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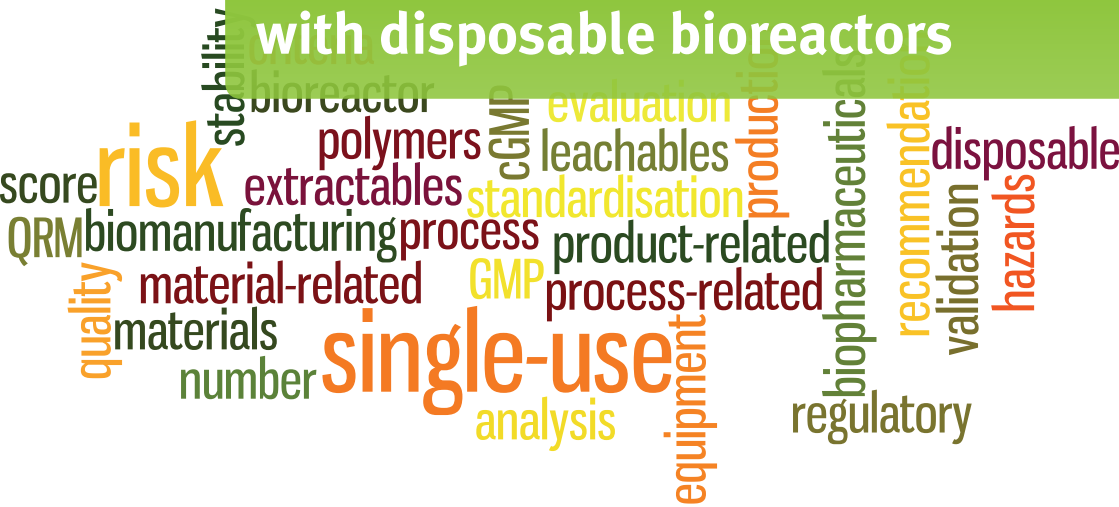
Recommendation for a risk analysis for production processes with disposable bioreactors



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Recommendation for a risk analysis for production processes with disposable bioreactors

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1 INTRODUCTION

The basis for this recommendation is threefold: Starting point was an internal paper of the Werthenstein BioPharma, a subsidiary of the MSD Company. This paper was subsequently in depth discussed by the four authors and the outcome of this discussion was a publication in Advances in Biochemical Engineering/Biotechnology (1), which serves as the scientific basis of the present DECHEMA recommendation.

Traditionally, quality management and control systems in pharmaceutical industry strongly relied on defined rules and well established standards and methods. The rules were given by governmental authority in the form of good manufacturing practices (GMP) and established methods were defined by qualification and validation processes within the pharmaceutical companies. This has led to a very conservative approach to new manufacturing methods and has its limits when it comes to innovative biological production systems. They may "display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials (...)" (2). In addition to the inherent variability of biological systems, the use of the latest flexible production systems using single-use manufacturing tools has a big implication on the quality control of such production processes.

Risk management is now integral part of new GMP regulation both in the EU and the USA. Production of pharmaceuticals in single-use systems by biological means is no longer controlled by applying standard GMP rules but is extended to methods of risk management as it is defined by guidelines like the ICH Q9 "Quality Risk Management" (3), which has been approved by the pharmaceutical authorities in the USA, EU and Japan. This approach has the advantage to be flexible enough for future development in both biological production systems and innovative single-use solutions. But there is also a certain shift of responsibility from authorities to pharmaceutical companies involved, which makes life for both more challenging. Inspectors may not only check compliance issues by defined lists, and companies have to create specific rules and specification based on scientific rational of their processes and systems. As there is a wide discretion, risk analysis tools are essential, which document judgements and scientific rational behind decisions out of risk evaluation processes.

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This recommendation is based on an article in Adv. Biochem. Eng. Biotechnol., Springer 2013 (1).

