



**Number:**

**Title:**

**Title (EN):**

**Type:**

**Scope:**

**Area:**

**Country:**

**Previous Number:**

#### Document Information

**Revision:**

**Status:**

**Effective Date:**

	Standard Operating Procedure Grünenthal, 52099 Aachen, Germany			
document no.	replaces document no.	from	page	of
GL-QA-094-A020-01	HQ-QA-171-A013-01	-/-	1	7
valid from	10 SEP 2019	attachments	-/-	
Check of Regulatory Compliance of GMP Documents				

SDN05-GL-QA-094-A009-V11

Regulatory area(s)  GCP  GLP  GMP  GVP  GDP  MedDev

Other area(s)  if "x" please specify otherwise delete text

Language version  Original  Translation

Prepared by Cinzia Benelli  
Global Quality Product  
Manager  
GQA CMC

18.06.2019   
Date Signature

Reviewed by Stefania Conta  
Head CMC Compliance  
Internal Manufacturing,  
GQA CMC

20/06/2019   
Date Signature

Silvia Alvarez  
Head CMC Compliance Chile,  
GQA CMC

21/06/2019   
Date Signature

Approved by Alexandra Scheier  
Head Global QA CMC  
Compliance,  
GQA CMC

02 SEP 2019   
Date Signature

This document is the exclusive property of Grünenthal. It is to be treated as confidential and may not be reproduced either in its entirety or in part, nor may it be distributed to third persons without permission.  
/-



## Table of contents

<b>1</b>	<b>Objective</b>	<b>3</b>
<b>2</b>	<b>Scope</b>	<b>3</b>
<b>3</b>	<b>Concerned roles</b>	<b>3</b>
<b>4</b>	<b>Terms</b>	<b>3</b>
4.1	Drug Substance	3
4.2	Excipient(s)	3
4.3	Bulk product	4
4.4	Finished product	4
4.5	Contract manufacturer / Contract Manufacturing Organisation	4
4.6	Registration documents	4
4.7	Abbreviations	4
<b>5</b>	<b>Compliance check at Grünenthal sites</b>	<b>4</b>
5.1	Documents	4
5.2	Procedure	5
5.3	Discrepancies between GMP and regulatory document	7
5.4	Documentation of compliance checks on GMP documents	7
5.5	Compliance check for production at CMO	7
<b>6</b>	<b>Cross references</b>	<b>7</b>
6.1	References to standard procedural documents	7
6.2	Legal references	7
6.3	Other references	7
<b>7</b>	<b>Attachments</b>	<b>7</b>
<b>8</b>	<b>Historical index</b>	<b>7</b>



## 1        Objective

The objective of this procedure is to describe how to perform the check of compliance between GMP documentation and registration documentation.

This procedure ensures that documentation related to manufacturing, testing (including stability studies), releasing activities on drug substances/products manufactured at Grünenthal production sites or by CMOs is in compliance with registration documentation approved by the relevant competent Health Authority.

## 2        Scope

The compliance check applies to drug substances, bulk and finished products manufactured by Grünenthal or by CMOs, for its own use or for customer business.

The procedure describes the parts in the GMP documents which have to be checked for regulatory compliance with the related registration documents however due to site specific differences not all GMP exist / will be checked by each GQPM at each site.

## 3        Concerned roles

This section provides information about the concerned roles in the described process.

Concerned Role	Responsibility
Global Quality Product Manager/Coordinator (GQPM)	Review of GMP documentation from a CMC perspective i.e. Compliance Check of GMP documentation vs. registration documentation  Information of relevant departments e.g. QP/responsible person or partner if non compliances are detected and trigger deviation if needed

## 4        Terms

### 4.1      Drug Substance

Any API that will be processed in a bulk product manufacturing process.

### 4.2      Excipient(s)

Any raw material different to API, that will be processed in a bulk product manufacturing process.



#### 4.3 Bulk product

Any product which has completed all processing stages up to, but not including, final packaging.

#### 4.4 Finished product

Drug product which has undergone all stages of production including packaging in its final container.

