Markus Roemer

GMP Series

Electronic Batch Recording for Drugmakers

Maas & Peither
GMP PUBLISHING

PDF Download

Excerpt from the GMP Compliance Adviser

Contents

1 Electronic Batch Recording and Batch Release

Markus Roemer

Here you will find answers to the following questions:

- What regulatory requirements must be considered when an electronic batch recording (EBR) system is implemented?
- What strategic goals should be defined and used as a basis for initiating and implementing an EBR system (project approach)?
- What is an automation pyramid and what models and/or standards are applicable to an EBR system?
- What basic functions and aspects must an EBR system have to ensure compliance with GMP requirements?
- How can EBR data models and system concepts be analysed and designed?
- What criteria for project planning and validation must be observed for the transition from conventional paper documentation to electronic documents and records?

1.1 Regulatory requirements

According to chapter 4 *Documentation* of the EU GMP Guide, GMP documentation can be kept in a variety of ways such as on paper or using electronic or photographic media. In order to achieve GMP compliance a distinction is made between two fundamentally different types of documentation: Instructions (directions, or requirements) and records or reports that confirm proper conformity to the regulations. Both GMP documentation types are component parts of batch records.

This provides the regulatory basis for using electronic media in lieu of conventional paper documentation to create and/or manage (batch) documentation. This is generally referred to as **electronic batch recording** (**EBR**).

If an electronic system is to be used to manage batch records (EBR), it will also be necessary to consider Annex 11 *Computerised systems* and Annex 16 *Certification by a Qualified Person and Batch Release*, in addition to Chapter 4 of the EU GMP Guide.

In Annex 11 the sections 14. *Electronic Signature*, 15. *Batch Release* and 8. *Printouts* in particular are to be assessed and interpreted accordingly for an EBR application. The **retention periods** for electronic records, in this case batch records, are stipulated in Chapter 4.11 of the EU-GMP Guide. Analogously, the legal requirements of the US FDA, 21 CFR Part 211 *Subpart J – Records and Reports*, 21 CFR Part 11 *Electronic Records; Electronic Signatures* and others must be observed, where applicable.

These regulatory requirements must be implemented using technical EBR functions in a computerized system (IT system/ IT infrastructure), which must be validated. This is illustrated below using the example of a batch release:

Requirement from Annex 11 – 15. Batch release
"When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches. The system should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature."

Conclusion and Interpretation – 15. Batch release
This means that an EBR system must have a role concept and/or a user concept and it must be able to manage the user group "Qualified Person" with special access rights. The appropriate procedural approach is also part of this functionality (e.g. SOP "Managing User Rights."). An **electronic signature** must also be implemented. An **advanced electronic signature** is recommended for signatures on batch processing and testing records and for confirmation of release. This would also be in conformity with the US FDA 21 CFR Part 11 – *Electronic Records; Electronic Signatures*. In an EBR system the elec-

tronic file (batch record) converts to the unique master document when it is provided with an electronic signature.

Furthermore, in addition to including the function of keeping batch records, an EBR system must also contain an electronic signature function for the batch release. However, according to Annex 16 of the EU GMP Guide, item 3.2, in an industrial situation it is usually not possible for a single QP to be closely involved with every stage of manufacture.

Therefore, the QP who certifies a finished product batch may need to rely on various different production and quality control stages. Different combinations and phases of batch production and release must be considered here for a planned EBR implementation. For example, this could be the case in different production stages of an intermediate product or a batch of bulk product at different production sites (internal or subcontracted). Moreover, they could also be imported into the EC/EEC from other (third) countries with which a treaty on mutual recognition exists between the Community or another third country.

Due to different business structures and (internal or external) intermediate production stages, written agreements between two or more companies may become necessary: If batch recording and release are performed in any phase with the aid of an EBR system, then this should be described and controlled accordingly, for instance for the handover of the relevant (electronic) batch documentation. Since these records could have been created in different IT infrastructures (networks), these aspects must also be assessed and recorded accordingly. The purpose of this approach is to avoid hybrid documentation structures which would otherwise detract from the advantages of an EBR system.

Since the batch release has to take place within the EBR system, properly signed batch records (Production) and testing records (Quality Control lab, analytical results) must be checked; essential information on environmental conditions (monitoring, for example), in-process controls, product specifications, including packaging instructions must likewise be checked and approval or registration documents must be (electronically) complete. The actual meaning of the Qualified Person's electronic signature for the batch release in the EBR system lies in the fact that it confirms conformity with the given requirements and certifies agreement with the approval or registration documents.

Modern quality paradigms propagate a batch release in real time, referred to as real-time release (RTR), which in turn is based on real time release testing (RTRT) or other methods (such as PAT *Process Analytical Technology*). For these requirements to be met, more information (data) must be available for the release than in the case of pure (classic) production records. Moreover, this information can only be handled efficiently if it is available in an appropriate electronic form.

