EBRO GENERAL APPLICATIONS
- PHARMACEUTICAL

The following notes are a summary of the main application of Ebro Validation System / Wireless data Loggers in the pharmaceutical industry. These notes are divided into sections detailing the different applications. There is a section dealing with compliance with FDA 21 CFR part 11. This is followed by guidance on how to present Ebro products to Pharmaceutical industry. The advantages of the wireless systems are discussed along with the information that is required from the company in order to enable the equipment to be presented effectively.

Guidelines for standards used in sterilisation are available in the following documents;

Health Technical Memorandum 2010 part 3: Validation and Verification.

EN554 / 17665-1 (moist heat sterilisation).

EN550 / 11135-1 (ethylene oxide sterilisation).

HTM 2010 is a UK guideline and EN554 and EN550 are European guidelines. There are no European standards for dry heat sterilisation at present. In the UK HTM 2010 is viewed as the working standard to aim for by many companies. Some believe that compliance with this standard will be found to be acceptable by FDA. Therefore, though it is only a guideline, some companies will insist upon compliance especially in the Asia-Pacific Region where climate and environment are extremes and due to the existing ASEAN Harmonization of Standards and References.

VALIDATION IN THE PHARMACEUTICAL INDUSTRY

The purpose of validation is to gain adequate evidence that a system will perform as intended, every time. As typical of the pharmaceutical industry, this procedure must be thoroughly documented. This must include Protocols that describe in detail what work is required, what results are expected and what constitutes an acceptable result. The results will then be written up as reports, which will include conclusions. However, when preparing validation documents it is essential that the whole validation exercise is viewed as one process and every part fits together perfectly. Therefore, in addition to the individual protocols, there will be a master document that links the whole process.

The hierarchy of documents for validation is represented below:

Validation Master Plan

Validation Protocols IQ, OQ, PQ

Validation Reports IQ, OQ, PQ

Validation can largely be divided into 3 main areas. These are Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ).

IQ is concerned with ensuring the equipment as bought and installed is exactly that which was proposed. In essence it can be rather like a checklist where a number of physical and functional checks are performed.

OQ is checking that the system performs as intended, regardless of the specific use to which it will be put. This essentially means testing, for example, that an autoclave works correctly and achieves the required temperature and pressure to achieve sterilization. It is at this stage that temperature mapping of the empty chamber of an autoclave, oven, or incubator etc. will take place. There may at this stage be some overlap between IQ and OQ as it may be more sensible to perform some checks at either stage.

PQ is the testing of the system to perform a defined task, which proves its suitability for a specific purpose. For example, an autoclave may be tested to sterilise a specified load. The hot and cold spots of the empty autoclave will be known from the OQ. Temperature mapping including heat penetration studies will therefore determine if the product achieves the temperature required for sterilisation. If a number of different loads are to be used, several PQ cycles may be required. Sometimes biological indicators are also used. These are known concentrations of microorganisms, which are placed adjacent to the temperature probes. These give additional assurance that the required temperatures are being achieve to sterilize

the content of the autoclave. Biological indicators are not normally used for well-established sterilization cycles at normal sterilization temperatures. They are used to test chemical sterilization cycles and any cycle which is thought to stray from the qualification conditions significantly. Also, as standard conditions for achieving depyrogentaion are less well defined, biological indicators are usually used for initial validation of these cycles.

In order to prove that a system performs reliably it is necessary to demonstrate consistency. This in many cases will mean performing the PQ on 3 separate occasions. This has become almost an industry standard. If at any point the results are not as expected and fall below the standard predicted, an explanation must be sought. If no reason can be found it becomes very difficult to release the equipment. A complete repeat of the 3 PQ runs would be expected. If a simple fault were identified it may be sufficient to repeat the failed run only. This is why 21 CFR Part 11 requires that data files cannot be changed or deleted without an audit trail.

Performance Qualification is repeated annually. In addition, quarterly tests are sometimes performed on smaller loads with a limited number of probes.

