It can be used for product, 619
process and facility design as well as to evaluate the types of hazards for the general product 620 type,
then the product class, and finally the specific product. PHA is most commonly used early 621 in the
development of a project when there is little information on design details or operating 622 procedures;
thus, it will often be a precursor to further studies. Typically, hazards identified in 623 the PHA are
further assessed with other risk management tools such as those in this section.

624 I.8 Risk Ranking and Filtering

625 Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex 626 systems typically involves evaluation of multiple diverse quantitative and qualitative factors 627 for each risk. The tool involves breaking down a basic risk question into as many components 628 as needed to capture factors involved in the risk. These factors are combined into a single 629 relative risk score that can then be used for ranking risks. “Filters,” in the form of weighting 630 factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or 631 policy objectives.

632 Potential Areas of Use(s)

633 Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by 634 regulators or industry. Risk ranking methods are particularly helpful in situations in which the 635 portfolio of risks and the underlying consequences to be managed are diverse and difficult to 636 compare using a single tool. Risk ranking is useful when management needs to evaluate both 637 quantitatively-assessed and qualitatively-assessed risks within the same organizational 638 framework.

639 I.9 Supporting Statistical Tools

640 Statistical tools can support and facilitate quality risk management. They can enable effective 641 data assessment, aid in determining the significance of the data set(s), and facilitate more 642 reliable decision making. A listing of some of the principal statistical tools commonly used in 643 the pharmaceutical industry is provided:

- 644 • Control Charts, for example:
 - 645 - Acceptance Control Charts (see ISO 7966);
 - 646 - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873);
 - 647 - Cumulative Sum Charts (see ISO 7871);
 - 648 - Shewhart Control Charts (see ISO 8258);
 - 649 - Weighted Moving Average.
- 650 • Design of Experiments (DOE);

- 651 • Histograms;
- 652 • Pareto Charts;
- 653 • Process Capability Analysis.

654

655 **ANNEX II: QUALITY RISK MANAGEMENT AS PART OF INTEGRATED QUALITY**
656 **MANAGEMENT**

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

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

663 **II.1 Quality Risk Management as Part of Integrated Quality Management**
664 **Documentation**

665 To review current interpretations and application of regulatory expectations;

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

667 **Training and education**

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

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

673 **Quality defects**

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

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

679 Auditing/Inspection

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

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

694 Periodic review

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

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

698 Change management / change control

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

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

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

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

706 Continual improvement

707 To facilitate continual improvement in processes throughout the product lifecycle.

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

709 Inspection and assessment activities

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

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

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

715 To evaluate information submitted by industry including pharmaceutical development
716 information;

717 To evaluate impact of proposed variations or changes;

718 To identify risks which should be communicated between inspectors and assessors to facilitate
719 better understanding of how risks can be or are controlled (e.g., parametric release, Process 720
Analytical Technology (PAT)).

721 II.3 Quality Risk Management as Part of development

722 To design a quality product and its manufacturing process to consistently deliver the intended
723 performance of the product (see ICH Q8(R2));

724 To enhance knowledge of product performance over a wide range of material attributes (e.g., 725
particle size distribution, moisture content, flow properties), processing options and process 726
parameters;

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

729 To establish appropriate specifications, identify critical process parameters and establish 730
manufacturing controls (e.g., using information from pharmaceutical development studies 731
regarding the clinical significance of quality attributes and the ability to control them during 732
processing);

733 To decrease variability of quality attributes:

734 • reduce product and material defects;

735 • reduce manufacturing defects.

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

738 To make use of the “design space” concept (see ICH Q8(R2)).

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

740 **Design of facility / equipment**

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

742 • flow of material and personnel;

743 • minimize contamination;

744 • pest control measures;

745 • prevention of mix-ups;

746 • open versus closed equipment;

747 • clean rooms versus isolator technologies;

748 • dedicated or segregated facilities / equipment.

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

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

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

755 Hygiene aspects in facilities

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

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

760 Qualification of facility/equipment/utilities

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

763 Cleaning of equipment and environmental control

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

766 To determine acceptable (specified) cleaning validation limits.

767 Calibration/preventive maintenance

768 To set appropriate calibration and maintenance schedules.

769 Computer systems and computer controlled equipment

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

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

773 • identification of critical performance parameters;

- 774 • selection of the requirements and design;
- 775 • code review;
- 776 • the extent of testing and test methods;
- 777 • reliability of electronic records and signatures.

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

779 Assessment and evaluation of suppliers and contract manufacturers

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

782 Starting material

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

785 Use of materials

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

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

789 Storage, logistics and distribution conditions

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

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

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

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

798 II.6 Quality Risk Management as Part of Production

799 Validation

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

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

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

805 In-process sampling & testing

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

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

810 Production planning

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

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

814 Out of specification results

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

817 Retest period / expiration date

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

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

820 Design of packages

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

823 Selection of container closure system

824 To determine the critical parameters of the container closure system.

825 Label controls

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

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

829 With regard to product availability risks related to quality/manufacturing issues, lifecycle 830
oversight of the supply chain includes maintaining current knowledge of quality/manufacturing 831
hazards and prioritizing efforts to manage such risks. Understanding hazards 832 to
quality/manufacturing is critical to maintaining supply predictability. When risks are well 833
understood and minimized, a higher confidence in product availability can be attained.

834 Manufacturing Process Variation and State of Control

835 To decrease variability in the manufacturing process (e.g., process drift, non-uniformity) and 836
associated capability gaps that can result in unpredictable outputs, adversely impact quality and 837
consequently timeliness, yield and product availability;

838 To design monitoring systems that are capable of detecting departures from a state of control 839
and deficiencies in manufacturing processes, so they can be appropriately investigated to 840
determine root causes and any required risk mitigations.

841 Manufacturing Facilities

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

844 To establish equipment and facility maintenance programs that assure reliable facility and
845 equipment performance;

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

847 To obtain efficiency gains (e.g. speed, throughput, supply timeliness, etc.) from investing in
848 quality through the utilization of digitalization, automation, isolation technology, and other 849
innovations.

850 **Supplier Oversight and Relationships**

851 To enhance review and monitoring activities (see Section 2.7 of ICH Q10) when substantial 852
variability is identified in the quality and safety of supplied materials or in the services 853
provided.

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