

Table 18 provides an overview about the most important regulations and the regulatory requirements for Batch Records and Batch Record documentation.

Table 1, Regulatory requirements

German laws and regulations	Requirements related to (Electronic) Batch Record
Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (Arzneimittel- und Wirkstoffherstellungsverordnung – AMWHV) vom 03. November 2006 (BGBl. I. S. 2523)	<ul style="list-style-type: none"> • Documentation management system must be available • Documentation system must be validated • Data must be protected • Access control must be in place • Traceability of all data must be given
Gesetz über Rahmenbedingungen für elektronische Signaturen (Signaturgesetz – SigG) vom 16. Mai 2001	<ul style="list-style-type: none"> • Legalizes use of electronic signatures in documentation
Signaturverordnung vom 16. November 2001 (BGBl. I S. 3074)	<ul style="list-style-type: none"> • Defines a long list of certificates which are needed for electronic signatures
European laws and regulations	Requirements related to (Electronic) Batch Record
EU COMMISSION DIRECTIVE 2003/94/EC §9 (8 October 2003) Festlegung der Grundsätze und Leitlinien der Guten Herstellungspraxis für Humanarzneimittel und für zur Anwendung beim Menschen bestimmte Prüfpräparate	<ul style="list-style-type: none"> • Includes instructions for the handling of documents • System must be validated • Data must be recorded in back-ups • Quality control has to be managed outside of production process (independent person) • Quality control must consider production conditions, in-process control, examination of manufacturing documentation
Richtlinie 91/412/EWG der Kommission vom 23. Juli 1991 zur Festlegung der Grundsätze und Leitlinien der Guten Herstellungspraxis für Tierarzneimittel	<ul style="list-style-type: none"> • Data must be recorded • Traceability must be given • Data must be protected

<p>Richtlinie 2001/83/EG des Europäischen Parlaments und des Rates vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel (ABl. L 311 vom 28. 11. 2001, S. 67)</p>	<ul style="list-style-type: none"> • Documents must confirm that the products correspond to regulations (traceability for 5 years) • Contains regularities for inspections (examination of documents) • Which information has to be given about the manufacturing process • Contains required information for an approval application • Lists information which have to be included in the batch record
<p>Richtlinie 1999/93/EG vom 13. Dezember 1999 über gemeinschaftliche Rahmenbedingungen für elektronische Signaturen.</p>	<ul style="list-style-type: none"> • Ensures the legal effectiveness of electronic signatures • Certificates confirm the security status of electronic signatures • Liability of certification service providers • Obligation to data protection according to guideline 95/46/EG
<p>Leitfaden der Guten Herstellungspraxis Teil I, Anlage 2 zur Bekanntmachung des Bundesministeriums für Gesundheit zu § 2 Nr. 3 der Arzneimittel- und Wirkstoffherstellungsverordnung vom 27. Oktober 2006 (Banz. S. 6887)</p>	<ul style="list-style-type: none"> • Process description of the EBRS has to be provided • Access to the system should be protected by passwords • Data have to be traceable and recorded twice
<p>Leitfaden der Guten Herstellungspraxis Teil II, Grundlegende Anforderungen für Wirkstoffe zur Verwendung als Ausgangsstoffe, Anlage 3 zur Bekanntmachung des Bundesministeriums für Gesundheit zu § 2 Nr. 3 der Arzneimittel- und Wirkstoffherstellungsverordnung vom 27. Oktober 2006 (Banz. S. 6887)</p>	<ul style="list-style-type: none"> • System has to be validated • Qualification of the system must be proven • Retrospective validation possible for commercial systems • Prevention of data loss has to be secured and changes must be recorded • Maintenance process must be reported • Manual entries must be controlled by a second employee • Possibility to print the documents should be provided
<p>EU-GMP-Leitfaden, Anhang 11 Computergestützte Systeme</p>	<ul style="list-style-type: none"> • Risk assessment of the system has to be conducted • If a third party should be involved, responsibilities have to be defined • User requirements should be met • List of essential GMP-systems must be provided (with descriptions of dataflow, security status, hard- and software requirements,...) • Periodic evaluation of the system should

