eon www.eonitaly.it
IT Partner for process industries

A step by step approach to the

ELECTRONIC BATCH RECORD

EON's perspective

Index

1 Introduction

This document contains a series of insights on the theme of the Electronic Batch Record (EBR), that is the possibility to trail, control and document in a digital form highly regulated production processes, such as those in the pharmaceutical and biotech industries, assuring a compliant execution.

Since more than 25 years EON provides IT consulting in the process industry, particularly in the chemical-pharmaceutical sector, and implementing information systems to support the process digitalization of the logistic and production areas.

On the basis of several and significant projects experiences for important national and international customers, EON has had the opportunity to deepen “on the field” all the aspects related the Batch Record implementation and its evolution from a paper to a digital on line form.

The following in-depth articles illustrate the implementation methods and the benefits that modern organizations can achieve by introducing an EBR management in terms of error reduction, quality and consistency improvement, and shortening time-to-volume product cycles.

The scope is to provide a collection of recommendations and to share food of thoughts on how can be possible to face in more efficient way the application of increasingly stringent manufacturing rules on which many organizations are today subjected.

2 Electronic Batch Record

2.1 EBR - Electronic Batch Record

The Electronic Batch Record, today, is the choice that can more benefit pharmaceutical industries, and not only in terms of safety and cost savings.

This statement may seem like a slogan, but we shall pass a series of recommendations to illustrate which should be the steps to enable an EBR adoption and the advantages associated with each of them.

The evidence of this aspect and the concurrent increase of computerized systems deployed in production has grown up the attention of control authorities which are now directed to issue ever more comprehensive and complete regulations.

It is essential to consider that the activation of the EBR can be implemented in stages, each of them defined in relation to the cost-benefit ratio. An accurate evaluation of the systems intended to be used for each phase is fundamental. Specific attention must be paid to the fact that as the number of systems increases, the complexity of the integration between them increases as well. Consequently, also the cost for both the implementation and the system validation rises.

It is crucial as well to dispel the idea that EBR means transferring the contents of a traditional paper batch record onto a portable electronic consultation system, such as a tablet. On paper batch records, data collection, especially if in tables, is expensive and a source of possible errors; transcription of the data on a tablet can be the same.

This data collection then risks being of difficult correlation with the productive event, untimely in terms of data analysis and not compliant enough from a regulatory point of view.

Collected data must be reliable and comprehensive of the control of the entire process and allow the RBE (Review By Exception) activity to be used to support the release of the finished product.

In other words, let us picture three different data ranges:

1. standard machine behaviour
2. machine regulation
3. out of specification

During the production phases, the system must drive the operator to correct the values by tuning the machine, if the deviation is in a specific range (tolerance), or to handle a deviation.

The system must highlight any data out of specification, and if so highlight the opening, the status, and the consequent closure of the deviation. It must also help to prevent the lot release if any deviation has not been managed until the end.

The list of components of an electronic batch record could be drawn up in a chronological sequence of use, facilitating the interpretation, but instead, let us make the effort to think about a list properly ordered according to an implementation simplicity criteria and cost/benefit ratio, like the following:

- Quantitative and qualitative management of components, mainly ingredients
- Availability of rooms, machines, and accessories (Cleaning)
- Availability of rooms and machines (Maintenance)
- Product IPC (In process control)
- Process IPC (In process control)
- Deviation management
- Consistency between operator training and tasks
- Serialization
- Environmental conditions control (Temperature, pressure, particles count, ...)

2.2 Quantitative and qualitative handling of products with bar-code

The first goal to be achieved is a reliable electronic traceability in the quantitative and qualitative management of all the components, which can be implemented primarily thanks to an appropriate labelling of everything that enters in the warehouse from the outside and of what is transferred from production, whether intermediate or semi-finished, through the different production steps. A controlled lot allocation in bound and uniquely coded containers is fundamental.

With that premise, it will be then necessary to check a reliable inheritance of the label's content of any single movement in logistic, dispensing and production, up to the on board machine or the entrance of classified areas – if there is the certainty of uniqueness of presence, beyond the barrier, by production lot.

The procurement planning of raw materials must have taken place considering all the constraints imposed in the dossier, such as, for example, the restricted choice of production sites, and the system must allow the compliance check with these constraints, stated in the master batch record and compared with the properties of the used lot.

