DICKSON
Environmental Monitoring + Compliance Experts

HANDBOOK

# PHARMACEUTICAL ENVIRONMENTAL MONITORING

## BY DICKSON

Environmental Monitoring
+ Compliance Experts

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# PREVENTION IS THE BEST MEDICINE

Benjamin Franklin said, “an ounce of prevention is worth a pound of cure,” and that certainly rings true today, especially in the pharmaceutical industry where safety and security are mandatory. That’s why there are stringent regulations in place to ensure that medications remain safe and effective for the patient. Whether you’re producing vaccines to eliminate disease or medicine to help fight illness, environmental monitoring is a crucial step in remaining compliant.

Because medications are exposed to a multitude of environments during the process of packaging, shipping, and on-site storage it is imperative that all the points in this process are monitored to prevent microbial contamination. When it comes to administering the most effective pharmaceutical treatments for better patient outcomes, prevention may well be the best medicine.

This handbook on pharmaceutical environmental monitoring is for industry newcomers and seasoned pros alike. We will explore trends that are shifting the market, essential regulations governing the industry, and how this translates to best practices.


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Dickson
720, rue Louis Lépine
34000 Montpellier, FRANCE

P: +33 4 99 13 67 30
support@dicksondata.fr

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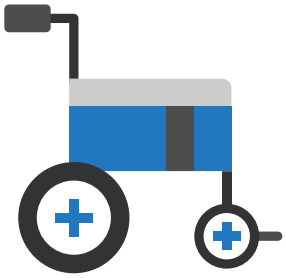
# THE PHARMACEUTICAL MARKET AND KEY CHALLENGES

The pharmaceutical industry has experienced significant growth over the last several years with numbers continuing to climb in 2019. The U.S. and Europe dominate the market with the U.S. alone accounting for around a third of the global market. In 2018, spending in the United States reached $485 billion, with anticipated spend for 2023 reaching over $625 billion. This growth is spurred by a variety of factors, which in turn create challenges for pharmaceutical companies.



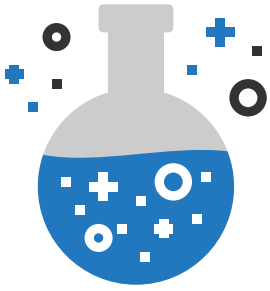
## An Aging, Ailing Population

There are more people in the world than ever before; the global population will increase by 1.24% per year until 2030. And while the population increases, it is also aging, with baby boomers at the core of this trend. The number of people aged 65 to 80 will rise to 28% compared to 22% in 2000. While increasing urbanization and a growing middle class will help to make drugs available and affordable for more people, it will also lead to a higher demand for medication.

Additionally, growing populations coupled with unhealthy lifestyles and various environmental factors are contributing to a surge of chronic diseases. From diabetes to cancer, these diseases require access to pharmaceuticals for more extended periods, sometimes indefinitely. In an early study (published in the American Journal of Public Health) on the impact of age and chronic diseases, researchers found that chronic conditions are directly correlated with increased spend on pharmaceuticals.

In the United States, the rise of anti-vaccination movements expands the threat of communicable diseases. As the number of vaccinated people decreases, the chance of contagious diseases increases. The Centers for Disease Control and Prevention reports that "704 measles cases in 22 states have been confirmed since Jan. 1. The numbers surpass the record of 667 set in 2014, the previous highest total since the disease was declared eliminated in 2000."

## The United States Driving Research and Development



The United States is the world leader in biopharmaceutical R&D, according to the Pharmaceutical Research and Manufacturers Association (PhRMA), U.S. firms conduct over half of the world's R&D in pharmaceuticals ($75 billion) and hold the intellectual property rights on most new medicines. The biopharmaceutical industry accounted for more than $1.3 trillion in economic output, representing 4% of total U.S. output in 2015.

The U.S. intellectual property system provides incentives for innovation with patent and data protection, a regulatory system that is considered one of the most rigorous in the world and the most significant scientific research base fostered by academic institutions and decades of government research funding, and robust capital markets. This system will continue to support the U.S.'s position as a leader in pharmaceutical R&D well into the future.

## Drug Pricing Pressure

The demand for lower drug prices has put significant pressure on the pharmaceutical industry over the past couple of years, and that trend will continue in 2019. According to Global Data Pharma's 2019 industry outlook survey, more than 50% of respondents (globally) believe that drug pricing and reimbursement constraints will have the most significant negative impact on the pharmaceutical sector in 2019.

