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Avoiding Errors With The Batch Release Process: Best Practice CGMPs

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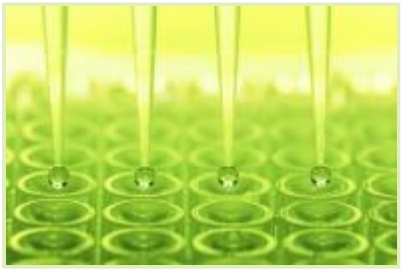

INTRODUCTION

Batch release testing is the final safety check that pharmaceutical manufacturers must perform. Before any therapeutic product is declared ready for distribution, the manufacturer must thoroughly analyze batch processing data and test samples to check that the product meets all safety and quality controls. Not a single dose from a batch should leave the manufacture until the batch is signed off, by the designated person, for meeting all release criteria. Hence, when manufacturing operations are complete, product that meets finished product specifications will be considered for release. When a batch of product is being considered for release, all information relevant to the manufacture of the batch needs to be considered. This includes a review of the batch manufacturing documentation as well as information that might indicate the acceptability, or otherwise, of environmental conditions prevailing during manufacture, of raw materials and intermediates used in manufacture and of personnel, equipment and processes involved in processing. The results of in-process tests, as well as tests on the finished product and a report on the inspection of the finished pack, will be reviewed prior to batch release.
The process of batch release comprises of:

- The checking of the manufacture and testing of the batch in accordance with defined release procedures.
- The certification of the finished product batch performed by the person responsible for signifying that the batch is in compliance with current Good Manufacturing Practice (CGMP).
- The transfer to saleable stock.

Hence, typical procedures are such that when final product that meets the requirements it will be released for use on the authority of the designated person (there are global differences in terms of who releases a batch of product onto the market). It is important that any product that is found to be unfit for release will be designated ‘rejected’ and will either be destroyed or offered for a non-clinical application.
Despite most companies having effective batch release procedures, errors can occur leading into products being released which are unsuitable (for the different reasons where a recall can occur). Such issues may be picked up by the company, consumers, or medical staff (such as in the form of a customer complaint). For example, one common reason for recalls is where process for testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications or identity and strength of each active ingredient prior to release (as per 21 CFR 211.165(a)).
To avoid such issues, this article considers some best practices for the batch release process.

BATCH RELEASE

Batch release is the process of reviewing and approving all pharmaceutical product manufacturing and control records and it performed by the Quality Unit to determine compliance with all established approved written procedures before a batch is released. The process of batch release, and the authority and training of the persons eligible to do so, varies according to different GMP systems. However, there should be in place a

procedure describing how the batch release is performed, including how batch deviations (changes to the predefined process or condition detailed in the batch manufacturing record) are assessed and how batches are assessed for release or for rejection.

GLOBAL DIFFERENCES FOR BATCH RELEASE RESPONSIBILITIES

The person responsible for certifying the batch needs to be responsible for ensuring all relevant duties have been met prior to certification in the relevant register. The individual will have responsibility to ensure that no product is released prior to the legal requirements CGMP, and supply being confirmed as met. Furthermore, the person should undertake their responsibilities in accordance with the Code of Practice and in the knowledge that the relevant quality systems are in place. Such individuals assess all the batch release test results alongside relevant manufacturing monitoring procedures and data (that is everything from spot checks and feedstock analyses to pipeline flow rates). Based on all this operational and analytical information, they decide whether a batch is acceptable for sale on the market or for use in clinical trials as an investigational medicinal product. The responsible must be satisfied that the product is fit for use, that it complies with the terms of the marketing authorization and will not put subjects at risk due to inadequate safety, quality, efficacy, or quality control. It is a highly responsible position requiring specialist knowledge and experience of the specific chemical and manufacturing processes involved.

The major differences are between the U.S. and Europe. In the U.S., batch release is typically instigated by the person responsible for quality control; in Europe, there is the system for Qualified Persons (as discussed below). In terms of the regulatory requirements for batch release, in the U.S. the Code of Federal Regulations has legal binding force; in Europe, regulations have binding legal force in every Member State and enter into force on a set date. Directives issued by the European Commission lay down outcomes that must be achieved and EudraLex, Volume IV: Rules governing medicinal products in the EU provides guidance on the required GMPs. The European Commission authorizes medicines on the recommendation of the European Medicines Agency (EMA); and the EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU.

