GUIDANCE NOTE 37

MEDICAL GASES

DATA INTEGRITY

2017

British Compressed Gases Association

GUIDANCE NOTE 37

MEDICAL GASES DATA INTEGRITY

2017

BRITISH COMPRESSED GASES ASSOCIATION
Registered office: 4a Mallard Way, Pride Park, Derby, UK. DE24 8GX
Company Number: 71798, England

Website:
www.bcga.co.uk

ISSN 2398 – 936X

PREFACE

The British Compressed Gases Association (BCGA) was established in l971, formed out of the British Acetylene Association, which existed since l901. BCGA members include gas producers, suppliers of gas handling equipment and users operating in the compressed gas field.

The main objectives of the Association are to further technology, to enhance safe practice, and to prioritise environmental protection in the supply and use of industrial, food and medical gases, and we produce a host of publications to this end. BCGA also provides advice and makes representations on behalf of its Members to regulatory bodies, including the UK Government.

Policy is determined by a Council elected from Member Companies, with detailed technical studies being undertaken by a Technical Committee and its specialist Sub-Committees appointed for this purpose.

BCGA makes strenuous efforts to ensure the accuracy and current relevance of its publications, which are intended for use by technically competent persons. However this does not remove the need for technical and managerial judgement in practical situations. Nor do they confer any immunity or exemption from relevant legal requirements, including by-laws.

For the assistance of users, references are given, either in the text or Appendices, to publications such as British, European and International Standards and Codes of Practice, and current legislation that may be applicable but no representation or warranty can be given that these references are complete or current.

BCGA publications are reviewed, and revised if necessary, at five-yearly intervals, or sooner where the need is recognised. Readers are advised to check the Association's website to ensure that the copy in their possession is the current version.

This document has been prepared by BCGA Technical Sub-Committee 7. It was approved for publication at BCGA Technical Committee 157. This document was first published on 24/10/2017. For comments on this document contact the Association via the website www.bcga.co.uk.

CONTENTS

* Throughout this publication the numbers in brackets refer to references in Section 8. Documents referenced are the edition current at the time of publication, unless otherwise stated.

TERMINOLOGY AND DEFINITIONS

Data	Information derived or obtained from raw data (e.g. a reported analytical result).
Data life cycle	All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive/retrieval and destruction.
May	Indicates an option available to the user of this Guidance Note.
Medicinal gas	Any gas or mixture of gases classified as a medicinal product (as defined in European Directives 2001/83/EC (2) and European Directive 2001/82/EC (1)). Throughout this document the term 'Medicinal Gas' is used to describe the products that are supplied in accordance with the Marketing Authorisation for medicinal use.
Raw data	Original records and documentation, retained in the format in which they were originally generated (i.e. paper or electronic), or as a 'true copy'. Raw data must be contemporaneously and accurately recorded by permanent means. In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes the raw data.
Shall	Indicates a mandatory requirement for compliance with this Guidance Note and may also indicate a mandatory requirement within UK law.
Should	Indicates a preferred requirement but is not mandatory for compliance with this Guidance Note.

GUIDANCE NOTE 37

MEDICAL GASES DATA INTEGRITY

1. INTRODUCTION

The supply of medicinal gases requires the manufacturer to operate under licences that are issued by the UK Regulators, the Medicines & Healthcare products Regulatory Agency (MHRA) and the Veterinary Medicines Directorate (VMD). These licences are used to specify the quality of the gas supplied and to ensure that the procedures used for filling and testing the cylinders are compliant with the basic principles of Good Manufacturing Practice (GMP) as laid down in European Directive 2003/94/EC (3), *Principles and Guidelines of good manufacturing practices for medicinal products for human and veterinary use*.

A fundamental requirement of the way in which medicinal gases are controlled is the ability to manage the extent to which all data is available, complete, consistent and accurate throughout the data life cycle. Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality.

The data governance system should be integral to the pharmaceutical quality system described in European Directive 2003/94/EC (3), Chapter 1. The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands. As such, manufacturers and analytical laboratories are not expected to implement a forensic approach to data checking on a routine basis, but instead design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale. Data integrity requirements apply equally to manual (paper) and electronic data. Manufacturers and analytical laboratories should be aware that reverting from automated / computerised to manual / paper-based systems will not in itself remove the need for data integrity controls. This may also constitute a failure to comply with European Directive 2001/83/EC (2), Article 23, which requires an authorisation holder to take account of scientific and technical progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Data integrity arrangements shall ensure that the accuracy, completeness, content and meaning of data is retained throughout the data lifecycle.

The MHRA provides guidance on data integrity, refer to *MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015* (4).