DOCUMENTATION IN THE PHARMACEUTICAL INDUSTRY

In any industry that is technically orientated there is always a need to build in suitable controls to ensure repeatability. Validation is an extension of this as it is intended to build quality into the manufacturing process rather than rely on final product testing. However, a simpler tool, which has been used for many years, is the use of controlled documentation. In essence this involves producing documents that describe how all procedures within an organisation are performed. This obviously includes manufacturing and analytical procedures but is extended to include all procedures that are not obviously understood and for which the incorrect performance would create a problem.

This is not simply a list of documents but a highly structured system. Top-level documents describing the documentation systems, how they are controlled and responsibilities must be produced first. These are cascaded down to the detailed description of how to operate individual pieces of equipment. There are many types of document including protocols, management procedures, training procedures and operating procedures.

The most commonly heard of procedures are the standard operating procedure (SOP) and batch manufacturing record (BMR). The SOP describes in great detail how a process is carried out and is used on the shop floor. The BMR is a record of a particular operation. Different names are sometimes used but essentially there is always a document that describes ‘how to’ and another that records what actually happened. The completed BMRs are always reviewed as part of the batch approval, then stored for several years after the product has passed its shelf life. They must be presented for review by the regulatory agencies on request.

The completion of a BMR is viewed very seriously and certain conditions are prescribed. Every significant action must be recorded. This could be key measurement of parameters or steps in the process. The operator must sign as prompted in the BMR. Any additions of raw materials must be accompanied by a check signature of a second person who must ensure the identity and quantity of any additive. A common occurrence is the omission of signatures and check signatures. Any falsification of information on a BMR is normally viewed as gross misconduct and renders the individual liable to dismissal.

All documents are controlled strictly. The revision and issue of documents itself will be described in a procedure and will involve a number of people who are authorised to approve the changes. The issue to the new document will be such that the previous version will be removed from circulation or destroyed. This is essential to ensure that 'old' versions do not exist. The receipt of the new document will normally have to be acknowledged with a signature.

The use of signatures to identify those responsible for certain activities is obviously very important. A list of recognised signatures and initials is held centrally so that any signature can be attributed to the individual responsible. As technology provides electronic methods or creating records, it is obviously important to retain the same ability to identify the individual responsible for any action. This has lead to the production of 21 CFR part 11 by FDA, which clearly outlines the requirements for use of electronic signatures and electronic data.

REGULATORY AGENCIES

Prior to the sale of a licensed pharmaceutical product, the company involved must receive approval from the regulatory agency of the country of sale. In the US the Food and Drug Administration (FDA) must approve any application for a new drug. This will include a pre-approval inspection, which will cover a multitude of issues, including production and validation of both final drug product and drug substance. Approval from FDA is confined to the manufacture of the specific product at the site that has been inspected. FDA must be notified of and approve any major change in the manufacturing process or the product in advance. In the UK the Medicines Control Agency (MCA) performs a similar role, although a license can be obtained for the product or the site. Also, the MCA will not inspect primary production (i.e. bulk drug substance), unless specifically requested to do so by the manufacturer.

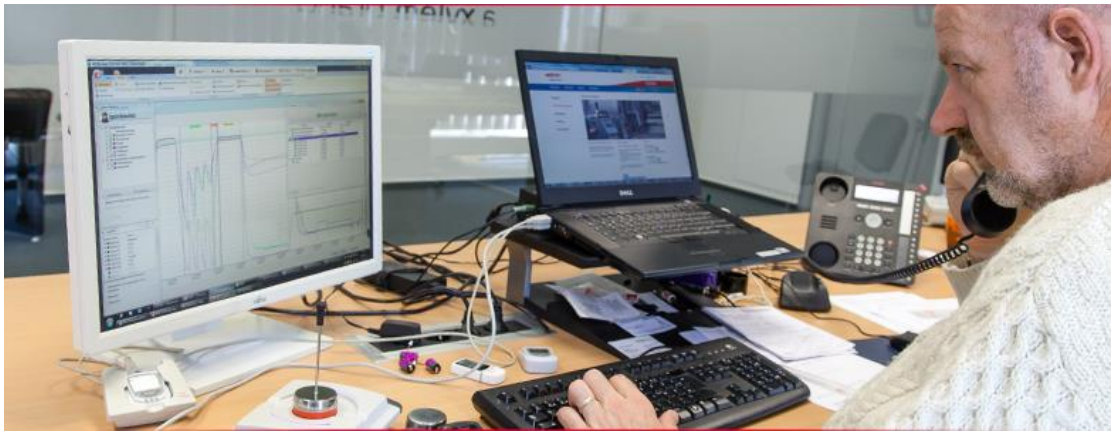
There are moves for harmonisation so that all regulatory agencies will require the same standard. However, this is not complete. In general terms FDA are more concerned with checking for fraud whereas the MCA are more concerned with checking for compliance with product or production licenses. Many look to the FDA to set the standard. A company will only need FDA approval if it markets its product in the US. Some companies will therefore seem less concerned with achieving these standards.