The regulatory weight of the batch documentation and release should be assessed as being at a very high level, and the relevant aspects to be mastered as a result are complex and extensive. Since in this case a manual activity is being replaced with a computerized system, this must not be allowed to impair the product quality, the process control or the pharmaceutical quality assurance system (EU-GMP Guide Annex 11 – Principle).

There should be close cooperation among key persons (established experts) such as process owners, system owners and Qualified Persons as well as IT (EU-GMP Guide Annex 11 – 2. *Personnel*) in order to introduce and maintain an EBR system.

"Paperless" systems such as LIMS (*Laboratory Information System*), and ELN (*Electronic Laboratory Notebook*) in laboratories, or electronic deviation or CAPA systems in Quality Management are comparable to the EBR system in Production. These systems can interact with the EBR system through qualified interfaces, since they also provide relevant data sets for the batch release.

Various different EBR models and strategies can be developed and executed on the basis of the knowledge and analysis of the regulatory requirements. The implementation also depends on the scope of the function and the degree of process automation, as well as the links to other systems (data sources).

1.2 Strategic goals and deployment possibilities of an EBR system

The following strategic goals can be pursued when an EBR system is deployed:

- to analyse and optimise workflows within the scope of the system deployment (dealing with process elements and parameters)
- to reduce complexity of data collection and documentation – in conjunction with freeing capacities on the management and operator levels
- to avoid errors by conducting plausibility checks in the planning phase and in production (such as cross-contamination), risk reduction
- to improve planning and availability of production (Supply Chain Management, resource planning and availability, adherence to shipping deadlines)
- to conduct searches and failure analyses (online analyses) up to and including active control loops (cf. design space – "Quality by Design" approaches)
- to efficiently and effectively create reports and forward documents to internal customers within the company (e.g. validation teams, project management, Regulatory Affairs)
- to improve data exchange with other units, departments, and/or systems (e.g. in-process control data to Analytics, research reports to Regulatory Affairs)
- to ensure consistency and conformity of production data as a prerequisite for documentation appropriate for the authorities
- to implement innovative, state-of-the-art technologies in science and engineering, improved runtimes and higher capacity

In addition, an EBR system can simplify the preparation and evaluation of data for statistical and analytical purposes, if relevant process data are present in the system in a form suitable for evaluation. In this way quality statements can be made or trend analyses and/or research can be conducted within a short time.

If a **batch recall** should become necessary, the required research can be supported by an EBR lot traceability function.

The effort involved in creating **Product Quality Reviews** can be reduced and results – in other words, actions – can be implemented more quickly and purposefully.

Furthermore, information from the EBR can be used to implement **Quality Risk Management** (cf. PIC/S Aide-Memoire PI 038-1 for assessment of the Quality Risk Management implementation).

In addition, the EBR system can be used for a modern interpretation of the **process validation**, i.e. there can be a continuous process validation (CPV) through critical quality attributes (CQAs) and the control strategy of critical process parameters (CPP).

The information requirements for **Management Review** and **Monitoring**, according to the revised Chapter 1 of the EU-GMP Guide, can also be provided through the EBR database.

The goals of an EBR system and the expectations placed on it must be appropriately defined and communicated within the scope of the project development, prior to the analysis, modelling, implementation and validation.

1.3 System types by extent of automation

It should be understood that the term "EBR" represents an application and not a separate IT system (cf. EU-GMP Guide; Annex 11 – Glossary: applications). The EBR application (see figure 1) can be realised on different levels of an **automation pyramid**.

Examples of the automation pyramid are shown below; each one in turn includes examples and designates different types of systems and definitions.

The **ISA-95 Model** (ANSI/ISA-95) is a standard of the *International Society of Automation (ISA)*, with which production processes on these levels can be evaluated. These levels are predefined there as

tions (control loops) are possible in real time. Entries are made by authorized persons and are checked as thoroughly as possible for plausibility and integrity during the input.
- **Definition of required fields:** e.g. devaluing commentary fields, verification steps, specifying a single or double signature in a process step or process transition or references to valid work procedures (SOPs).
- **Specifying fixed sequences:** Using several dialogs for the data entry (e.g. wizard) prevents false and incomplete workflows. The EBR walks the operator through the process flows.
- **Automatic posting or clearing:** e.g. of consumption, indicating required time (times required for refitting, production, maintenance, transport and cleaning).
- **Creating records and passing on information:** e.g. conspicuous issues during processing, which may be sent directly to the Quality Department for assessment (deviation notification if applicable).