2 REGULATORY BACKGROUND FOR THE PRODUCTION OF MEDICINAL PRODUCTS

The production of pharmaceuticals is based on good manufacturing practices (GMP), which gives a framework for the manufacture of safe and effective drugs at a constant quality level. GMPs are released and controlled by regulatory authorities and are justified by the potentially devastating impact on the health of a patient. Authorities act on two levels to ensure patient safety: First by the registration process for new drugs and second by the application process for a production licence. The relevant regulatory authority is always the office of the country, where the medicinal product is marketed and distributed to the patients. For most countries in Europe this is the European Medicines Agency (EMA) in collaboration with the authorities of the EU member states and for the USA, this is performed by the Federal Drug Administration (FDA). Both authorities are connected through several harmonisation agencies, of which the most important is the International Conference on Harmonisation (ICH).

Basic GMP rules are set in the EU by EMA through the EU-GMP. They consist of three parts and 19 Annexes. The first part is called "Basic requirement for medicinal products" (4), the second part is based in ICH Q7 (5, 6) and deals with specific issues for the manufacturing of active pharmaceutical ingredients (API). The third part is called "GMP related documents". It is this part citing the ICH Q9 (3) as the basis for quality risk management in Europe. Although Switzerland is not part of the EU, all three parts of the GMP guidelines are applicable, as there is a fully operational mutual recognition agreement with the EU and Switzerland has access to ICH as representative of the European Free Trade Association (EFTA) for this organisation.

The basic set of the GMPs comparable to the EU-GMP part I is set for the USA by the Federal Code of Regulation CFR Part 211 "Current good manufacturing practices for finished pharmaceuticals" (cGMP, 7). This regulation is further specified by documents called "Guidance to the industry", which cover specific topics of pharmaceutical manufacturing. The basis of ICH Q9 in the USA is given by the guidance to the industry Q9 "Quality risk management" (8). GMPs in both the USA and EU are supplemented with the United States Pharmacopeia (USP, 9) and the European Pharmacopeia respectively (EP, 10), which contain specifications and description of standard pharmaceutical ingredients and basic requirements for methods in pharmaceutical analytics and production. They also include acceptance criteria for extractables for product-contact materials (11).

Besides regulation by governmental authorities and ICH, additional information and rules are provided by organisations like the International Society for Pharmaceutical Engineering (ISPE), the International Organisation for Standardisation (ISO) or the Parenteral Drug Association (PDA). They publish information as handbooks or technical reports, which are considered as state of the art, when it comes to the transfer of regulatory requirement to manufacturing processes.

Although this recommendation aims for pharmaceutical production systems, methods for the evaluation of medicinal products like the ISO 10993 series may also be used as knowledge base.

3 HAZARDS OF SINGLE-USE MANUFACTURING

Risk management for single-use equipment starts with the evaluation of potential hazards as possible causes for patient risk. These hazards are related to the material of the single-use equipment, to the specific process design or to the product produced. Supply chain and lifecycle management for disposable processes are very different from traditional single-use processes in biomanufacturing. Quality risk management issues must therefore not only cover the manufacturing site but includes suppliers, contract partners and internal departments from development to product discontinuation over the whole product lifecycle (12).

3.1 Material-related hazards

The material used for single-use equipment should show as little interaction with biological material or process medium as possible or as specified for the intended use. There are specific tests available to test bioactivity either by contacting material or extracts of the material to mammalian cells and looking for changes in cell morphology or by injecting extracts to mice and rabbits. These tests should not show activity to biological material and the polymers should belong to the class VI (USP 87, 88).

Mechanical stability is also a prerequisite for the use in pharmaceutical production. At smaller scale the problem is normally well under control, but in larger scale this is the limiting factor for the use of single-use equipment. Different mechanical properties may be tested depending of the use of the material.

The origin of the polymeric material, its additives, lubricants or cleaning agents may also cause problems. Especially material, which may transmit animal spongiform encephalopathy agents, must not be used as they may impose a severe risk to patients. In addition material of animal origin may be the cause for virus transmission or allergenic substances. It is therefore necessary, that the origin of all materials can be tracked down to the source for risk evaluation.