QUALIFIED PERSON STATUS

The release of final product needs to be carefully controlled. An error or misjudgement due to inexperience could have dire consequences. It is European law that licensed final product can only be released by a Qualified Person (QP). This is someone that has received sufficient training and education to make judgements involving a wide range of disciplines. Originally the QP was nominated by the company as the approved person. However, over the last few years this has changed and it is now an industry recognised qualification for the individual.

It is up to individual European countries to decide the requirements for a QP. A joint body representing the Royal Societies for Chemistry, Microbiology and Pharmacy has agreed the requirements in the UK. All QPs must have a first degree in one of the above disciplines and they must also have at least 2 years experience of working on industrial licensed premises. In addition they must demonstrate the appropriate level of knowledge in an oral examination.

The training and development of QPs requires a considerable investment and as a consequence the larger pharmaceutical companies spend time and money training people. These individuals are then in demand across the whole industry. The downside is that these people are ultimately responsible for guaranteeing that the product released for sale is suitable for use.



STEAM STERILISATION

The use of steam to sterilise pharmaceutical products, equipment and reagents is the most common sterilization method. Much lower temperatures are required compared to dry heat sterilises due to the latent heat released when the steam condenses on the items to be sterilised. This is advantageous, particularly for pharmaceutical products, which may be destroyed by the higher temperatures required for dry heat sterilisation.

Steam sterilisers (or autoclaves) come in a wide variety of sizes, from small bench-top laboratory autoclaves to large production autoclaves as big as 17m^3 in volume. The larger autoclaves are used for sterilising large volume parenterals such as those found in pouches, up to 5L in volume. These autoclaves can sterilize up to 5 Tonnes of product per batch. They tend to be cylindrical in shape as they are almost modular. Bottles and ampoules are sterilised in smaller autoclaves, generally, although these are often up to 2.5m^3. Whatever the nature of the load, the product is loaded in trays or cages to optimise the distribution of the load. It is important for validation purposes that the load is standardised, therefore full loads are usually used. The value of the content of a sterilizer can vary enormously but batches of new product can be worth in excess of Euro 500,000.

Many pharmaceutical and healthcare products are manufactured in sterile form. The manufacturers will obviously have equipment for sterile production. The focus of the regulatory agencies such as MCA or FDA has largely been on secondary production, i.e. the formulation of product into the dosage form that the user will see. As a consequence much emphasis has been placed on the production of sterile products and all organisations producing sterile products will already be validating their sterilizers. FDA has committed to inspect suppliers to FDA markets every 2 years. This is true generally for sterile production units.

An important factor when performing validation studies is that all the temperature probes must have been calibrated shortly before the validation run0 referred to as Pre Cal). They must also be checked afterwards to ensure that they are still within predefined tolerances (referred to as Post Cal). Generally, thermocouples must be +/- 0.5°C. Pressure gauges should be +/- 0.25% of maximum scale range.

Although some sites may not have any sterile production facilities, all bulk manufacture (or primary production) will require a significant degree of microbiological support. Water and several other raw materials will require regular microbial analysis. Also, environmental monitoring (final product areas) may also be required. It is highly likely that bulk production facilities will have a microbiological laboratory, unless this work is contracted out.