Along with a demand for better visibility to the entire pharmaceutical process, patients are becoming more wary of drug prices. Additionally, regulators and politicians are facing pressure from the current administration to freeze price increases. Pharmaceutical manufacturers are then faced with shrinking profit margins and a desire to find more cost-effective ingredients. As we look to the future, regulators, patients, politicians, and payers will continue to play an essential role in forcing the industry to drive down costs of medications.

## Artificial Intelligence in Manufacturing

As the Industrial Internet of Things (IIoT) becomes more ubiquitous, companies are looking to use artificial intelligence (AI) to innovate further and optimize their manufacturing practices. AI can help improve production line efficiency, automate reporting and proactively address potential errors before they occur. Many pharmaceutical companies have been cautious in the speed at which they've integrated AI in their processes to date. That's because the cost of even one failure can total in the millions, not to mention the impact on patient lives.

Ultimately, the potential benefits are beginning to outweigh the risks slowly. According to Sarah Rickwood, VP at IQVIA, "Integration of data science with human science will really start to address the complexities and challenges of clinical research; this is absolutely necessary as R&D costs continue to rise faster than is sustainable for large pharma."

## Visibility and Patient Input

Accessibility to increasing amounts of personal health data via wellness tracking plans and technology has fundamentally shifted how individuals view healthcare. Patients are demanding more and more control, and in turn, they want more visibility to the ingredients of their pharmaceuticals. In response, companies are including patients across the entire drug lifecycle – from concept to R&D to post-production. "The shift to patient engagement/involvement will continue with the FDA moving close to mandating it," says MSD's Paul Robinson. "Companies will embed this into their SoPs for clinical development. Patients will continue to push for involvement and will get more recognition."

# 5 TOP TRENDS IN PHARMA

Five key trends are emerging in 2019 that will significantly influence the way pharmaceuticals are manufactured and distributed around the world.

## 1 Transparency in Clinical Data Reporting

- Only 38% of consumers trust the pharmaceutical industry
- Regulators are demanding more transparency in clinical data reporting
- FDA imposed new penalties for failing to register clinical trial data in a timely fashion
- Pharma organizations must now embed transparency into all steps of the clinical process

## 2 Research & Development Innovation

- Greater adoption of virtual trial processes to improve R&D efficiency and participation
- Pressure to manage R&D costs in disease areas where patients are hard to come by
- Pragmatic clinical trials (PCTs) will be a growth area in 2019

## 3 Data Integrity

- Pharma embracing new digital tools and capabilities to collect and store more data points
- The adoption of personalized medicine will lead to more extensive monitoring
  - › Treatments are sensitive to fluctuations in temperature and require tedious data collection and monitoring
- Pharmaceutical companies will need to adopt a culture of quality to improve data integrity

# 4 Changes in Clinical Trials

- Traditional randomized clinical trials can no longer generate the data needed to satisfy regulators and payers fully
- Regulators are increasingly adopting real-world evidence
- Pragmatic clinical trials (PCTs) will be a growth area in 2019
  - › PCTs measures treatment effectiveness, as opposed to efficacy
  - › They represent the most rigorous real-world research design

# 5 Value-Based Healthcare

- Value-based Healthcare will become more prevalent in 2019 to ease the rising cost of care
- 30% of Medicare payments are tied to alternative payment models based on quality and value
- New programs being developed based on the quality of care by providers
- Need to educate patients on the value medications have in improving quality of life

# KEY U.S. REGULATIONS

The pharmaceutical industry is subject to a multitude of guidelines, regulations, best practices and many other types of documentation directing the data collection, monitoring and delivery of medications. The three central agencies that issue these regulations are as follows:

## » Federal Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is "responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation."

### › 21 CFR Part 211: Current Good Manufacturing Practices (cGMPs) for Finished Pharmaceuticals

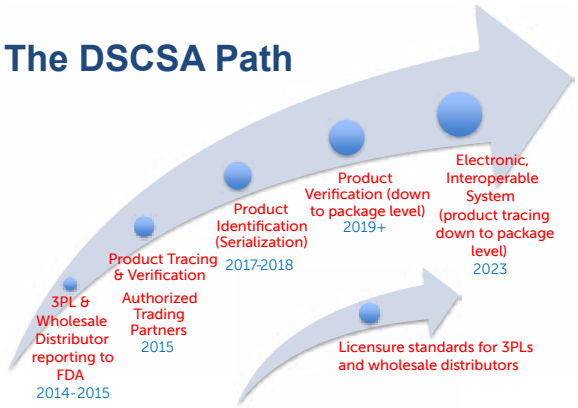
Current Good Manufacturing Practices are the primary FDA regulation to ensure the quality, safety, and effectiveness of human pharmaceuticals. CGMP standards outline the appropriate systems and processes that pharmaceutical companies must follow. This covers the following:

- Raw material sourcing and quality
- Quality management systems
- Establishing "robust operating procedures"
- Training qualified employees
- Properly maintaining and calibrating equipment
- Identifying and addressing quality deviations
- Maintaining reliable and accurate testing laboratories

To ensure compliance with these regulations, the FDA conducts regular inspections of pharmaceutical manufacturers. Inspections may also occur after reports of product issues from consumers.