The material used for single-use equipment should also be conforming to endotoxin levels required in the pharmacopoeias, as many of the products are for parenteral use.

3.2 Process-related hazards

The most important hazards are leachables and extractables from polymer material as they can possibly migrate into the drug formulation. An assessment for the chemical interaction of the container material and pharmaceutical content follows three phases: Material screening and selection, simulation study including evaluation of worst case conditions and product assessment of the actual case (13). Extractables studies are more related to the material of single use equipment, whereas leachables studies are more focused at the actual process. It is important not only to consider the risk for patient but also the risk to the drug-producing organism (14).

Table 1: Material-related hazards

Hazard	Standards
Interaction with biological material	
Impact on bioactivity and cell morphology by contacting material	USP 87 USP 88 (Definition of plastic classes I to VI)
Mechanical stability of containers and films	
Puncture and impact resistance	ASTM D1709, ISO 7765-2
Tear resistance	ASTM D1004
Particles	USP 788, 790
Tensile strength	ASTM D882, ISO 527-3
Seal integrity	ASTM F88
Brittleness	ASTM D746, D1709, ISO 8570
Mechanical stability of tubing and connectors (additionally)	
Compression	ASTM D395
Resistance to penetration and impact	ASTM D256, D2240
Tear resistance	ASTM D624
Elongation and tensile strength	ASTM D412
Burst resistance and pressure rating	ASTM D1599, ISO 7241-2, EN 12266-1
Integrity	ASTM D4991, E515
Chemical stability	
Resistance to chemical reagents (solvents, acids, bases, metals)	ASTM D543
Heavy metals	USP 231
Gas permeability	
Gas transmission rates	ASTM D3985
General characterisation of plastic material for pharmaceutical use	
Plastic materials and systems	USP 661.1 to 661.4
Origin and contamination of the plastic material (including additives, lubricants, cleaning agents)	
Material of animal origin including animal spongiform encephalopathy agents	EP 5.2.8., CFR part 94.18
Endotoxins	USP 85, EP 2.6.14

Table 2: Process-related hazards

Hazard	Standard
Leachables and extractables migrating into the pharmaceutical product	
Study design	FDA (1999) Guidance for Industry, Container closure systems for packaging human drugs and biologics EMA (2005) Guideline on plastic immediate packaging materials PQRI (2006) Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products BPSA (2010) Recommendations for testing and evaluation of extractables from single-use process equipment USP 1663 Assessment of extractables associated with pharmaceutical packaging/delivery systems USP 1664 Assessment of drug product leachables associated with pharmaceutical packaging/delivery systems
Sterility and aseptic processing	
Sterilisation process	EP 5.1, USP 71, ISO 11137
Aseptic processing	EU GMP Annex 1 (2008) Manufacture of sterile medicinal products FDA (2004) Guidance for Industry, Sterile drug products produced by aseptic processing – current good manufacturing practice
Microbial challenge tests	USP 71
Unspecific contamination	
TOC (total organic carbon) migrating into drug formulation	EP 2.2.44., USP 643

3 HAZARDS OF SINGLE-USE MANUFACTURING

Extractables studies will create a design space of substances, which may depending on the material processed in single-use containers contaminate the product. Testing conditions must be exaggerated to cover all possible extraction conditions for substances from container material. However, reasonable test conditions should be used to generate relevant data for worst case but not impossible process conditions (15).

Solvents used should be of polar (e.g. water, ethanol) and of non-polar (e.g. hexane, isopropanol) type. Solvents tested based on systems with water should include different pH-values, ionic strength and detergent concentration. Extraction conditions should vary temperature (e.g. 20 – 80°C) and contact time (e.g. hours to days). An in depth example of an extractables study has been published and should start with a complete list of product-contact material before clinical phase 1 and completed with quality assurance approved test results before phase 3 clinical trials (11).