The final product quality control determines whether the medicinal gas meets the specification. The practical intention of applying data integrity techniques is to ensure that when delivered to the end user the product meets the required specification. This guidance note provides advice on determining the critical data that needs to be recorded, how it is recorded and to ensure that there is an audit trail behind it.

2. SCOPE

This document explains the policy of BCGA members for compliance with the data integrity requirements for batch documentation relating to medicinal gases.

3. BACKGROUND

Historically the medical gases industry has used manual observation techniques to record analytical results. As technology has developed the use of manual techniques is gradually being replaced by analytical equipment which is capable of capturing the analytical result electronically. This has the benefit of removing human error or the potential threat of data being falsified. Electronic recording devices have the ability to provide a permanent, auditable record of any results obtained.

Once the gas is mixed there are no issues around content heterogeneity.

4. RISK MANAGEMENT

The European Directives as applied to medicinal gases and GMP create a minimum standard that a manufacturer is required to meet in their production processes. GMP requires that medicinal gases:

- consistently meet the requirements of the marketing authorisation or product specification;
- are appropriate for their intended use.

To achieve this, it is necessary to ensure:

- the batch meets the analytical specification as stated in the Marketing Authorisation;
- the analytical result is directly linked to the batch number and the batch production record;
- the link between the analytical result, the batch number, and the batch production record are verifiable.

The main principles of data integrity are that records are:

- **A** - Attributable to the person generating the data
- **L** - Legible and permanent
- **C** - Contemporaneous
- **O** - Original record (or true copy)
- **A** - Accurate

The above principles should be considered when performing any risk assessment on the integrity and management of data.

A risk assessment of the criticality of the data in batch records has shown that the analysis of each batch against the specification in the Marketing Authorisation is the most significant issue, refer to Appendix 1. The primary requirement is to therefore to concentrate on batch analysis data and to ensure that in all respects it meets the requirements of data integrity.

Data may be generated using:

- a paper-based record of manual observation; or
- a spectrum of simple machines to complex computerised systems.

The inherent risks to data integrity may differ depending upon the degree to which data (or the system generating or using the data) can be configured, and therefore potentially manipulated.

5. RECOMMENDED POLICY

The medical gases industry has recognised the potential for data to be manipulated and therefore the use of manual observation techniques is gradually being replaced by analytical equipment which is capable of capturing the analytical result electronically.

BCGA members have committed to moving away from manual observation techniques to capture and record analytical results.

BCGA members will interpret their data integrity requirements, perform gap analyses to identify where improvements can be made to current processes and equipment, and through risk assessment prepare a data integrity implementation plan that describes what actions will be put in place to improve data integrity to acceptable levels, along with associated timescales for implementation.

The data integrity implementation plan should cover the following points:

- Development of a data integrity policy;
- Identify current equipment / processes associated with quality control and batch management;
- Identify additional equipment, systems and/or resources required;
- Set timescales to develop and implement the data integrity policy;
- Include information on data integrity in staff training.

As part of the data implementation process, the following activities should be considered:

- Cyber security;
- Determine what is critical equipment and what is not critical equipment.

- Consider what data relates to gas quality and which to gas quantity;
- Management of change procedures;
- Managing legacy equipment;
- Document control;
- How current and future systems and processes can be audited.

Methods of recording analytical results, in order of preference are:

(i) Electronically captured, for example via an analyser where the result is securely retained electronically.

(ii) Printed results, for example a stand-alone analyser with a printed analytical result.

(iii) Manually recorded results, for example chemical analysis, where the data is recorded in accordance with good laboratory practice.

In all cases the systems and processes used should be validated and the results should be linked to the batch record.

Following the life cycle of equipment, where such analytical equipment is replaced or new analytical equipment is installed, where practicable it will be replaced by an instrument which captures and retains the result electronically.

All captured data will be retained for a minimum period of five years or the product expiry period plus one year, whichever is the longer.

6. WHAT IS RECORDED

The items listed in Appendices 1 and 2 should be considered for their data integrity.

All data must be recorded in such a way that the result cannot be tampered with or falsified and any alterations made should be auditable.

Data should be generated in a contemporaneous manner and captured via validated equipment, in accordance with a quality management system.

7. DATA INTEGRITY IMPLEMENTATION PLANNING

The BCGA members of the UK medical gas industry will continue to improve their data governance systems ensuring they meet the requirements of a pharmaceutical quality system as described in European Directive 2003/94/EC (3), Chapter 1.

BCGA members will each conduct a risk assessment and then develop a data integrity implementation plan by the end of 2017 for medical compressed oxygen for submission to the MHRA.