If all the blocks are already correctly functioning at the pick-up in the warehouse and the procedure validated, the information about the production balance becomes redundant.

Complete labels allow the identification of components in the scale rooms or in the production departments when they are dispensed on board machine. The system must precisely identify who is handling which component and, above all, it must acquire the quantitative data through an electronic dialogue with scales or dosing systems operating on the machine.

The fact that all the scales have been verified can be taken for granted, proving that the system does not allow their use without control or, being more zealous, this can be reiterated on the BR indicating the date of execution and the results.

As a consequence of the detailed recording of any activity performed in the dispensing area, the log-book too can be automatically recorded.

If the substance to be dosed is titrated, the electronic dialogue with the laboratory must be activated so that the system may provide a correct quantitative indication considering the titration for the active ingredients and, when necessary, the quantity of the excipient/s defined as compensation element. This applies both to components and semi-finished products when the concentration conditions the dosage of raw materials for the for subsequent production phases.

The dosage operation of the components must prevent the usage of quantities that deviate from the standard beyond the expected tolerance. The system must report any inconsistencies, allowing eventually the error balance by increasing the components already measured out and the successive ones in case of cumulative dosages in blender. It must also provide evidence and track which criteria has been adopted in managing the excess of the production quantity.

The evidence of the Quality Assurance approval, via the electronic signature of the manager, determines the closure of the controlled deviation. On the BR, this occurrence will be highlighted.

The system must also report the detection of inventory differences that may cause critical issues from an economic point of view (raw material cost), or regulatory (controlled components, such as drugs). This evidence may not have an impact on the analysis of the specific product, but it must be appropriately assessed when it can raise a reasonable doubt about the consumptions in previous productions.

Integration with the analytical laboratory, which usually holds information about components shelf life and holding times, is essential to determine the interdiction of lots usage whose expiry dates aren't compatible with the production process.

A well-designed system will also determine the specific shelf life for components stored in bins already opened and the specific holding time for the intermediate product in transit through different work centres.

2.3 Availability of rooms, machineries and tools (Cleaning)

In the traditional batch record, the operators in production were forced to collect conscientiously any kind of labels to demonstrate the cleaning status of rooms and machine/equipment, and in the meantime it was necessary to check the information collected in the log-books to control the exact sequence of usage in order to be sure of the consistency of the cleaning method used. Log-books had to be compiled manually describing every single detail relevant for production and cleaning process.

With a computerized system, each room, equipment, or tool must be marked with its own unique identification code or it must be stored in an envelope or box, appropriately labelled, which must be read at the usage time, allowing the system to confirm the cleaning status. The identification code/the label must be read at the time of use, allowing the system to confirm the cleaning status. Rooms and machines may be identified through an indelible and not removable label. Tools, bins, and machine parts must be identified on their body or on specific packaging. Every mobile device must be identified and checked when it is introduced into the production area.

Every time an operator accesses a room or starts using a machine, the control system verifies the coherence between the production that is intended to start (or already in progress) and the cleaning status, taking into account all various possible aspects, such as:

- the cleaning expiration date in case of productions that occupy the equipment for long times

- the type of cleaning performed for production campaign

- cleaning for production of specialties which shares the active ingredients

- cleaning or using different active principles.

The system must check that all the machines in the premises are in the same cleanliness status, as well as it must check the cleaning outcomes of all objects used in production, from interchangeable machine parts, i.e. punches and dispensers, up to the common bailers.

The control function should prevent proceeding if the required conditions do not occur. However, the system must report the carried out checklist on accesses, rooms status and present machines, and the results must be recorded in the batch record. This for two main and fundamental reasons: avoid mistakes by immediately informing the operators about the situation and avoid recording mistakes or deviation in the batch record.

If problems occur, regardless of their significance, and if these critical conditions must be managed both via a deviation or a simple verification by the supervisor, all this this must be traced in the EBR, and the adopted solution must be highlighted.

Evidently, for those open problems with a deviation relevance for which there is not yet an accepted solution, the release of the lot must be suspended.

Cleaning methods design

Cleaning methods must be defined detailing every single operation that has to be done and all substances that have to be used, with or without lot tracking. In the cleaning method, also equipment must be defined in the same way normally typically adopted for a Master Batch production.