Within Europe, the relevant legislative requirements for Qualified Person certification are contained in Article 55 of Directive 2001/82/EC (EC, 2001a) and Article 13.3 of Directive 2001/20/EC (EC, 2001b). The principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use also apply. The “Qualified Person” (QP) is formally designated within the legislation as the person given ultimate authority to sign off a batch of pharmaceutical product for medicinal (or veterinary) use. A QP is certified through national professional bodies, although they are licensed to practice across the EU. The QP may come from the pharmaceutical company, or the person can be an external consultant. The concept of the qualified person according to EU regulations is unique. It does not exist in the U.S. or in any other state outside of the European Union. The personal responsibility and liability of the QP is a very specific requirement. Every qualified person needs to be registered or appointed or approved with the competent authority of the EU member state in which they are operating. Therefore, not only the pharmaceutical company for which they are acting, but also the registered qualified person, is personally responsible for their duties.

While there are global differences, the internationally harmonized PIC/S guidance (2008) outlines the common areas in relation to the Pharmaceutical Quality System. The Pharmaceutical Quality System requires:

- Good Manufacturing Practice (GMP), so that products are consistently produced.
- Good Distribution Practice (GDP), so that product quality is assured throughout the supply chain.
- Quality Control (QC), which is the testing to assess the quality of the product.
- Product Quality Review (PQR), which are annual product reviews. This is to confirm that every batch of product released during the review period complied with the registered process and specification.
- Quality Risk Management (QRM), which concerns systematic process assessment and control. This is about establishing a control strategy for process performance and product quality, plus the use of tools for measurement and analysis of process performance and product quality. In addition, there is the aim of demonstrating a state of control as well as the identification of opportunities for potential continuous improvement.

The Pharmaceutical Quality System needs to be supported by a company with good leadership, a focus on regulatory compliance and where quality is embedded into each aspect of the operation (1).

In addition, for many types of products mutual recognition agreements between different territories are becoming more common. These types of agreements provide specific details about the standardized accepted procedures for medicine manufacturing, shipping, storage, and quality control.

BATCH DOCUMENTATION

As a pharmaceutical product is manufactured, information relating to the batch manufacturing activity needs to be recorded. It is essential that everything is either written down or digitally captured, to enable the person tasked with batch release to undertake their duties in a compliant manner.

Batch documentation needs to be reviewed at key steps to confirm, for example, compliance with CGMP, procedures, specifications, and licenses. This can be carried out in conjunction with Quality by Design approaches, in relation to equipment and workspace optimization (2); process can also be designed so they are

more continuous and less error-prone (3). In addition, space should be provided in the documentation to record any comments required to be brought to the attention of the reviewing manager. When comments are necessary, this should include information like:

- The nature of the issue.
- The reason it is or is not considered a concern.
- Reference to any deviation report (which must describe corrective action taken).
- Any preventive action taken or planned.

In this article the focus is not with record design but with how records are reviewed.
Each review stage should be signed by the reviewer and dated. If errors or omissions are found, then the record must be completed and/or corrected by the relevant staff members. At the end of the last process stage/test, or as soon as practically possible, a supervisor or manager should review the record for at least the following:

- Completion (that the process/test was satisfactorily completed and all required entries present) and accuracy (batch numbers and dates, etc. are correct).
- Compliance to procedure, specification and CGMP.
- That critical parameters have been met (e.g., sterilizer charts).
- That any critical data such as weights or calculations are appropriately supported. (e.g., checked by second operator).
- Ensure any unexpected results, yields, or reject material, any deviations, adverse results investigation, reconciliations, and any other notes must be put to file.
- Review the record for any other entries and details as appropriate (e.g., expiry dates).
- All relevant information has been commented on the relevant page of the batch record.