	<ul style="list-style-type: none"> be organized Electronic signatures should be linked to the current date and time
EU-GMP-Leitfaden Anhang 16 Zertifizierung durch eine sachkundige Person &Chargenfreigabe	<ul style="list-style-type: none"> Qualified Person must release BR Handwritten or electronic signatures necessary
EFG Votum V11003 Anforderungen an elektronische Unterschriften und Handzeichen), ZLG 2010.	<ul style="list-style-type: none"> Advanced electronic signatures should be used Use password when signing electronically
U.S. laws and regulations FDA	Requirements related to (Electronic) Batch Record
21 CFR Part 211 Subpart J Records and Reports	<ul style="list-style-type: none"> Computers must be calibrated and inspected (written records must be kept) If automated equipment is used, only one person must approve that the process ran properly Maintenance has to be recorded in logbooks and (if used in electronic form) must be confirmed by an electronic signature
21 CFR Part 11 Electronic Records; Electronic Signatures	<ul style="list-style-type: none"> Public docket no. 92S-0251 declares which documents are allowed to be provided paperless Audit trails have to be performed to record users' actions Persons which use the electronic signature must certify that it's equivalent to their hand written sign If there is no use of biometric procedures, users have to be identified by ID and password User's identification has to be made once if there is a continuous access to the system (no more entry of ID and password necessary) Declaration of loss management procedures
FDA: Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application	<ul style="list-style-type: none"> System will be approved from FDA if it is fit for its intended use and meets all applicable predicate rule requirements It is recommended that there should be an investigator with access to records for an inspection FDA does not object any type of backups Electronic and paper records can co-exist as long as predicate rule requirements are

met	
International Society for Pharmaceutical Engineering (ISPE)	Requirements related (Electronic) Batch Record
GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach , 2010	<ul style="list-style-type: none"> • Introduction MES and EBRs/ MES system • Requirements for use and implementation of MES systems
GAMP@5 A Risk-Based Approach to Compliant GxP Computerized Systems, 2008	<ul style="list-style-type: none"> • Guideline to computer system validation • Guideline for integration
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)	Requirements related to (Electronic) Batch Record
PIC/S PE 008-4: Explanatory Notes for Industry on the Preparation of a Site Master File, 2011	<ul style="list-style-type: none"> • Site Master File including production layout must be available • Lists information which have to be included in the Site Master File • Quality management system has to be described briefly • Description of documentation system and types of documents should be listed
PIC/S PI 038-1: Aide-Mémoire on Assessment of QRM Implementation, 2012.	<ul style="list-style-type: none"> • Recommends, which questions should be asked in an inspection referring to the QRM process • Systems should be assessed, controlled, communicated, reviewed as part of the QRM routine • Defines areas of operations, where QRM principles should be implemented (e.g., validation)
Further guidelines	Requirements related (Electronic) Batch Record
VOI VerbandOrganisations- und Informationssysteme. V.: Legal Requirements for Document Management in Europe, 2010.	<ul style="list-style-type: none"> • Stored data must be true to the original documents • Documents are only legal effective with a qualified electronic signature
ANSI/ISA 95 Enterprise-Control System Integration, International Society of Automation	<ul style="list-style-type: none"> • Overview about integration of EBRs and other layers of automation pyramid

Table19 provides an overview about the most important functional requirements for Electronic Batch Recording Systems.

Table 2, Functional requirements

Required Function	Explanation
Validation	<ul style="list-style-type: none"> • Meet computer system validation requirements
Audit trail (electronic)	<ul style="list-style-type: none"> • Log recorded data • Changes must not delete previous entries • Accurately and comprehensively reflects the development of the batch • Use secure, computer generated time stamps for entries
Electronic signature	<ul style="list-style-type: none"> • Equivalent to hand written signature • Establish a written policy to hold individuals accountable • Unique to one individual • Verification through password & ID • Must be identifiable on print-outs • Necessary for batch processing, reviewing batch records and batch release
Electronic (long-term) archiving	<ul style="list-style-type: none"> • Establish archiving system • Maintain records for the required retention period of time (10 years) • Transfer to magnetic tapes etc.
Data consistency	<ul style="list-style-type: none"> • Check that entered data is correct & complete • Detect changed records by system
Data security	<ul style="list-style-type: none"> • Protected against unauthorized use and manipulation • Version control in place • System rights administered and controlled • Regular backup copies of data available • Critical process parameters must be checked twice (check by second operator or plausibility checks in system) • Control distribution of data
Failsafe state of the system	<ul style="list-style-type: none"> • Validated back-up solution must be available in emergency situation
User administration/rights management	<ul style="list-style-type: none"> • Authorized user only can access system • Authority checks • Establish training concept with user rights
Records	<ul style="list-style-type: none"> • Data must be retrievable in easy to read form
Role concept and/or a user concept	<ul style="list-style-type: none"> • Only Qualified Persons can certify the release of batches • System must be able to manage the user group “Qualified Person” with special access rights • Signature of Qualified Person necessary
Support Qualified Person	<ul style="list-style-type: none"> • Report special observations and changes to critical data • Report any non-conformances in the manufacturing process before releasing the batch

© Springer Fachmedien Wiesbaden 2018, Monika Futschik, An evaluation model for electronic batch recording solutions in the pharmaceutical industry, Universität Duisburg-Essen.