Test of the cleaning condition must be described as well as the pick-up of samples in various areas of rooms/machines.

The system must allow the creation of a grid that relates the conditions before the cleaning (substances handled in the finished product production) and the necessary conditions for the next production (substances that will be handled in the next production order) assigning a proper cleaning method to all the possible occurrences.

Inheritance of the "dirty" condition

By codifying all machines with the proper room number, the system ensures that, even when only one of them has been used, all the others are turned in "dirty" condition. An advanced system should also differentiate if the condition is direct, due to the usage of the machine, or not direct if this can influence the cleaning method.

The implementation of this procedure requires the availability of a planning and balancing system for the cleaning operations.

This system must consider the utilisation sequences of the rooms, and it must manage cleaning orders referred to real MBR. Once the cleaning activities have been executed, it must collect the necessary signatures necessary for the release of the premises and the machines.

All information must be recorded in specific archives and must be connected to the batch records of running productions in relation to the production times.

2.4 Rooms and machine availability (maintenance)

The availability check of production resources during production planning and scheduling is critical and complex, especially when the cleaning and configuration times of the machines have a significant impact on the length of production processes.

Moreover, this complexity is increased by the availability check of the equipment when subjected to scheduled maintenance. The planner must know in advance when these activities have been planned and their expected duration.

The same condition occurs if a machine must be, in addition to being maintained, partially overhauled with an intervention that involves a revalidation. This operation is often burdensome in terms of direct time and analysis of the issued documentation produced that has to be evaluated before the machine is made available again for production.

The capacity scheduling software must guarantee visibility for all the activities that make the machines unavailable, starting from the most frequent ones, such as format changes, to those scheduled for ordinary maintenance, repairs or modifications.

With this data available, the planner could decide to differentiate the process executing the activities on an equivalent machine or a similar one, if approved. This choice involves the availability of specific Master Batches introducing the concept of production variant.

The choice of the machine must be possible before the printing of the Batch Record and must be clearly indicated.

The operator must not be forced to specify this option on the batch record manually, having to verify its availability, the state of cleanliness or any downtime for maintenance.

Electronic choice means that all the necessary checks are performed by the system, leaving no room for errors.

The production documentation, EBR, will give evidence of the real availability of the machines adopted, giving evidence as well of the date of the last maintenance done and the date of approval of the performed intervention.

It is also possible to specify the planned date of the next maintenance to make clear, in percentage terms, in which range of usage time it had been operated. This information suggests that operating in proximity of the scheduled maintenance can increase the attention in checking of specific parameters.

For format changes, the positive outcome of the line manager's check can be collected, highlighted together with the product IPC that defines the correct operation of the machine at the end of the calibration phase.

A further opportunity to strengthen the process comes from the possibility to trace incidents that may occur during the production phase.

These incidents usually involve a machine downtime and the lengthening of production times with the consequent increase of the exposure of the semi-finished and components to the production environment.

It must be carefully checked whether the machine has altered the characteristics of the product before the fault has occurred. This activity is supported by the analysis of the product IPCs through which it is possible to verify and evaluate the actual occurrence of a problem and the size of the sub lot to be isolated isolate and to put out of specification.

Whatever event occurred, it must be tracked by the system. The Quality Assurance must identify all the elements that allow defining the extent of the deviation and the consequent partial or total damage to the production lot.

The batch record, particularly in the electronic form, cannot miss the evaluations about its closure together with the signature of the manager.

If an internal maintenance order has been used to overcome the inconvenience, it is appropriate to mention it.

The malfunctioning of equipment that have even only partially compromised the production must be described, and evidence must be given of the criterion used to define the extent and boundaries of the sub lot to be segregated. The closed deviation typically involves the definition of a CAPA (Corrective Action and Preventive Action) which, in most cases, can be limited to a reduction of time between one maintenance and the other.

Another aspect not to be overlooked is the identification of the operating parameters of the machine which can be monitored to forecast a future malfunction.

Temperature changes in parts such as gear motors or motors, or more generally in the vicinity of moving parts may indicate poor lubrication or a state of non-standard wear.

The engine absorption check too can be a reasonable indicator of unexpected frictions or a bad wrong machine setting that can increase the wear.

