Review Prozess für elektronische Batch Records

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Abkürzungen

- **MBR** – (electronic) Master batch record
- **EBR** – electronic (executed) batch record
- **MES** – Manufacturing Execution Systems
- **ERP** – Enterprise Resource Planning (System um Personal, Ressourcen, Kapital, Betriebsmittel, Material sowie Informations- und Kommunikationstechnik im Sinne des Unternehmenszwecks rechtzeitig und bedarfsgerecht zu planen, zu steuern und zu verwalten)
- **ESP** – Equipment Specification (Elektronische Herstellvorschrift in BioMES8, welche prozessvorbereitende Tätigkeiten (z.B. CIP / SIP von Equipment) abbildet und keinen Produktbezug besitzt, bzw. kein Zielmaterial erzeugt.)
- **PLS** – Prozessleitsystem
- **VTSB** – verfahrenstechnische Steuerungsbeschreibungen

Guidelines – EU 1

- **EU GMP Chapter 4 (Documentation):**

Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For **electronic records** regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should **be fully defined in the manufacturer's Quality Management System**. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.

Guidelines – EU 2

- **EU GMP Chapter 4 on electronic records:**

4.1 Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented.

4.21 Batch Packaging Record: [should contain the following]: The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information

Guidelines – EU 3

- **EU GMP Annex 11 (Computerized systems):**

Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.

Guidelines – EU 4

- **EU GMP Annex 11 (Computerized systems): Validation**

4.3 For critical systems an **up-to-date system description** detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

4.4 **User Requirements Specifications** should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be **traceable throughout the life-cycle**.

4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

Guidelines – EU 5

- **EU GMP Annex 11 (Computerized systems): Further points**

  - Data transfer
  - Accuracy checks
  - Data storage
  - Printouts
  - Audit trails
  - Change and configuration management
  - Periodic evaluation
  - Security
  - Incident management
  - Electronic signatures

Guidelines – US 1

21 CFR Part 11 berücksichtigt seit 1997 electronic batch records.

- Part 11 beinhaltet Vorgaben für: Validierung, Audit trails, record retention, etc.
- Beschränkung des Systemzugangs auf autorisierte Personen
- Einsatz von Systemkontrollen, von Berechtigungskontrollen, von Gerätekontrollen
- Feststellung, dass Personen, die elektronische Systeme **entwickeln, warten oder nutzen**, über die erforderliche Ausbildung, Schulung und Erfahrung verfügen, um die ihnen zugewiesenen Aufgaben zu erfüllen
- Festlegung und Einhaltung schriftlicher Richtlinien, die Personen für Maßnahmen, die unter ihrer elektronischen Signatur eingeleitet werden, zur Verantwortung ziehen
- angemessene Kontrollen der Systemdokumentation
- Kontrollen für offene Systeme, die den oben aufgezählten Kontrollen für geschlossene Systeme entsprechen (§ 11.30) Anforderungen in Bezug auf elektronische Signaturen (z. B. §§ 11.50, 11.70, 11.100, 11.200 und 11.300)

Guidelines – US 2

- EBR Software Systeme müssen in compliance mit Regulations 21 CFR Parts 210-211 sein.
- 210: “cGMP in manufacturing, processing, packaging or holding of product, general” Status and applicability of cGMP regulations, Definitions of cGMP
- 211: “cGMP for finished pharmaceuticals”

Subpart D- Equipment

- § 211.68 **Automatic, mechanical, and electronic equipment**

  (a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

Guidelines – US 3

- § 211.68 Automatic, mechanical, and electronic equipment

  (b) **Appropriate controls** shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy.

  The degree and frequency of **input/output verification** shall be based on the complexity and reliability of the computer or related system. A **backup file** of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with **appropriate validation data**.

Guidelines – US 4

- § 211.68 Automatic, mechanical, and electronic equipment

  Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

- Subpart J—Records and Reports § 211.180 General requirements.

  (c) All records required under this part, or copies of such records, shall be **readily available for authorized inspection** during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

Guidelines – US 5

Medical devices:

- **21CFR Subchapter H, Subpart M § 820.184** Device history records

  Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR (device master record) and the requirements of this part.

The DHR shall include, or refer to the location of, the following information:

(a) The dates of manufacture; (b) The quantity manufactured; (c) The quantity released for distribution; (d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR; (e) The primary identification label and labeling used for each production unit; and (f) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used.