This sort of test should be supplemented by leachables studies, which show migration of substances under actual process conditions like temperatures and time applied and media used. These leachables study results are normally a subset of the data covered by extractables studies. Examples of programs for extractables and leachables studies are given in the literature (16). However, finding substances leaching out of the plastic material is only the first step, subsequent studies of the interactions between leachables and target proteins may follow (17).

Sterility testing is a prerequisite for producing medicinal products for parenteral or ophthalmic use. For traditional multi-use equipment, the pharmaceutical manufacturer does the validation of sterility processes. However, with single-use equipment delivered as sterilised components, the supplier has to guarantee sterility. Most of the equipment is made from polymers and thus sterilised by radiation. But sterility is not only about sterile manufacturing components, it is also about aseptic manufacturing processes. These processes demand specific requirements for production areas, where the processing steps will be performed. Single-use equipment allows completely closed system processing, which may be done in areas with lower clean room classification (18).

For safe processes management systems are crucial. This is particularly true for supply chain management and change control systems, as for typical single-use systems, the responsibility for the process is shared in a different way compared to traditional multi-use systems. As an example the pharmaceutical company must be informed on changes of the polymers used for the equipment.

3.3 Product-related hazards

Many products manufactured by single-use equipment contain proteins as pharmaceutical active substances. It is important, that the container material does not reduce the activity of these substances. Due to the chemical nature of polymers and proteins, possible interaction can lead to adsorption and thus loss of pharmaceutical activity. Variation in amount of the adsorbed protein is highly dependent on container material and protein type. Therefore proteins need to be individually evaluated (19).

3 HAZARDS OF SINGLE-USE MANUFACTURING

Specific hazards have to be considered when producing viral vaccine material as it may demand a biosafety level 2 or 3 environment. In many processes multiple cell lines are used, which further increases complexity of the risk evaluation process. Moving from stainless steel containers to disposable equipment weakens the primary containment barrier and thereby increases operator contamination or product loss probability and requirement to the secondary containment reliability (20). Retention vessels, overpressure and leakage detection and safe disposal of the bags have to be installed.

The intended use of the drug product is also worth consideration (21). On the one hand, there is the intended therapeutic dose, which can be calculated into accepted residue levels of impurities. On the other hand, drugs addressing specific patient population with its specific vulnerability have to be regarded like immune-compromised, infant or elderly patients.

4 RISK EVALUATION CRITERIA

After determining hazards connected to the use of disposable bioreactors, containers, fittings and connections as part of the risk identification and analysis the risk evaluation phase will follow. This is to set priorities for the subsequent risk mitigation process and to establish a basis for risk acceptance decisions. Both are essential requirements to perform the qualification and validation process needed for the approval of new equipment or processes (22). Basic criteria for this evaluation process in the manufacture are proximity to active pharmaceutical ingredient (API), extraction capability of the solvent, duration of contact, product contact surface area, toxicity of the extractables, temperature and inherent material resistance to extraction (10).

On the basis of material-, process- and product-related hazards, impurity concentrations of different scenario can be calculated in the final product (23). In worst-case scenario, purification steps will cause no decrease in impurities, but in reality protein purification steps will at least decrease impurities of low molecular weight, which are typical leachables substances. For final risk evaluation, residual concentrations have to be evaluated in the process validation step based on toxicological expertise.

5 EXAMPLE OF AN INDUSTRIAL APPLICATION

The goal of industrial application of risk analysis is to set priorities for taking effective measures in order to maximise safety by optimum use of means. Basis is the evaluation of separate risk dimensions like probability or severity and creating a risk matrix. This matrix is subsequently reduced to one single risk number, which is then used as basis for management decisions. This step has to be performed with caution, because information is lost and different dimensions have to be weighed against each other (24).

Single risk dimension should not be zero, as the product of the risk dimensions would also be zero. In addition the risk levels for each dimension should be kept at a minimum to have an unambiguous assignment of each situation to a well-defined level. This minimises the seduction to manipulate the risk analysis for a favoured outcome.