It has to be assessed whether these data can be reasonably collected in the BR, however, this opportunity entails that well-skilled personnel, such as those who are normally involved in the "Batch review", must be made aware of the onset of problems and can raise awareness of who should define the corrective actions.

2.5 IPC (In Process Control) on products

The quality of the production processes has a significant impact on the final quantity and the finished product stability. When a high number of doses has to be produced, it is as much essential to monitor that the quality has been constant during the entire production. A considerable number of sampling can ensure that quality constancy.

Areas that definitely imply a considerable effort before the Batch Record compilation and the later data analysis, is the control execution on the products during the production, and this takes a lot of time of qualified people.

The number of values and attributes to be collected is usually considerable, whether controls are planned at intervals on a temporal or quantitative basis. All these values are generally collected in tables and inserted manually. The effort is significant, and the risk of errors not negligible. In addition, data must be checked by two operators when the devices are not designed to produce physical support to enclose in the batch record.

Often the evaluation time takes a long time, i.e. when checks are performed in a dedicated room far from the production lines. This delay has the risk that, once the problems are solved, the amount of product out of specification will appear bigger than it would actually be.

The subsequent evaluation of the filled out tables costs a vast amount of time and, not only, it risks highlighting out-of-specification values. These values, if immediately detected, would have allowed an immediate correction of the process, while, in retrospect, they risk is to invalidate the whole lot.

The computerized management of IPCs brings two quite significant advantages:

- The first one is the comparison immediacy between the measured and the specification data, and the instantaneous evidence of a possible deviation and its significance. In this way, a data which is not compliant but falls within the permitted values, allows an immediate intervention on the process in order to overcome the problem without the need to open a deviation.
- The second one concerns the immediate identification of a problem and its possible circumscription, so that it is possible to isolate and keep the unsuitable part of the lot as small as possible.

The IPCs are carried out at all stages of preparation and packaging, and often data are not immediately detectable, but are the result of the application of a usually quite simple algorithm, such as gross weight minus tare for fills with gross weights recorded as average or unitary.

Once the software modules have been implemented, and all the necessary equipment has been supplied to each production and packaging line, the electronic collection of IPCs can prudently be approached in two implementation phases.

- In the first phase, the collected data will be input manually into the system, which can immediately supply the result of the comparison between the permitted values or, mainly in case of multiple samples, can ask the input of the values for each sample and only later show the check results (blinded input).

All the data must be logged, and corrections in the data entry must be clearly tracked.

- In the second phase is expected to read the data directly form the instrument that has generated the values.

For both it is fundamental to determine the frequency of data collection, numeric or temporal, and the evidence of the single and whole evaluation.

Data can be entered in the system with evidence of the result only at the end of the sample measurement, for example, by weighing a known number of soft capsules before and after having dripped the filler and by displaying unitary and average data only at the end of the operation. This method makes the execution of the process control much more reliable than giving evidence of the unitary data, where a suspect of possible manipulation is plausible.

The results can be used to refine the process for calibrating the machines, in the event of non-critical deviation, or to highlight incorrect measurement data that, after a further confirmation test, involve the suspension of the production process to fix the cause of the non compliance.

The online real time availability of all previous results allows confining a not compliant sub-lot/batch.

Many instruments are able to provide data in a digital format, such as the devices for measuring size and weights of tablets and capsules, the thermo-scales and scales itself, the ph-meters etc.

The data can be collected in a MES system or stored in a vertical ERP system, if it provides this kind of functionalities.

Data must be available for single checks and in the final control in order to use a batch review for exception and define the minimum, the maximum, and the average values often published on the analysis certificate.

In the batch record, both detailed and summary data can be made available with clear evidence of the correct progress of the production process. Once the QA department has gained confidence with the system, the electronic analysis will replace the manual one.

The system must provide evidence that none of the values is out of specifications or, in the case of a deviation, that it has been properly managed and closed before the lot release.

These data, organized correctly, must also be made available for the processing of the APR. (Annual Product Review).

2.6 IPC (In process control) on processes

The process parameters determine the conditions that must be created and maintained in the shop floor during each production phase. Simple examples of process parameters could be temperature, pressure, engine speed, fluid speed, and so on.

The possibility to manage electronically these parameters can be considered both from the plant set-up and control activities and from the detections of process stability and quality.