Guidelines – GAMP

Good Automated Manufacturing Practice

Das Forum wurde 1991 von Experten der pharmazeutischen Industrie in UK gegründet, um dem Bedürfnis der Branche nach einem besseren Verständnis und den Erwartungen der Regulierungsbehörden in Europa Rechnung zu tragen. Die Organisation versuchte auch, das Verständnis dafür zu fördern, wie die **Validierung von Computersystemen** in der pharmazeutischen Industrie durchgeführt werden sollte.

- 1994 wurde (in Zusammenarbeit mit International Society for Pharmaceutical Engineering (ISPE)) die erste GAMP guideline herausgebracht.
- Seit 2008 ist Version 5 (GAMP 5) verfügbar, Version 5 second edition seit 2022 (mit erweiterten Anhängen)
- **Die GAMP-Regelwerke haben jedoch keine gesetzliche Bindung.**
- Muss käuflich erworben werden (695 $ für Nicht-Mitglieder)

Anbieter


MasterControl


ampleLogic


Lonza


SIEMENS


SimplerQMS


Opvia


Labguru


FASTEC
Software for Production


TULIP

Vorteile

- Reduzieren menschlicher Fehler- „right first time“
- Nachverfolgbarkeit „Traceability“ – regulierte Berechtigungen, eSignatures, Time stamps, etc.
- Reporting – automatisierte Datensammlung und Auswertung, vereinfachtes Erkennen von Abweichungen und Trends (z.B. kritische Parameter)
- Compliance- entspricht 21 CFR Part 11 und eSignatures

Für die QP:

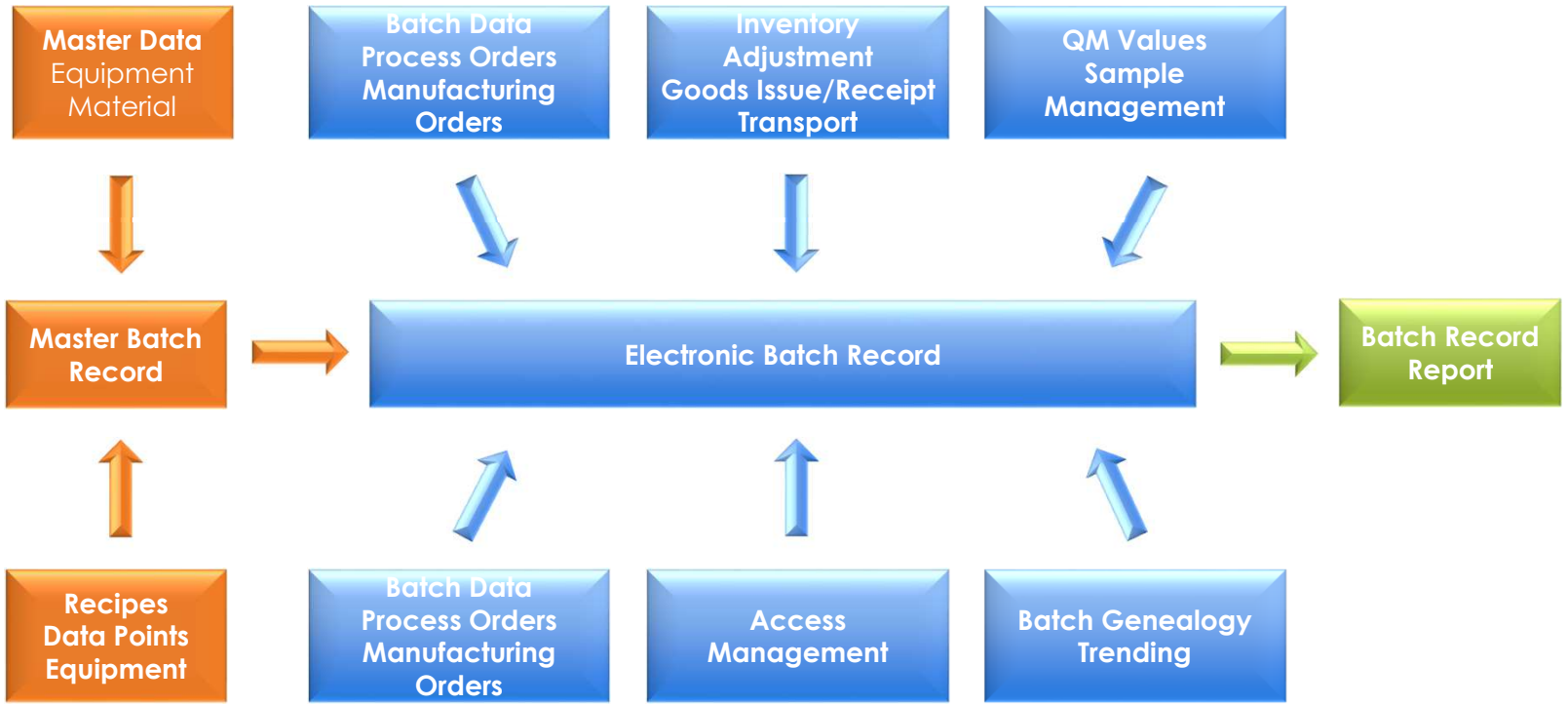
- Jederzeit Zugriff auf MBRs und EBRs
- Live-Tracking von Prozessen

