



**Good  
Practice  
Guide**

# Heating, Ventilation, and Air Conditioning (HVAC)



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Humidity

Air Movement

Air Quality

ENGINEERING PHARMACEUTICAL INNOVATION





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# Heating, Ventilation, and Air Conditioning (HVAC)

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# Preface

Heating, Ventilation, and Air Conditioning (HVAC) systems can critically affect the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. The design of these systems requires a blend of Good Manufacturing Practice (GMP) and Good Engineering Practice (GEP) to help provide a safe and healthy work place, protect the environment, and manage energy responsibly. HVAC can consume a major portion of the energy used by a facility and must be considered in any company's sustainability and carbon management policies.

This Guide aims to clarify GMP HVAC issues, those critical to the Safety, Identity, Strength, Purity, and Quality of pharmaceuticals, biopharmaceuticals, and medical devices from raw materials to finished goods, including the requirements for HVAC control and monitoring. This Guide also addresses issues of GEP related to sustainability, economics, and environmental health and safety.

To achieve these goals, the Guide Team aims to provide the Life Science Community with common language and understanding of critical HVAC issues, guidance on accepted industry practices to address these issues, and a common resource for HVAC information currently included in appendices of the various ISPE Baseline® Guides.

The intended audience for this Guide is global with particular focus on US (FDA) and European (EMEA) regulated facilities.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers with input from members of the ISPE HVAC Community of Practice (COP). There is no single approach to satisfy every HVAC situation; therefore, this Guide cannot address every HVAC situation. A recurring theme throughout the Guide is the importance of understanding the role of HVAC performance in protecting product, personnel, and the environment.

This Guide includes appendices which provide industry examples and templates that may be of use to the reader.

## **Disclaimer:**

This Guide is meant to assist pharmaceutical companies in determining a common understanding of the concept and principles of HVAC. The ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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## Section Writers and Reviewers

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# 1 Introduction

## 1.1 Background

Heating, Ventilation, and Air Conditioning (HVAC) can be a critical system that affects the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. Environmental control systems that are appropriately designed, built, commissioned, operated, and maintained can help ensure the quality of product manufactured in a facility, improve reliability, and reduce both initial costs and ongoing operating costs for a facility.

The design of HVAC systems for the pharmaceutical industry requires additional considerations, particularly with regard to providing a clean and safe space environment. HVAC can consume a major portion of the energy used by a facility, and requires a blend of Good Engineering Practice (GEP) and Good Manufacturing Practice (GMP).

## 1.2 Purpose

This Guide is intended to supplement published ISPE Baseline® Guides for facilities (Reference 13, Appendix 12), providing detailed information and to recommend practices for implementation of HVAC systems in pharmaceutical facilities.

This Guide emphasizes the importance of understanding the role of HVAC system performance in protecting product, personnel, and the environment. Air filtration, Differential Pressure (DP), and airflow/air change rates are covered in detail to assist comprehension of airborne particulate control.

The information provided in this Guide reflects the cumulative knowledge and experience of the authors and reviewers with input from members of the ISPE HVAC Community of Practice (ISPE HVAC COP).

## 1.3 Scope

The ISPE Good Practice Guide: HVAC provides:

- supporting information and HVAC practices for facility types covered by ISPE Baseline® Guides
- an overview of the basic principles of HVAC to facilitate a common understanding and consistent nomenclature

This Guide addresses HVAC requirements in areas of the facility life cycle, including:

- establishing user requirements
- design, including the requirements of outdoor conditions
- construction, including good practices for equipment specification and installation
- commissioning/qualification
- operation/maintenance

Requirements of regulatory agencies other than the FDA may differ significantly and may not be covered in the facility ISPE Baseline® Guides (Reference 13, Appendix 12), and therefore, they may not be considered by this Guide.

This Guide references ISPE Baseline® Guides (Reference 13, Appendix 12) and provides associated examples. The relevant Baseline® Guide should be consulted for regulatory expectations in a specific topic area.

GEP should be applied in assessing which of the recommended practices is most applicable to a situation.

This Guide refers to recommendations, standards, and guidelines published by:

- World Health Organization (WHO)<sup>1</sup>
- International Conference on Harmonisation (ICH)
- International Standards Organisation (ISO)
- Institute of Environmental Sciences and Technology (IEST)
- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE)
- International Society for Pharmaceutical Engineering (ISPE)
- American Society for Testing and Materials (ASTM) International
- Chartered Institute of Building Services Engineers (CIBSE, UK)
- American Council of Government Industrial Hygienists
- Instrumentation, Systems, and Automation Society (ISA)
- Sheet Metal and Air Conditioning Contractors National Association – (SMACNA (North America))
- National Environmental Balancing Bureau – (NEBB (US))
- Heating and Ventilating Contractors Association (HVCA) (UK)

The Guide is not intended to be a complete handbook for HVAC design and does not address every HVAC situation.