The EBR form design is fundamentally based on the existing master and dynamic data sets, on the design capabilities of the EBR system itself and on dynamic rules and definitions of qualitative and business aspects.

Example: An operator must register 50 drums of an incoming material with a handheld scanner. Having to confirm every single identification on the monitor with "OK" that was made using the scanner would be impractical and inefficient. However, for quality assurance reasons it is necessary to record and identify each single drum. An adequately intelligent EBR could tally up a total at the 50th drum.

In this way an EBR system can be used to link process-relevant and regulatory intelligence and efficiency together.

1.7 Converting paper documentation to EBR

The possible design and configuration of records and forms are weighted and formulated differently in different EBR systems. Ideally, graphic design methods or templates / defaults are used to render them user friendly, with the result that learning to use them is relatively quick and easy. Thus the in-house creation, optimising and maintenance of electronic batch processing records are also possible. If a large number of different batch processing documents has to be converted from paper to electronic form, it is important to establish a defined method for the conversion beforehand.

Likewise, in a conversion of this nature, it is advisable to hold regular *Design Reviews* of the electronic batch records with participation of a Qualified Person and the Head of Quality Assurance, since in dealing with the technical process steps the actual requirement of data and information for testing and releasing a finished batch has to be checked repeatedly. Moreover, testing items can be simplified or even omitted from the test altogether by the electronic processes, since other mechanisms are in place that already avoid incorrect performance (avoidance strategy, risk-based approach). These mechanisms or functions are tested and proven to be acceptable in the **validation** of the EBR system.

The validation strategy of the EBR system contains
- the IT system itself
- the qualification of the IT network
- the verification of external interfaces or measuring chains in the automation pyramid (e.g. interfaces to LIMS, DMS, LVS, PAT- and/or IPC instruments).

Hardware components used, e.g. components at stationary work-centers or stations (such as in cleanrooms, weighing cubicles, goods received, machine terminals) must be splash-proof, explosion-proof, or suitable for use in cleanrooms, as applicable, and they must be qualified accordingly. PC workplaces close to production areas, for example, are equipped with stainless steel surfaces, passive cooling,

easy-to-clean foil keyboards or touchscreen functions. Mobile EBR workplaces, for example, can be implemented on so-called tablet PCs (via Wi-Fi) or with intelligent handheld scanners with displays.

The EBR application should be validated in a manner that is oriented towards the ISPE GAMP®5 standard (International Society for Pharmaceutical Engineering; Good Automated Manufacturing Practice; Version 5). Annex S2 (Electronic Production Records) contains a general observation and interpretation of the topics of the EBR on data sources and functional requirements.

The ISPE has published a Good Practice Guide for this special topic (GAMP® *Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach*). With approximately 135 pages, this document content is significantly more extensive. The contents are depicted from the project phase up to the operational phase of an EBR system and include approaches and methods for step-by-step implementation with different topical aspects.

Summary
EBR data management system concepts can optimise processes and render them more efficient. Process risks can be reduced preventively and the observance of legal requirements is ensured right up to supporting the pharmaceutical quality system.
EBR systems create relevant documents and records pursuant to the EU-GMP Guide Chapter 4 and they implement the release and certification of batches in accordance with Annex 16. For this purpose, Annex 11 refers to special chapters for electronic batch certification and release.
Introducing and implementing an EBR system requires systematic analysis, definition and assessment of the regulatory requirements, process-based data and product-relevant information. It is recommended that preparations be made for the conversion to an electronic system within a data-oriented transfer and project method which could include existing standards or norms.
The validation and implementation strategies and periodic reviews are to be defined and communicated on a risk basis during implementation and realisation. EBR project teams must be made up of authorised and qualified experts (IT, Qualified Person, project leader, suppliers).
EBR systems or concepts are to be placed in various levels of the automation pyramid and are to be defined in keeping with project requirements.

Index

Contributor

Markus Roemer
markus.roemer@comes-services.com

Consultant
comes compliance services, Ravensburg

Markus Roemer works as an independent consultant for comes compliance services in Ravensburg, Germany. He deals with a wide variety of topics, including validation of computerised systems, auditing, quality management, project management and compliance management. He has acted since 2008 as ISPE Ambassador for the Germany/Austria/Switzerland Affiliate.

After completing his studies in engineering, Mr. Roemer began his career as a team member in computer validation at Vetter Pharma-Fertigung in Ravensburg. After changing to the MES system provider Propack Data GmbH in Karlsruhe, he served there as Quality Manager for EBR projects.

In 2003, Mr. Roemer moved on to become Senior Validation Consultant for Invensys Validation Technologies in Montreal, Canada. He also accompanied global IT and validation projects abroad, following which he applied his global experience with customers and suppliers in his capacity as Head of Compliance Services and Quality Management at Systec & Services.