The supervisor or manager should sign and date each record pertaining to separate process stages. Where errors are recorded these should be trended and addressed. The reasons for errors, especially human error, should form part of training program for personnel. Error-proofing ways of structuring and writing knowledge documents, procedures, batch records, as well as practices for structuring, conducting, and documenting training to assure competence, are each useful activities. It can be hopeful if organizations shift form the common 'training for compliance' paradigm to a 'training for competence' paradigm, since training for competence focus is more likely to achieve CGMP compliance (4).
As well as the batch production process, supporting laboratory testing is required. Laboratories running batch release testing must demonstrate that they can execute the specified tests reproducibly and follow the methodologies and processes outlined in the marketing authorization without deviation. As well as testing to specification, trend analyses offer additional insights on the quality and control of manufacturing processes, so sites can take all necessary action to prevent any batch from ever failing the release tests. All laboratories offering a batch release testing service must be certified by the relevant authority to provide this service.
Sometimes records can go missing. In such circumstances, any missing documentation should be requested from the originating department. Batches should not be ‘dispositioned’ until all records are confirmed as being present.
Where intermediate results do not meet specification, this does not necessarily mean that the finished product will be out of specification. Such a scenario may need assessment by a subject matter expert, such as a Product Champion based on compliance with the historical data, a product license and so on. Such an assessment will determine whether or not the intermediate is suitable for further processing or requires substituting with an alternative batch.

BATCH RELEASE PROCESSES

The batch manufacturing process should be captured fully within a Batch Processing Record. This can be paper-based or electronic (and in both cases must meet data integrity expectations). This record must be combined with the records of quality control tests. Paper records should be bound, and computer records arranged logically a be easily accessible. The record should be subject to a rigorous review; for this task, the use of checklists can prove useful. It is typical for such records to be retained for at least 30 years, although this is product dependent and there are national variations.
The finalized record should be considered for release by the responsible person, provided that this designated person has sufficient knowledge of the manufacturing processes of a product to perform a meaningful review of the records. The complete record is reviewed to ensure that the product concerned meets the agreed specification and the production history and quality control test results indicate that the product is fit for release. Each product needs to have:

- Batch Number.
- Product Code.
- Expiry Date.

There are numerous generic and specific analyses that the person tasked with batch release will expect to see to demonstrate that the product has been made according to CGMP and that it complies fully with its marketing authorization. The suite of tests (including specifications and details of laboratory methodologies where

appropriate) is agreed between the pharmaceutical manufacturer in consultation with regulators during the application for marketing approval. The specific tests vary widely between product types, their mechanisms of action and manufacturing processes. However, a laboratory will typically analyze the physical characteristics of batch samples (for tablets, this could be their color, shape, solubility, etc.) along with a host of tests on the active ingredients to ensure that their concentrations (and any degradation products) are within regulatory tolerance and the manufacturer's own tolerance range. In addition, samples will undergo microbiological and chemical scrutiny to verify the product contains no hazardous materials (for example remnants of the manufacturing process).
The assessment of test data is an iterative process which involves discussion among a wide range of experts from the regulator's advisory boards, research scientists and personnel involved in the manufacturing process.
As part of the review, the responsible person should perform the following checks on each batch record:

- Check that all entries are complete, including signatures and dates on attached chits and traces
- Ensure that batch processing limits have been met, or that deviations are identified where limits are not met. Here it is also important to look wider and consider any other batches which might be implicated from the cited error.
- Check if calculations have been performed in line with the agreed formulae. Check that the calculation been correctly performed.
- During document review ensure that approval boxes have been completed.
- Confirms that transcriptions are correct.
- Confirms that operators have been signed off to identify that a step has been completed but is not an independent verification of a step being completed.
- Confirm that temperature readings have been completed.
- Ensure that corrections are made in compliance with good documentation practice.
- Assess whether specification codes have been checked against the presentation, bottle / vial / bag size and relevant prefix of the product. This will apply to all product streams,
- Check each page for comments and satisfactory outcome to deviation reports.
- Check printing materials are legible and apparently correct for the dose strength.
- Check all checklists are completed and review comments.
- Check that intermediates certificates are present when intermediate records are filed elsewhere.
- Any controlled changes have been taken account of.
- Any additional sampling, tests, checks or investigations have been carried out or initiated.
- Check that the finished product test results are in compliance.
- That quality department checks have been completed.
- That deviations reported in the record have been satisfactorily resolved.
- Batch number.
- Quantity.
- Expiry Date.
- Date of Manufacture (as a technical characteristic.)
- Potency, as required.

Batch specific investigations need to be closed when the root cause has been determined, and the corrective and preventative actions have been assessed and implemented. Corrective action involves finding the causes of some specific problem and then putting in place the necessary actions to avoid a reoccurrence. Preventive actions are aimed at preventing the occurrence of potential problems. No batches should be released or distributed until such investigations are closed with root cause assigned, and the corrective action(s) completed. In some companies, preventative actions arising from the initial investigation can remain open after the individual investigations are complete in order to implement, review and assess root cause any follow-up monitoring that may be required in order to ensure the effectiveness of initial corrective actions.