Caveat: Entwicklungsprodukte!

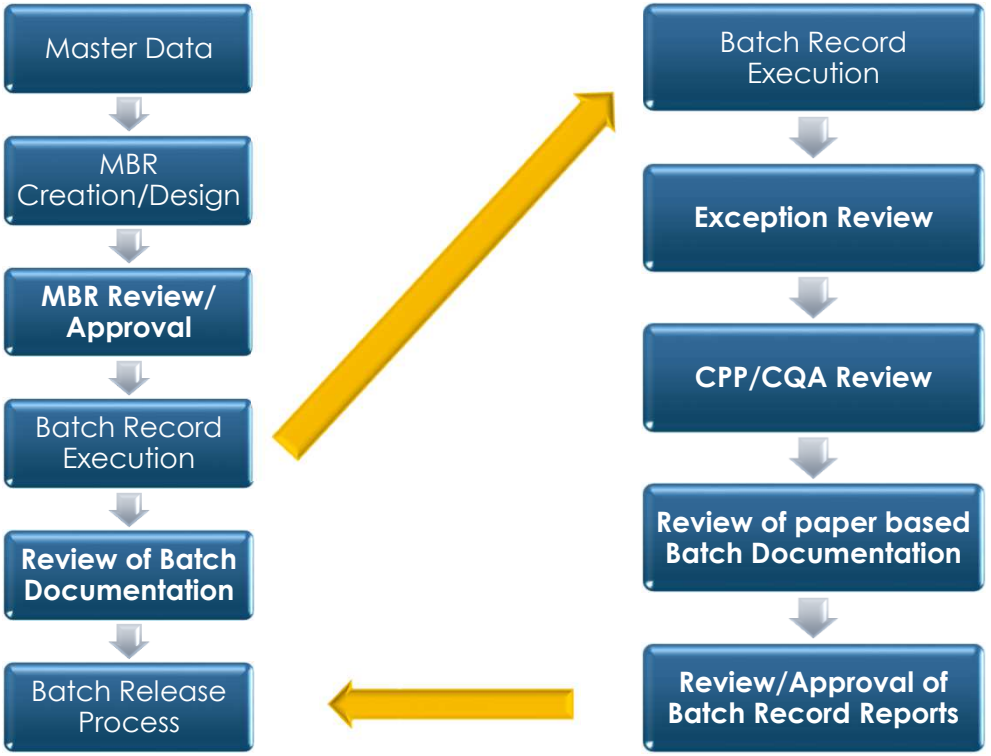
Funktionen

- Master data management for MBR creation
- Master Batch Record (MBR/ ESP) creation
- Electronic Batch Record (EBR) Execution
- Batch Record Review
- Order Handling
- Equipment Status Management
- Compliance (Logs and audit trails, User and permission management, Release workflows, Electronic signatures)