Sending the process parameters to the field control devices means the availability of systems able to operate each machine or that, at least, give the operator, generally on a screen, clear instructions on how to operate, asking to declare the conclusion of each operation.

Advanced systems can both return elapsed times and process parameters, but also a complete alarm management. All these data can be used for a real time control of the production phases and for the final verification of the process progress and its quality.

In case of less advanced production systems, an acceptable step can be the manual detection through the transcription of what the operator reads on the equipment onboard the machine or provided from additional shop floor control retrofitting devices installed with the only purpose of computerizing the final controls and balances.

This situation, which is one of the most common, still involves significant savings in time and increased reliability in the batch review phase.

The computerization of process IPCs can be approached in phases by modulating the implementation effort in terms of time savings and reliability.

The first phase approach requires to equip itself with a software that allows the composition of the masters batch assembling standard elements, as operations and relative instructions, each of which including as many set-up and control parameters as desired, to identify adjustment and the out-of-specification ranges.

The difference between the use of a Master Batch in text format and in a structured one is substantial. A text can only be read and interpreted by an operator, having a total discretion over the identification of out-of-specification data. With a structured BR, data are collected by through a mobile device like a tablet and values are immediately validated by the system, including the reporting of any deviation.

Once such a system has been set up, the manual transfer of the data must be validated. This data can be read and transcribed by an operator and controlled by the system. Based on criticality, it has to establish the presence of a double signature and the indispensable time stamp.

The second phase becomes feasible once the machines have been equipped with automation control systems capable of sending, with appropriate communication protocols, both the detected data and any possible alarm.

It is also important to consider the critical aspect of the alarms management process. They must be all evaluated, even if not critical, but significant enough to be recorded with low criticality and immediately closed by the operator. Critical alarms, in relation with the process type or the length, must be recorded and analyzed to verify the closure of the anomalous condition, providing the impact assessment on the process and of the possible need to manage the data as a deviation.

The complete list must then appear on the batch record, electronic o paper-based.

Data collection can take place directly from the machines, if equipped with advanced PLCs, or through a layer of software developed to collect and possibly analyze the data.

On the vertical ERP system, the duplicated data can be the values in full, only part of them, once the criticality intervals have been identified, or just the summary data. The quality of the software systems for industrial automation and the compliance of use in the pharmaceutical environment, as the presence of the validation based also on the criteria imposed by the Data Integrity rules, can determine which one is appropriate.

An example to make clear the above: if a PLC controls a mass temperature in a ten-second cycle and holds detailed data, but there is evidence that to get out of the target value it must occur an alteration of at least fifteen minutes of the heat or cold source, it is obvious that, in the EBR system, the detection of data every ten minutes is sufficient.

The data made available can be thus used for the electronic automated analysis of the process quality.

The third phase sees the so called ERP system (because the availability of such specific functionalities characterized it as a strongly verticalized solution for the process industry) not waiting for the data from the factory to be analyzed, but makes them available, properly formatted, to control the shopfloor. This possibility goes beyond the concept of EBR and control, but it offers a step forward compared to this.

2.7 Consistency between operator training and tasks

The computerized attendance of the operators and the tasks assignment allow to control two significant aspects: the numerical check of the presences in classified environments and the assignment of tasks to personnel with an adequate qualification profile.

The data relating to the workforce must be entered in the batch records, where, normally, a part is provided with the space for the collection of the initials of those present per shift and its confirmation. It is a duty of the final verifier to check that there are no names of workers with an unsuitable qualification profile. This case is not frequent, where the composition of the teams for the various departments is constant, but not all companies operate with a fixed number of employees per department and it is not possible to foresee the need to make replacements in the event of holidays or illnesses. Adjacent periods of layout modification or replacement of machineries are particularly risky from the point of view of the qualification compliance.

Getting from system the record of attendance and the evidence of the required qualification profile and that obtained for each person, greatly increases security.

A by-product of these controls is the achievement of efficiency statistics by teams, given that it helps in compiling industrial accounting and planning.

In classified environments the number of employees must be limited. The system can set the block by denying the access authorization once the maximum number of allowed employees has been reached or it can take note of a particular condition, of the possible authorization and its motivation, and report everything on the production report.