- An additional requirement for Investigational Medicinal Products (IMPs) is that there needs to be written evidence of clinical trial approval.

In completing the review, the responsible person must satisfy themselves that the batch meets the requirements of relevant marketing authorizations. If it does not, then the batch should not be released to that market without consulting the regulatory authority. Where the responsible person is not satisfied with the information provided in the records then further information will need to be supplied to assist the with the release decision. With this process, if further information/testing is required before a decision on release can be given, the batch is typically placed 'on hold' for the duration of this time period. If the product is not fit for release or rework, then the batch is rejected. Depending upon the reason for rejection the product will either be destroyed or offered for non-clinical application.

PARAMETRIC RELEASE

It is permissible to release some pharmaceutical products through parametric release. Parametric release is a system of release based on information collected during the manufacturing process and based on verifiable compliance with CGMP. It means, for example, the release of sterile products without recourse to a

pharmacopeial sterility test (5). The principle is normally applied to all terminally heat sterilized products but cannot be applied to aseptically filled products. For a sterilization process to be eligible for parametric release:

- It should have been validated through thermal and biological qualifications and should demonstrably be capable of achieving 10-6 Sterility Assurance Levels referencing a Biological Indicator of defined resistance to the sterilization process.
- The integrity of the containment system for products proposed for parametric release must have been qualified through microbiological challenges
- The pre-sterilization bioburden must be tested for each batch of product eligible for parametric release. All spore formers isolated must be identified and have their resistance to the process determined. If any such organism is found to be more resistant than the Biological Indicator used in validation of the process, the sterilizer load must be rejected.

Some inspectors are wary about parametric release and the company should prepare an appropriate rationale.

ELECTRONIC RECORDS

The move away from traditional paper records to electronic records allows pharmaceutical manufacturers to more easily review data and provides a higher level of data security. Nonetheless, electronic data also present problems in terms of control, security, and safety. A central part of CGMP concerns electronic data management. CGMP points in relation to electronic records include:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation

One study looking into electronic batch records found a 75% decrease in human errors in electronic batch records, compared to a hardcopy system, thereby yielding improvements in production efficiency. The main disadvantages were cost, implementation resources and the in-built obsolescence of manufacturing software systems. Despite these disadvantages, the study found that implementation of an electronic batch record system resulted in a significant increase in production efficiency (6).

Guidance on electronic records is provided by 21 CFR Part 11, 73 Electronic Records, Electronic Signatures, ISO/IEC 17799114, Good Automated Manufacturing Practice and the FDA document Part 11, Electronic Records, Electronic Signatures.

PROCESS ANALYTICAL TECHNOLOGY

For some intermediate manufacturing and final products, progress to the next stage can be facilitated through process analytical technology (PAT). Provided this is qualified correctly, then real-time automation can assist with the reduction of errors. With the concept of real-time release this refers to the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data (7). For this, both PAT and parametric release (used for products sterilized using terminal sterilization methods) stand as methods that can be used for real-time release for the examination of critical quality attributes (these are the physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality). PAT also includes risk assessment approaches, centered on identifying critical control points (utilizing risk assessment methods such as HACCP). PAT tools typically enable non-destructive testing and provide the opportunity for enhanced monitoring. This is achieved through utilizing technology such as on- or in-line analyzers. Examples include near-infrared; particle-size analysis by laser diffraction and by ultrasonic extinction; and light-induced fluorescence instrumentation. One of the reasons that regulatory authorities are promoting real-time release is because quality can also be improved through higher yields or lower rework or rejection rates. Studying the process in real time allows for greater product and process understanding (8).

Real-time-release is not applicable for all tests or all types of products (aseptically filled products still require an end products sterility test, for example. However, here there are advantages afforded by some rapid methods which speed up the time-to-release). Furthermore, there is difference between regulatory agencies as to which aspects of real-time monitoring they will accept. However, for nonsterile pharmaceutical manufacturing, such as tablets, real-time analysis can assess a range of essential parameters including size, moisture content and blend uniformity (9).

Understanding the pharmaceutical manufacturing process and being able to make controlled modifications in order to improve the quality of the product is a further dimension of CGMP. Such an understanding can also connect with real-time release for understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimize the need for end product testing.