### › Drug Supply Chain Security Act (DSCSA)

The Drug Supply Chain Security Act (DSCSA) enacted by Congress in 2013, outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. Designed to enhance the FDA's ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful, the DSCSA has been continually updated since its' inception to include stricter guidelines. The diagram below outlines these updates throughout 2023.




Major changes for 2019 and beyond will significantly affect the data reporting down to the package level. This reinforces the need for better data integrity, monitoring, and reporting for pharmaceutical companies.

### › 21 CFR Part 11

21 CFR Part 11, established in 1997, is part of the overall Code of Federal Regulations, and deals with electronic records and record-keeping. It "requires that closed computer systems must have a collection of technological and procedural controls to protect data within the system. Open computer systems must also include controls to ensure that all records are authentic, incorruptible, and (where applicable) confidential."

It also requires that companies have implemented controls for:

- Internal roles and user access
- Audits and audit trails
- Electronic signatures
- System validations
- Software/system documentation

# QUALITY AND COMPLIANCE CHALLENGES

Keeping up with changing regulations is one of the most significant pain points for Pharmaceutical Manufacturing and Distribution companies. Remaining compliant is critical but can be quite challenging in any size organization. It takes a systematic approach with involvement across multiple departments and specialties to make that happen.

Many companies rely on Regulatory and Quality Assurance leaders to manage changes and issues in these areas, but senior leadership, manufacturing/plant management and operations all play a role.

## Awareness

Companies must maintain an internal policy for tracking changes to existing standards or new regulations. By staying aware of potential changes in the industry, it prevents organizations from being caught off guard to address new requirements and can ultimately help save money. Constant monitoring and follow-up on regulations and compliance are necessary to ensure the quality of the products that reach the market.

## Education

Once new or changing regulations have been identified, you should begin internal education efforts. At this stage, selecting a few internal experts will help ensure that there are a unified approach and understanding. The team should contain representatives from each major part of the business so that all potential implications are discussed.

These experts should become familiar with the intricacies of the standard, and should also use external resources (consulting firms, lawyers) to understand the full impact of the change. Last, the team should create documentation for how the regulations will change company policies, procedures, and expectations.

## Communication

Once internal documentation is completed, the internal team should communicate all changes to employees. Employees should have an understanding of how the regulations impact the company as a whole, their department and their specific job. Communication should be positive, consistent and educational.

## Training

The last step before regulations are changed or adopted is training. At this point, your entire organization should have a clear understanding of what (if anything) is changing. If there are operational changes, detailed training sessions should be conducted with all individuals impacted. This should be a cross-functional approach including written documentation, on-the-job training as well as seminars, webinars or third-party education.

# PREPARING FOR AN AUDIT

One of the biggest issues pharmaceutical companies have is complying with and passing audits – whether planned or surprise. If you're not ready, this can make for a sticky situation and even cost the organization in both lost time and money. Don't stress though; there are plenty of steps you can take that will make it easier to always be audit ready. Follow the helpful checklist below:

## 1. REVIEW ALL DOCUMENTS

- A list of all documents related to the audit should be prepared
  - Batch manufacturing data
  - Master formula records
  - Facility and equipment maintenance records
  - Calibration records
  - Stability testing data
- Review qualification documents
  - Equipment and instruments used for production & quality control
  - Process validation and analytical method validation
  - Facility validation records

## 2. PREPARE GXP AUDIT PLAN

- Prepare an audit plan and agenda
- Address all applicable departments
- Note all strengths and weaknesses of each respective department
- Perform audit tasks by starting on the areas with the greatest needs
- Review notes of historical audits to address any corrective actions that may still be open
- In large matrixed organizations ask other departments if they have experience with a particular auditor

## 3. IDENTIFY KEY PERSONS

- Identify 1 or 2 persons from each department with knowledge of documents and have them available for the audits
- These persons shall explain things to the auditors

## 4. ASSIGN AUDIT RESPONSIBILITIES

- Assign tasks to every area identified in your audit plan
- Head of department(s) should ensure completion of assigned tasks

## 5. CONDUCT ROUTINE INTERNAL AUDIT(S)

- Routine internal audits are part of every good quality system and help you get in the routine of an audit, as well as prepare for any unexpected audits

# ENVIRONMENTAL MONITORING

Environmental monitoring is the observation and collection of environmental data (e.g., temperature, humidity, pressure), typically to ensure consistency in the conditions and meet regulatory requirements. Monitoring systems can also act as alarms, warning companies as certain conditions may go out of their desired range, so that action can be taken before product potency is impacted.