## 1.4 Benefits

This Guide introduces the fundamentals of HVAC systems that control the GMP workplace environment and provides:

- the life science engineering community with common language and understanding of critical HVAC issues

<sup>1</sup> The WHO TRS 937 reference document, (Reference 2, Appendix 12) aims to promote discussion regarding quality in preparation of Oral Dosage Pharmaceuticals and provide practical guidance for inspectors in countries without a robust history of GMP regulations (particularly in support of WHO HIV/AIDS, Tuberculosis, and Malaria programs). Per the WHO purpose statement:

*“These guidelines are intended as a basic guide for use by GMP inspectors. They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation. Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised.”*

WHO TRS 937 (Reference 2, Appendix 12) has been adopted as the GMP standard in some countries where prior regulation was inadequate or did not exist. (In regions with existing regulation (e.g., the US, Japan, Australia, and the EU) this document normally does not carry the force of law.)

HVAC engineers should understand the applicability of WHO TRS 937 before discussing user requirements for new OSD facilities.

- guidance on accepted industry practices to address these issues
- a common resource for HVAC information currently included in appendices of the various ISPE Baseline® Guides
- help to less experienced personnel in understanding the options available to HVAC designers
- assistance with prevention of airborne product contamination to assure product quality
- quality professionals with an understanding of which HVAC parameters are important to product quality and patient safety
- information on how to avoid increasing facility costs without providing benefit (e.g., over-designing of room classifications for aseptic processing)
- highlights on the differences between HVAC parameters that address product requirements and “discretionary” HVAC specifications that tend to be more business driven, such as custom air handlers, redundant systems, all stainless air duct, and DP controls

## 1.5 Objectives

The Guide:

- aims to clarify HVAC issues critical to product quality for the production of drug substances and drug products, and biopharmaceuticals
- considers the requirements for HVAC control and monitoring systems
- addresses how to implement the recommendations provided in relevant ISPE Baseline® Guides to meet FDA and EMEA regulatory expectations for HVAC system design

This Guide is intended for a global audience with particular focus on US (FDA) and European (EMA) regulated facilities, including:

- HVAC personnel, including those less experienced with HVAC systems
- quality professionals

## 1.6 Key Concepts

This section is intended to introduce Key Concepts, which are essential to understanding this Guide. Further detailed information on these concepts is provided in Appendices 1 to 3, in addition to a primer for readers unfamiliar with HVAC equipment and theory. Readers with limited experience in either HVAC or design for pharmaceuticals, biologics, and medical devices are encouraged to examine Appendices 1 to 3 before reading and interpreting this Guide.

### 1.6.1 Ventilation

Ventilation is the movement and replacement of air for the purpose of maintaining a desired environmental quality within a space. The term “Ventilation” has two common uses:

- It may refer to the movement or exchange of air through a space, which is responsible for the transport of airborne particles, the mixing, or displacement of masses of hot or cold air, and the removal of airborne contaminants (e.g., vapors and fumes).

- It may refer to the supply of “fresh” oxygen-rich air.

This Guide uses the definition only for movement or exchange of air through a space (see Appendix 1).

### **1.6.2 Product and Process Considerations**

HVAC aims to make personnel comfortable and to protect both workers inside a facility and the environment outside a facility from airborne materials that could be hazardous. In pharmaceutical manufacturing facilities, there also is a specific requirement to control the impact of the environment on the finished product (to assure product quality).

Products may be sensitive to temperature, humidity, and airborne contamination from outside sources or cross-contamination between products. Process operators may need protection from exposure to airborne hazardous materials.

Understanding the product and process is the key to good HVAC design (see Appendix 1).

### **1.6.3 Contamination Control**

Pharmaceutical HVAC should control airborne contamination and needs to help to ensure the “...purity, identity and quality...” of the product (21 CFR Part 211) (Reference 8, Appendix 12). Room contamination control generally is achieved by filtering the incoming air to ensure that it does not carry unwanted particles, then introducing the air to the work space to mix with ambient air and dilute any contaminants (see Appendix 1).

### **1.6.4 Impact of Temperature and Humidity on Contamination Control**

Comfortable personnel produce fewer environmental contaminants: a typical worker will discharge 100,000 particles (sized 0.3 µm and larger) a minute doing relatively sedentary work. A worker who is hot and uncomfortable may shed several million particles per minute in the size range, including a greater number of bacteria. Additionally, environmental conditions inside a building, such as high humidity, can influence the product by increasing microbial and mold growth rates on surfaces (see Appendix 1).

### **1.6.5 Total and Viable Particulate**

The majority of airborne particles are non-viable. A fraction (< 1%) of airborne particles are viable, e.g., bacteria and viruses; however, these can multiply. Viable particles travel with non-viable particles; therefore, controlling the total number of airborne particles also controls the number of viable particles (see Appendix 1).

### **1.6.6 Classified Space**

The concentration of total airborne particles and microbial contamination within the space is a key measurement of room environmental conditions for pharmaceutical operations, particularly for sterile products and some biopharmaceutical API. The target maximum reading for these measurements is referred to as the “classification” of the space.

Several similar systems exist for the classification of space; however, there is no consensus on a single terminology for classification. This Guide uses the term “Grade” (from the EMEA standard) followed by an ISO level number. Therefore, “Grade 7” meets ISO 7 (10,000 0.5 micron particles per cubic foot or 352,000 per cubic meter) in use only with bioburden limits of 10 per cubic meter. By comparison, a Grade 7 space looks much like a European Grade B space, but the European Grade (A, B, C, D) also has at-rest limits. This terminology was developed within ISPE to help bridge the gap between the various standards (see Appendix 1).