DISTRIBUTION

The batch release process and the duty of the responsible person needs to exercise due diligence in understanding the risks to the product and subject / patient as part of their certification for release of each batch. The supply chain for manufacture, testing and packaging of the product need to be assessed, as failure to do so can result in a recall. It is important to conceptualize the supply chain as a living document which should be maintained to reflect current supply chains.

Control of the supply chain is an important consideration and there are situations that can either trigger a recall or lead to counterfeit drugs entering the market, such as (10):

- Delay of essential medicine supply to a patient.
- Diversion of medicines to unauthorized consumers.
- Diversion into the authorized supply chain of medicines damaged by handling in inadequate conditions.
- Increased cost of medicines due to cost of replacement and additional preventive measures.
- Increased insurance cost to distributors.
- Loss of good reputation of distributors.

Where issues arise, the batch/product distribution records should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those medical samples and should be readily available to the persons responsible for recalls.

When products are shipped to foreign markets with dataloggers, the information from the dataloggers should be downloaded and maintained as originals in the quality department. The quality department should assess the downloaded datalogger information against the labelled storage conditions of the product. If the storage temperatures have not been maintained throughout the shipment, then a deviation/customer complaint should be raised.

Controls are in place in many regions. For example, with the U.S. when a foreign manufacturer’s products are subject to automatic detention, the shipper or importer must prove to the FDA that the product meets its requirements before they can be released by the US customs agents. In instances when inspectors find significant deviations from drug CGMPs, favorable sample test results alone are unlikely to help gain the product’s admission into the United States. The manufacturer typically must also change its operations and procedures, often requiring independent confirmation (11). When a foreign manufacturer’s products are subject to automatic detention, the shipper or importer must prove to the FDA that the product meets its requirements before they can be released by the US customs agents. In instances when inspectors find significant deviations from drug CGMPs, favorable sample test results alone are unlikely to help gain the product’s admission into the United States. The manufacturer typically must also change its operations and procedures, often requiring independent confirmation.

CUSTOMER COMPLAINTS

Whenever the market complaints are made about, thorough revision of those complaints and other information related to the batches affected must come into action and the reasons behind complaints must have to be investigated and corrective action should be taken immediately. In the event of a customer complaint or adverse event, a review of the batch record should be conducted, covering the following areas as a minimum:

- Check each batch record for comments and satisfactory outcome to deviation reports.
- Check that intermediates were within specification.
- Any Controlled Changes have been taken account of.
- Any additional sampling, tests, checks or investigations have been carried out or initiated.
- Check that the finished product test results are in compliance.
- That deviations reported in the record have been satisfactorily resolved.
- Check for any previous adverse events or customer complaints.

All the documents relating to market complaints and recalls should be referenced to corresponding batches and archived. These archives are regularly reviewed to look over the sign of specific and repetitive complaints that require attention.

The results of this review should be recorded, such as:

- Confirm all deviations are closed and assess their influence on the event
- Confirm all intermediates were within specification

- Confirm all Controlled Changes are closed and assess their influence on the event
- Confirm that all out of specification reports are closed and assess their influence on the event
- Confirm that the Finished Product Results were within specification.
- Confirm the results of previous adverse events or customer complaints.

OUTSOURCING AND BATCH RELEASE

Regulators allow the batch testing to be contracted out to third parties provided the laboratories have been verified. The facility that will conduct European batch release testing must be identified in the marketing authorization application for the product. The selection process will need to include processes like questionnaires, audits, and bid proposals, and it will include an assessment of the laboratory's accreditation in relation to a national regulator together with an assessment its suitability to handle the particular product type and its analytical tests.

Once the laboratory has been selected, the process of method transfer can start. The methods and specifications that will be used by the contract laboratory will be those detailed in the product license. It is important that the manufacturer maintains control of these documents throughout the testing period because any change made by the contracting laboratory will probably need regulatory approval. It is important that the contractor has established procedures for preventing any deviation from the methods as supplied. It is worth noting, for future planning, that the method transfer process generally takes a considerable period of time, especially where complex, specialized assays are involved. Furthermore, the partnership between the contract laboratory and the manufacturer must ensure that sufficient staff are trained to perform all the batch tests within the required time period (12).