Whether researching and producing a cure for an illness or transporting and storing consumer-ready medicine, consistent quality in the pharmaceutical industry is mandatory. Having environmental monitoring systems in place can mean the difference between business as usual and a failed audit, or even failed treatment. Monitoring essential data from R&D to production can help protect assets, the bottom line, and patients.

## The Benefits of Monitoring

**Drug quality:** When you're manufacturing pharmaceuticals, there needs to be assurances that your product identity, strength, quality and purity are not compromised. Temperatures that are too hot or too cold can degrade the potency of medicines. Finding the right temperature monitoring system can guarantee audit compliance and patient safety.

**Long-term ROI:** Upgrading environmental monitoring to more automated, cloud-based solutions can save manufacturers money in the long run. These systems reduce the chance for human error and provide real-time excursion alerts – preventing costly product loss and freeing up employees to handle other tasks. The automation and long-term savings offered by these systems can help companies realize a significant return on their initial investment.

**Audit compliance:** continuous monitoring and digital logs can help you easily adhere to regulatory requirements and reduce the risk of non-compliance during audits. By having ongoing data on key environmental conditions, you can provide documentation on consistency as well as evidence on how excursions were addressed.

**Operational efficiency:** Cloud-based solutions eliminate the need to manually go to each sensor and collect charts or download data. Instead, environmental data is pushed automatically to a central location that can be accessed by anyone with permissions, from anywhere, at any time. Cloud options also save time and resources for internal IT teams, who no longer need to dedicate extended periods of time on maintaining servers and software.

**Research accuracy:** In the laboratory, results must be repeatable, and you need to understand the exact conditions that resulted in your success. Environmental monitoring solutions can be the difference between an IND application and going back to the drawing board.

**Patient safety:** Since environmental monitoring tracks essential environmental conditions, you can ensure that your products are consistent throughout the entire process – from lab to pharmacy shelf. This helps guarantee that the end users-the patients who will benefits from your products-are safe and that their treatment is effective.

## Clinical Trial Medications: Environmental Monitoring from Start to Finish

Clinical trials are an essential step when it comes to determining the impact of a new potential treatment. They provide the FDA with valuable information needed to weigh the benefits and risks of a new medication to decide whether it is safe for patients.

To stay compliant and ensure the safety and effectiveness of new medications it is essential that you follow strict guidelines for monitoring and reporting.

### The Right Tools are Critical

During a trial, medications are exposed to a multitude of environments during the entire process of packaging, shipping, and on-site storage. It is imperative that all the points in this process are monitored so that the appropriate people are alerted to any temperature excursions. It is critical that once in storage, site staff can frequently monitor loggers in the refrigerators as well as have visibility of any excursions before dispensation.

### Frequent Temperature Monitoring

Packaging a temperature logger in with the medication enables temperature tracking through shipment and storage. This end-to-end approach provides a temperature history of the medicines.

### Proper Data Logging Techniques

Most loggers in use today, including DicksonOne data loggers, allow for the viewing of real-time data from any mobile device, thus removing the need for manually uploading data. In cases where Wi-Fi or Ethernet signal is not available, Dickson offers loggers that can download data directly into the DicksonOne portal through our Legacy Uploader tool, providing actual end-to-end monitoring everywhere in the supply chain.

# SPOTLIGHT ON THERMAL MAPPING

Mapping the differences and changes in temperature and relative humidity within a three-dimensional space can provide valuable data. Thermal mapping services offer a data-driven rationale for permanent monitoring placement to protect environmentally sensitive products. Periodic mapping of a facility can also assist in determining whether your preventive maintenance activities are effective at maintaining your environmental control systems.

## How do you go about performing a thermal mapping to ensure you get the data required and documentation required by your auditing body?