BCGA members will prioritise their action on data categorised with a high residual risk in Appendix 1.

Appendix 2 is provided for consideration by individual companies.

As the largest number of batches of medical product supplied to the UK market is medical oxygen this is likely to take precedence over other medical products. However, consideration should be given to the number of batches for each medicinal gas produced on individual sites.

8. REFERENCES

Document Number		Title
1.	European Directive 2001/82/EC	Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.
2.	European Directive 2001/83/EC	Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
3.	European Directive 2003/94/EC	European Directive 2003/94/EC – Principles and Guidelines of good manufacturing practices for medicinal products for human and veterinary use. Annex 6, Manufacture of Medicinal Gases.
4.	MHRA Guidance	MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015.

Further information can be obtained from:

UK Legislation	www.legislation.gov.uk
EU Legislation for medicinal products - EudraLex	www.ec.europa.eu/health/documents/eudralex/vol-1_en
Medicines & Healthcare products Regulatory Agency (MHRA)	www.mhra.gov.uk
British Compressed Gases Association (BCGA)	www.bcga.co.uk

DATA INTEGRITY ASSESSMENT

Batch information (from Annex 6 (3))	**Residual Risk* H/M/L Patient Safety**	**Justification for residual risk rating**
Product name	Low	Level of detectability of error high at both QC and QP approval process
Batch number on batch record	Medium	Key information to link a quantity of product to a batch record
Date & time of filling	Low	Traceability of product performed via batch number
Identification of the person(s) carrying out each significant step (1) Pre-fill: Container – Product – RPV - Label	Medium	Identification of status of training. Validation of status of the signatory.
Batch(es) reference(s) for the gas(es) used for the filling operation (1) APIs / Starting material	Low	QC check and approval prior to use in product manufacture
Equipment used	Low	Validated system with planned preventative maintenance
Quantity of: (1) cylinders (2) mobile cryogenic vessels	Low	Only relevant for traceability
Confirmation that pre-filling operations preformed (1) Pre-fill inspection of the cylinder	Low	Manual task conducted in accordance to validated procedures and with trained operators. Verification against trended quality data.
Key parameters that are needed to ensure correct filling at standard conditions (1) Temperature - Pressure	Low	Quantity is not a unit dose.
Results of appropriate checks to ensure the cylinders / mobile cryogenic vessels have been filled	Low	Quantity is not a unit dose.
A sample of the batch label (1) Validated electronic method	Low	Reconciliation of batch labels where used, or validated electronic method
Specification of the finished product and results of quality control tests (1) specification of the finished product and results of content tests	High	Quality of product directly impacts patient safety. Key identifier of product. Result can be manipulated by retesting sample into specification.
Quantity of rejected cylinders/mobile cryogenic vessels (1) Need batch reconciliation	Low	Only relevant for traceability

Details of any problems or unusual events.	Low	Deviations and CAPA associated to quality assurance processes
Date and time of completion of the production.	Low	Traceability of product performed via batch number
Production control - Operator identifier	Low	Identification of status of training. Validation of status of the signatory.
Quality control - Operator identifier	Medium	Identification of status of training. Validation of status of the signatory.
Certification statement by the Qualified Person, operator identifier and date. (1) Date and time stamp	Medium	Identification of status of training. Validation of status of the signatory.
Number of cylinders released to market	Medium	Only relevant for traceability. Final reconciliation of quantities.

* Residual risk is based upon data integrity requirements.

EXAMPLE LIST OF DATA GENERATORS

Process step	**Device used**	**A** Attributable	**L** Legible Permanent	**C** Contemp-oraneous	**O** Original	**A** Accurate
Temperature measurement	Handheld infrared					
	Handheld thermocouple					
	Fixed infrared					
	Fixed thermocouple					
Pressure measurement	Analogue pressure gauge					
	Pressure transducer					
Flow measurement	Flowmeter					
Weight measurement	Manual read only scales					
	Weigh scales – result captured electronically					
Gas purity analysis	Portable analyser – Direct read out only					
	Fixed analyser – Direct read out only					
	Portable or fixed analyser with printed result					
	Fixed analyser – Result captured electronically					
Gas impurity analysis	Portable analyser – Direct read out only					
	Fixed analyser – Direct read out only					
	Portable or fixed analyser with printed result					
	Fixed analyser – Result captured electronically					
Personnel identification	Handwritten					
	Barcode / electronic user ID					
Date & time stamp	Handwritten					
	Electronic system					
Packaging identification & type	Handwritten barcode / ID					
	Barcode / scanned					

British Compressed Gases Association

www.bcga.co.uk