Technical and quality agreements are required between the manufacturer and the outsourced facility. Agreements between the parties need to define delivery notice periods and turnaround times for reporting results. The lines of communication, especially in the event of unexpected or out-of-specification results and deviations, must be clearly stated. It is important to ensure that the agreement is long term in nature, since changing the testing laboratory will require an amendment to the license.

SUMMARY

Good pharmaceutical manufacturing practices directly concern production departments and packing area, control laboratories, storage areas, purchasing departments, departments receiving raw materials and dispatching finished products. Each of these areas provides information for the batch record. In generating batch records, everything relating to the quality of the batch needs to be recorded. Here the old adage - 'If it's not written down, then it didn't happen!' - comes into play. The basic rules in any CGMP regulations specify that the pharmaceutical manufacturer must maintain proper documentation and records. Documentation helps to build up a detailed picture of what a manufacturing function has done in the past and what it is doing now and, thus, it provides a basis for planning what it is going to do in the future. Regulatory inspectors, during their inspections of manufacturing sites, will spend considerable examining a company's documents and records. Effective documentation enhances the visibility of the quality assurance system.

It is an important part of the assessment of pharmaceutical products that adequate manufacturing standards and quality control testing measures are employed to assure that the product meets its quality specifications at time of release to market (and at the end of its shelf life). Failure to do so can result in products being recalled from the market (for various issues). This article has considered some good practice examples designed to strengthen the batch release process. A focus on designed batch records as so to minimize errors and instigating regular checks and ensuring that deviations and out-of-specification incidences have been carefully examined, represent important steps for making the batch review process more robust and for consequentially making recalls that could have been prevented due to issues with batch release procedures less likely.

REFERENCES

1. Boan, D. & Funderburk, F. (2003). Healthcare quality improvement and organizational culture. Delmarva Foundation a link to better health. At: http://www.delmarvafoundation.org/newsAndPublications/reports/documents/Organizational_culture.pdf
2. Djuris, J. and Djuric, Z. (2017) Modeling in the quality by design environment: Regulatory requirements and recommendations for design space and control strategy appointment,*International Journal of Pharmaceutics*, 10.1016/j.ijpharm.2017.05.070, 533, 2: 346-356
3. Capozzi, L. C., Trout, B. L. and Pisano, R. (2019) From Batch to Continuous: Freeze-Drying of Suspended Vials for Pharmaceuticals in Unit-Doses.*Industrial & Engineering Chemistry Research*, 58 (4): 1635-1649
4. Bodmann, K.; Reinhard, C.; Mödler, M.; Tinson, K.; and Johnson, M. (2016) Lonza Error Prevention System (EPS) – Changing Human Performance in Pharmaceutical Operations,*CHIMIA International Journal for Chemistry*, 70 (9): 610-615
5. Halls, N.A. (1994).*Achieving Sterility in Medical and Pharmaceutical Products* New York: Marcel Dekker

6. Marsh, J.L. and Eyers, D. R. (2016) Increasing Production Efficiency Through Electronic Batch Record Systems: A Case Study. In: Setchi R., Howlett R., Liu Y., Theobald P. (eds) Sustainable Design and Manufacturing 2016. SDM 2016.*Smart Innovation, Systems and Technologies*, vol 52. Springer, Cham: https://doi.org/10.1007/978-3-319-32098-4_23
7. FDA (2004) Guidance for industry: PAT – A framework for innovative pharmaceutical development, manufacturing and quality assurance; September 2004. Food and Drug Administration, Rockville: MD
8. Scott, B. and Wilcock, A. (2006) Process analytical technology in the pharmaceutical industry: A toolkit for continuous improvement.*PDA Journal of Pharmaceutical Science and Technology*, 60(1): 17–53
9. Drakulich, A. (20110 Real Time Release Testing,*Pharmaceutical Technology*, 35(2): 42 –49.
10. Madigan, T. (2019) Supply chain security: part 1 – introduction, MHRA Blog. At: https://mhrainspectorate.blog.gov.uk/2019/09/16/supply-chain-security-part-1-introduction/
11. Mailhot, S. and Blackwell. H. (2019) FDA drug regulation and enforcement. In Saghee, M. and Sandle, T. (Eds.)*Pharmaceutical Regulatory Inspections*, Euromed Publications UK, pp77-102
12. Sandle, T. and Leavy, C. (2017) A focus on regulatory trends: MHRA annual deficiency review,*Pharmig News*, Issue 69, pp2-5