1. Create a test plan or protocol to define requirements such as critical areas to be mapped, data logging sample interval, length of study, data logger placement and acceptance criteria. Use risk-based decisions on where to place data loggers and guidance from the World Health Organization, USP, or ISPE. The more you understand your product storage requirements, the better the rationale will be for quantity and placement of the data loggers

2. Select and prepare your data loggers:
    a. Calibrate to a NIST traceable standard
    b. Ensure adequate memory to cover your intended study period. Most data loggers today are capable of handling multiple weeks of data storage depending on your sample rate
    c. Choose a data logger with the appropriate sensor and range
    d. Choose a logger that is Part 11 compliant, if you're working in an FDA compliant environment
    e. Label all data loggers with their specific location

3. Begin placing your data loggers according to the documented test plan

4. Remove loggers after the defined test period and begin downloading and analyzing data

5. Perform post-calibration verification to ensure your data loggers remained in calibrated state

6. Write a Summary Report:
    a. Summarize details of data logger setup, time and dates of study, any notes that were taken during study period
    b. Include tables and graphs to easily summarize data. Include all data for a specific area within 1 graph or table to assist in determining if data meets acceptance criteria
    c. Determine all high and low points within your study. These points are typical points for permanent monitoring as they bracket the operating range of the facility
    d. Document deviations from acceptance criteria and corrective action(s) for those areas. Corrective actions may entail avoiding storage in specific areas, adding ventilation to specific areas, or even adjusting HVAC systems

7. Use your summary report as justification for permanent monitoring locations (high and low points) and as supportive data for preventive maintenance tasks that have been performed or need to be performed

8. Perform mapping in extreme weather conditions for your area (e.g. summer and winter) to ensure the facility environmental control systems (e.g. HVAC) can perform at these extremes

## Common Abbreviations:

When it comes to storing temperature sensitive products, sometimes the long list of terms and information involved in mapping can get a little confusing. Below is a list of abbreviations and key terms to help make digesting your mapping report and validation easier.


## Key Terms:

**Component:** Any major piece, part, or assembly of the main equipment or sub-equipment that does not have its own power supply and could not operate as a standalone unit (valves, switches, etc.)

**Controller:** A device that interprets a mechanical, digital, or analog signal, generated by a sensor, to control equipment or components.

**Deviation:** For IQ: Any discrepancy between the installation specifications and the actual (as found) installation.

For OQ: Any discrepancy between the protocol and the actual performed test, test function methodology, testing equipment, testing material, etc.

**Electronic Data Logging Monitor:** A small portable device that measures and stores environmental data (temperature, humidity, pressure, etc.) at predetermined time intervals using an electronic sensor.

**IQ (Installation Qualification):** The process of obtaining and documenting evidence that the premises, equipment, and supporting systems have been provided and installed in compliance with their design specifications.

**Instrument:** A device that interprets a mechanical, digital, or analog signal generated by a sensor and converts it into engineering units (°C, % RH, mA, etc.) through scaling.

| | |
|---|---|
| **Key Operating Parameters:** | Parameters that must be maintained to process or produce products with consistent quality attributes and those that may have an impact on the proper operation of the equipment. |
| **Thermal Mapping:** | Documented measurement of the temperature or relative humidity distribution within a storage area, including identification of hot and cold spots. |
| **OQ (Operational Qualification):** | The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment, and supporting systems operate following their design specifications. |
| **PQ (Performance Qualification):** | The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected, will consistently perform per the approved process method and specifications. |
| **Refrigeration Equipment:** | The term 'refrigeration' or 'refrigeration equipment' means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity. |
| **Sensor:** | A mechanical device (pressure switch, bimetal temperature switch, etc.), or a digital or analog transducer (limit switch, pressure sensor, temperature sensor, etc.) that generates a mechanical or electrical signal to an instrument or a controller to be interpreted. |
| **Service Level Agreement:** | A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees, and communication mechanisms. It can either be legally binding or an informal agreement. |
| **Standard Operating Procedure:** | A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results. |
| **Temperature Controlled:** | Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits |
| **Validation:** | Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria. |

# SUMMARY

The safe and successful manufacturing and distribution of pharmaceutical products require constant environmental monitoring to remain compliant. There are very stringent regulations in place by a variety of government agencies to ensure that medications are safe and effective for patients.

It's critical for pharmaceutical companies to understand these regulations and to have the right tools in place to adhere to them. That requires navigating a rapidly changing industry, adhering to ever-evolving regulatory standards and addressing fluctuations in drug prices. To succeed, companies must be rigorous and standardized in their processes but also flexible enough to respond to innovation...all while ensuring ongoing compliance and consumer safety.

# ABOUT DICKSON

Since 1923, Dickson has been changing the way organizations monitor their temperature, humidity, and pressure-controlled environments. By incorporating the best and newest innovations, Dickson enables organizations to manage compliance, asset protection, data analysis, and quality control with confidence.

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720, rue Louis Lépine
34000 Montpellier, FRANCE

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