Typical steam sterilization cycles as recommended in HTM 2010, are given in the table below:

Sterilization Temperature (°C)	**115**	**121**	**126**	**134**
Max. Allowable Temperature (°C)	**118**	**124**	**129**	**137**
Holding Time (Min)	**30**	**15**	**10**	**3**

The most common temperatures used are 121 and 134°C. Please note that there is a definite upper limit to the target temperature range.

The market is dominated by Kaye and Ellab Instruments and almost all organisations are either using Kaye equipment or have heard of them. The most recent range of equipment includes an automated calibration system, which is timesaving.

Solution: **EBRO EBI 12 T / EBI 12-TP SERIES**

DEPYROGENATION/DRY HEAT STERILISATION.

Pyrogens are substances released by microbes that cause increased body temperature when injected. Endotoxins are lipopolysaccharides from the cell wall of gram-negative bacteria, which act as pyrogens. The two terms are used synonymously, although there is a fine distinction between the two. As with microbial contamination, it is vital that products are free from pyrogens. Pyrogens are destroyed only at very high temperatures. The products themselves are also usually destroyed by such high temperatures; therefore depyrogenation is usually only used to remove pyrogens from equipment. This can include process equipment but almost always includes vials and bottles etc that will contain parenteral products. The treatment for depyrogenation also sterilises.

Depyrogenation can either be performed using ovens in a batch-wise manner or using tunnels in a continuous process. In many cases the ovens or tunnels empty into a sterile area. The target for depyrogenation is a 3-log reduction in endotoxin content. Ovens are generally operated at 250°C and process times are between 2 and 6 hours, although it is generally accepted that 1hour at 250 °C is sufficient to cause the required reduction in endotoxin levels. Higher temperatures are being used but each cycle usually requires validation with biological indicators as part of the PQ. Tunnels operate at higher temperatures up to almost 400°C but the exposure time is only a few minutes.

Dry heat sterilizers are like depyrogenation ovens, although the temperatures are lower (up to 180°C).

Typical dry heat cycles as recommended in HTM 2010 are given in the table below;

Sterilization Temp (°C)	**160**	**170**	**180**
Max. allowable temperature (°C)	**170**	**180**	**190**
Minimum Holding time (min)	**120**	**60**	**30**

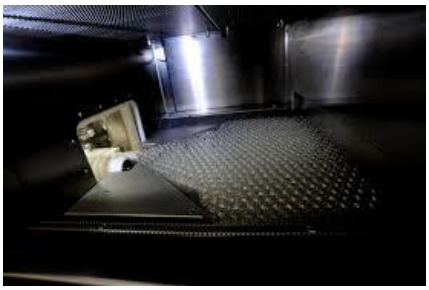
Ovens can hold up to several thousand vials or ampoules at a time. However, tunnels can depyrogenate hundreds of vials or ampoules per minute. The containers that are sterilized using ovens and tunnels tend to be relatively inexpensive. However, the product that is placed inside these bottles and vials can be worth in excess of $1M per batch.

Operational and performance Qualification for ovens and tunnels is similar to that for autoclaves. Temperature mapping is performed both on empty equipment and with full loads. PQ is repeated annually, although often, additional quarterly checks are performed also.

As with autoclaves the calibration of the temperature probes is required before use and verification afterwards. The only difference is the temperature range involved.

For dry heat sterilizers, thermocouples must be +/- 0.5°C. For depyrogenation ovens and tunnels there is no specified requirement, although +/- 1°C is considered appropriate.

Solution: **EBRO EBI 12-T22X / EBI 12-T24X / EBI 12-T42X / EBI 12-T44X**



STABILITY CABINETS

All pharmaceutical products must be placed on stability trial. Even after approval it is normal to have ongoing stability trials, which continually monitor quality throughout the lifetime of the product. Storage conditions have been standardised to some degree. Normal conditions are 25°C, 60%RH and 40°C, 75% RH. However, with biotechnology and the development of more biological products, storage at –20, -40 and even –80°C is not uncommon. Some products are stored in relatively small cabinets but bulk materials are often stored in very large rooms or warehouses. It is important that the normal storage conditions do not deviate from those of the stability trials. The cost of product in stability chambers is not significant, as the material will have been written off. The loss of stability samples will result in additional cost and time. However, storage of final product, be it in warehouses or freezers, can result in stocks of several Million Euros being held in one place. The cost of a monitoring system with alarm conditions is insignificant compared to the cost of the product it is safeguarding.