Systemübersicht



High Level Process



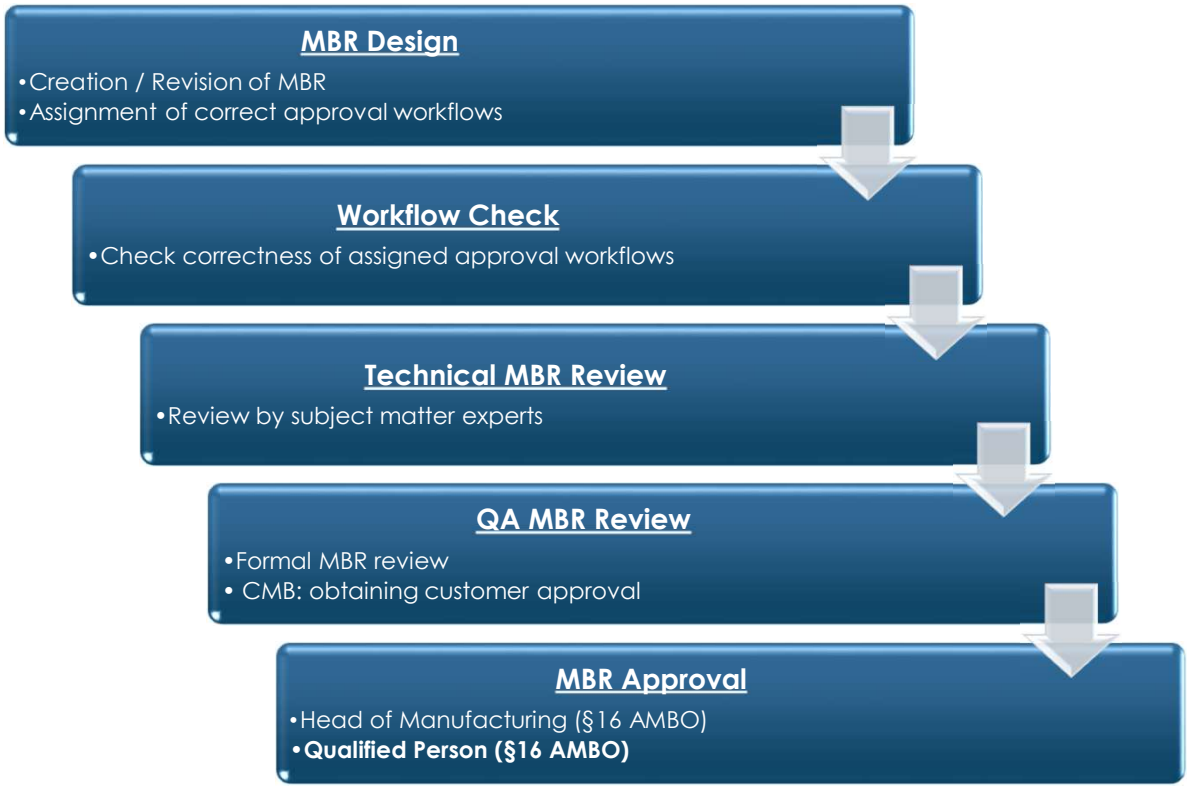
Definition of run types (GMP/non-GMP), e.g.:

- Inbetriebnahme
- Test
- Engineering
- GMP

Element approval:

- Separate approval workflows for different elements: MBR, ESP, etc.
- Most restrictive workflow: MBR for GMP main process

MBR Review and Approval



Review of Batch Documentation

Exception Review
- Exception type priority → Definition in SOP based on RA
- Acknowledgement (Acknowledgement role → SOP/RA)

CPPs and CQA Review
- Actual value check
- Technical prerequisite for finalization of BRR if parameters are flagged as CPP | CQA
- Four eyes principle: CPP / CQA review by Operations and QA

Paper based Batch Documentation
- Any batch-related document in hardcopy, e.g.: Forms, Attachments/raw data
- Four eyes principle: CPP / CQA review by Operations and QA

Review/Approval of Batch Record Reports
- BRR elements
- Executed batch record (actual values, time stamps, signatures, materials, …)
- External documents
- Exceptions

Approval of Batch Record Reports
- Completion of respective Manufacturing Order (MO)
- Completion / Acknowledgement of all required Exceptions
- Completed review of all MO related CPPs and CQAs
- Completed review of MO related paper-based batch documentation

- MO Execution
- Unexpected Occurence
- Exception Generation
- Comment by Operations
- Review by Operations
- Review by Quality
- Exception Acknoledgement

Empfehlungen für die QP

Kennenlernen

- Neuer Ansatz (Papier vs EBR)
- Verstehen des Systems (Maschinencode)
- Entwickeln der MBRs (Modellierung benötigt Zeit)
- Revisionen!
- Wichtig: Anlernen und Schulung des Personals
- (Bottleneck bestimmter Funktionen)

Schnittstellen

- Welche Informationen sind in welcher Form notwendig
- z.B. Prozessleitsysteme steuern (VTSB)
- Parameterübergaben

Compliance

- Information in adäquater Form verfügbar?
- Genehmigungsprozess