Table 3: Definition of risk values

Risk	Risk description	Risk value
Pharmaceutical application	Inhalation, injection, nasal, rectal	10
	Transdermal	5
	Topic, oral	1
Distance to the patient	Final filling	10
	Production of final API	5
	Production of API intermediate	1
Time of exposition	More than 7 days	10
	48 hours to 7 days	5
	Less than 48 hours	1
Surface to volume ratio	More than 0.01 $cm^2\ mL^{-1}$	10
	0.01 – 0.001 $cm^2\ mL^{-1}$	5
	Less than 0.001 $cm^2\ mL^{-1}$	1

For the industrial production of an API (active pharmaceutical ingredient) the four risk dimensions "pharmaceutical application" (A), "distance to the patient" (B), "time of exposition of the API to the polymeric material" (C) and "surface to volume ratio of the container" (D) are risk rated. The risk values (Table 3) of the four dimensions are only indicative and must be set according to the actual process evaluated. The four risk values are then multiplied to a risk score number.

Risk score number = A x B x C x D

This risk score number is used to categorise each hazard to one of three risk levels for the reviewed process. Again, the actual limits for the classification of the risk level have to be determined with the validation process of the product (Table 4). The risk levels are used to decide about the measures, which have to be taken.

Table 4: Possible risk scores and their classification to the risk levels

Risk score number	Risk level
1 to lower limit of medium risk level	Low
Lower to upper limit of medium risk level	Medium
Upper limit of medium risk level to 10000	High

The risk levels determine the measures, which have to be taken for the evaluation of the process. The range of measures to be evaluated for process safety is given in table 5. Using this procedure, the rational of the decision is well defined and the process can be tracked down to the evaluation from the initial position to the final actions. This not only helps to allocate financial and personal resources within the company, but also to successfully perform in an inspection or customer audit.

Table 5: Measures based on the risk levels

	Risk levels		
Measures	**low**	**medium**	**high**
Leak, preasure, crack verification	Y	Y	Y
Tear evaluation	Y	Y	Y
pH-value: change evaluation	N	N	Y
Sorption test	N	Y	Y
Leachable test	N	N	Y
Particulate evaluation	N	N	Y
Sterility evaluation	Y	Y	Y
Depyrogenisation evaluation	Y	Y	Y
Spallation test for peristaltic pump tubing	N	Y	Y
Filter integrity test	Y	Y	Y

Y = Measures have to be taken, N = Measures are not necessary

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7 ANNEX

Annex 1: Abbreviations

API	Active Pharmaceutical Ingredient
ASTM	American Society for Testing and Materials
BPSA	Bio-Process Systems Alliance
BSE	Bovine spongiform encephalopathy
CFR	Code of Federal Regulation
cGMP	current Good Manufacturing Practice
EFTA	European Free Trade Association
EMA	European Medicines Agency
EP	European Pharmacopeia
EU	European Union
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ISPE	International Society for Pharmaceutical Engineering
LAL	Limulus amebocyte lysate
PDA	Parenteral Drug Association
PQRI	Product Quality Research Institute
PW	Purified water
QRM	Quality Risk Management
SOP	Standard Operating Procedure
TOC	Total organic carbon
USA	United States of America
USP	United States Pharmacopeia
WFI	Water for injection

Annex 2: Definitions

Hazard	"The potential source of harm" (ISO 14971) Hazards are therefore qualitative descriptions of sources, which may lead to hazardous situations or harms of different risks.
Severity	"A measure of the possible consequences of a hazard" (ICH Q9)
Harm	"Damage to health, including the damage that can occur from loss of product quality or availability" (ICH Q9)
Risk	"The combination of the probability of occurrence of harm and the severity of that harm". Risks are in most cases quantitative and serve as the basis of risk management systems. This system allows the "assessment, control, communication and review of risks" with the aim to mitigate risk for patient safety within the whole life cycle of medicinal products. (ISO 14971)
Risk analysis	"The estimation of the risk associated with the identified hazards" (ICH Q9)

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