Most companies will already have systems in place whereby stability chambers are continuously monitored and recorded, often using chart recorders. Alarm conditions are usually included so that it is immediately obvious when a cabinet strays from its normal conditions.

Continuous monitoring of cabinets does not need the accuracy and durability of equipment such as that made by Ellab. Some organisations are happy to continue to use chart recorders. However, the validation of stability cabinets, rooms and warehouses does require similar standards as that applied to the validation of autoclaves and ovens etc. Some organisations rely on initial OQ to map cabinets and then continuous monitoring afterwards. However, more companies are realising the need to increase their validation effort with respect to stability cabinets and validate on an annual basis.

Solution : **EBI 300 and 310 Series**

FREEZE DRYING

Freeze drying (or lyophilisation) is the process of removing water from a frozen solution by sublimation. The product is frozen to very low temperatures (-40°C and below) and then slowly heated in the presence of a vacuum. The result is the water sublimes and is captured on condensers at extremely low temperature (-80°C and below). The critical factors in a freeze-drying process are the shelf temperature, chamber pressure and the product temperature. The first 2 determine the last.

Freeze drying consists of 3 stages: Freezing, primary drying (removal of water present as ice crystals) and secondary drying (removal of water bound to the product).

Shelf and product temperatures often start at -40 to -50°C and rise to ambient. Chamber pressures are controlled between 0.08 and 0.1mbar absolute during primary drying then much lower during secondary drying. All production driers come with temperature and pressure sensor included.

As with autoclaves, freeze driers come in a wide variety of sizes from bench-top to the size of rooms. The larger driers can hold up to 1 Tonne of water and can be used for batch sizes of tens of Kg. They can also hold thousands of vials. Bulk drying takes place in trays and can be sterile or non-sterile. The only difference with drying in vials or bottles is that a stoppering mechanism is present to stopper the vials while under vacuum. Whether bottles are used or not, the product is frozen and dried on a system of shelves with heating/cooling fluid. Many biotechnology products are freeze-dried to allow the product to be formulated in a stable form. These products, although required in relatively small quantities, tend to be very expensive. As with any new chemical entity batches worth over Euro 500,000 are not uncommon. The cost of validation equipment is therefore relatively small.

The opportunity for using **Ebro** equipment for monitoring and validating freeze driers may be limited. The extremely low pressures make the introduction of cables very difficult. Also, the operating range of Tracksense pressure and temperature sensors rule out their use in many cases, although some companies do validate temperature distribution at –50°C and above, even though the product cycle goes well below this temperature. However, it should be remembered that many freeze driers are used to produce sterile product. As a consequence they also have sterilisation cycles prior to loading. These cycles need validating in the same way as any sterilizer and present the same opportunities.

Solution: **EBRO EBI 12 T / EBI 12-TP SERIES**

ETHYLENE OXIDE (ETO) AND HYDROGEN PEROXIDE (H_2O_2) STERILIZERS

These compounds are strong oxidising agents which are used to sterilize products that cannot withstand heat, e.g. plastic bags etc. The agents are used in the gaseous phase and penetrate the products over a period of hours. There also needs to be a decontamination period to let the oxidisers desorb from the products before they can be despatched. The two most important factors after ETO (or H_2O_2) concentration are temperature and RH. It is important to have moisture present and a temperature of approx 50°C. It is also important to note the ETO is highly explosive. As a consequence the use of intrinsically safe loggers is preferred to cables. Due to the toxicity of ETO and risk of explosion, ETO use is becoming very specialised and used by a small number of contract companies or large volume producers.

The size of sterilisers can range from small bench-top sterilisers to large rooms. ETO use by contract sterilising companies can take place in very large rooms with products being stored on pallets. H_2O_2 is still more developmental and tends to be used on a smaller scale however the biggest use of H_2O_2 is in sterilising/cleaning incubator tunnels in aseptic environments. The materials sterilized using ETO and H_2O_2 are relatively cheap as they are generally packaging items. However, the large volume of the sterilizers can lead to batches being worth thousands of pounds.

Mesalabs/Datatrace and Madge Tech dominates the market but they are not as robust and well-engineered as compared to the **EBI 12-T441-EX.**

LABORATORY REFRIGERATORS / LAB FRIDGES
COLD STORAGE AND PHARMACEUTICAL WAREHOUSES

There are specific storage temperature requirements for some Pharmaceutical Lab samples and Product samples that it becomes very necessary to perform Thermal Mapping of these facilities or units.

Minimum Mapping Duration required is 72 hours but it has become common to some major Pharma Companies to require the thermal mapping and validation of these units for 7 weeks, preferably during the warmest season of the year.

Aside from the scheduled thermal mapping / validation procedures, a mandatory issue for compliance is to install fixed temperature (and %RH sensors when necessary) monitors/recorders in the storage areas, warehouses and refrigerators.

Guidelines / Standards can be found in the USP General Chapters 1079 / USP and ASEAN Harmonization References and in the WHO Technical Report Series No. 961, 2011 “Qualification of Temperature-Controlled Storage Areas”.

Solution: **EBRO EBI 25** (Wireless Data Logger System for Monitoring and Recording) **/ EBI 310** (for Thermal Mapping) **and EBI 330** (for Transport / Shipment Monitoring)

Aside from the **EBI 25** Wireless Data Logging System, the **EBI 300** and **EBI 310** Data Loggers are suitable for these applications.

For Continuous Monitoring and Recording of Shipment or Transport conditions, the **EBI 330** (single-use version) is recommended.

Sensors: Temperature and Humidity

FDA 21 CFR Part 11 – ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES.

The above document is published by FDA and is concerned with the production, maintenance and storage of electronic documents, which are subject to FDA inspection. This includes electronic data files that provide evidence of satisfactory validation of equipment as well as batch manufacturing records. If the primary source of the record is electronic, the storage of the electronic record is subject to this regulation. In Europe the definition of the primary record is largely left to the company concerned. As far as FDA is concerned, it is not permissible to print out a paper copy and claim that to be the primary data.

The purpose of 21 CFR Part 11 was originally to ensure that electronic records and signatures were afforded the same protection against fraud as paper records. However, FDA has been quick to realise the potential of such technology and requirements are now higher than originally intended. For example, it is a requirement that systems detect actions such as unauthorized attempted access and deletion of files. These facilities would never have been possible with paper systems

There is uncertainty as to when this regulation will come into effect and when inspectors will look for non-compliance. The fact of the matter is that customers are asking for compliance now. Compliance will be expected within the next 12-24 months, therefore any equipment that companies are buying now is with a view to ensuring compliance in this time frame. The kind of capital investment that Ellab equipment involves requires the customer to be looking at least 5 years ahead, if not longer.

As with any documentation in the pharmaceutical industry, the overall purpose of 21 CFR part 11 is to record:

- Who did what and when did they do it?
- Proof that the documents are the original versions, i.e. they have remained unaltered
- If altered, who altered them, when and why?
- If altered, what was the document originally like?
- Was the person who created, altered or deleted the document authorised to do so?

In order to satisfy the above it must be impossible to sign as another person, or create, alter or delete a document without leaving a trail.

The above is not meant to be a conclusive summary of the requirements but outlines the main themes of the regulation. These are the basic requirements of the industry regardless of the technology used. Non-compliance with the above can only occur due to incompetence or fraud by a company's employees. However, this is no defence. FDA will wish to see evidence of compliance, not lack of evidence of non-compliance. Companies therefore seek to have proof of compliance and make it impossible not to comply.

Ebro is compliant to the FDA 21 CFR Part 11.