#### 4.5 Contract manufacturer / Contract Manufacturing Organisation

A site performing aspects of manufacturing and/or testing on behalf of a contract giver.

#### 4.6 Registration documents

Registration documents are documents which were prepared, sent to Authorities as part of an MAA or NDA and that are considered "Approved" by the Competent Health Authority.

#### 4.7 Abbreviations

Abbreviations of terms used in this document are explained here:

Term	Definition/Explanation
API	Active Pharmaceutical Ingredient
BRC	Batch Release Certificate
CMO	Contract Manufacturer Organization
CMC	Chemistry Manufacturing and Control
COA	Certificate of Analysis
NDA	New Drug Application
MAA	Marketing Authorization Application
MBR	Master Batch Record
PI	Product Instruction

### 5 Compliance check at Grünenthal sites

#### 5.1 Documents

The documents that can be examined for their regulatory compliance are:

- Manufacturing documents (e.g. manufacturing formula, master batch records, PI-Sheet)
- Specification documents (e.g. release or shelf life specification, master certificates e.g. CoA, BRC)
- Test instruction documents (e.g. analytical procedure)

- Validation protocols (e.g. process validation protocol, analytical validation protocols)
- Stability protocols and reports.

## 5.2 Procedure

The reference documents for the review are the documents, which are approved by Authorities in the registration file or any available Health Authorities Certificates or any information published in the relevant Health Authorities website.

The GMP documents to be checked are provided by the relevant department or by the CMO.

For the GMP documents listed the completeness and the consistency of the information is checked as detailed below:

GMP documents	Examples	Parameters to be checked if applicable	Registration documents
Manufacturing and packaging documents	Master batch record Manufacturing formula Packaging material list PI-Sheet	<ul style="list-style-type: none"><li>• Manufacturing sites</li><li>• Amounts and kind of the components</li><li>• Batch size</li><li>• Overage</li><li>• Equipment</li><li>• Manufacturing steps</li><li>• In-process controls</li><li>• Release testing parameter</li><li>• Packaging material</li><li>• Holding times</li><li>• Storage conditions</li><li>• Shelf life</li><li>• Registry number / MA number</li></ul>	3.2.P.1 3.2.P.3.1 3.2.P.3.2 3.2.P.3.3 3.2.P.3.4 3.2.P.5.1 3.2.P.7 3.2.P.8
Specification	Release specification Shelf life specification	<ul style="list-style-type: none"><li>• Testing parameter</li><li>• Acceptance criteria</li><li>• Frequency</li><li>• Analytical procedure</li></ul>	3.2.S.4.1 3.2.P.4.1 3.2.P.5.1 3.2.P.7

GMP documents	Examples	Parameters to be checked if applicable	Registration documents
Test instruction documents	Analytical procedures	<ul style="list-style-type: none"> <li>• Methods used for Calculation formula</li> <li>• Analytical conditions</li> <li>• Equipment</li> <li>• Solutions and reference standards</li> <li>• Dilutions</li> <li>• System suitability tests</li> </ul>	3.2.S.4.2 3.2.P.4.2 3.2.P.5.2 3.2.P.7 Relevant Pharmacopoeias
Validation protocols	Analytical Validation protocols	<ul style="list-style-type: none"> <li>• Amounts and kind of the components</li> <li>• Instruction (analytical method)</li> <li>• Parameters and Acceptance criteria according to specification</li> </ul>	3.2.P.5.1 3.2.P.5.2 3.2.P.5.3
	Manufacturing process validation protocols	<ul style="list-style-type: none"> <li>• Amounts and kind of the components</li> <li>• Batch size</li> <li>• Overage</li> <li>• Equipment</li> <li>• Manufacturing steps</li> <li>• In-process controls</li> <li>• Holding times</li> <li>• Storage conditions</li> <li>• Release testing parameter</li> </ul>	3.2.P.3.2 3.2.P.3.3 3.2.P.3.4 3.2.P.5.1 3.2.P.8
Stability protocols and reports		<ul style="list-style-type: none"> <li>• Amounts and kind of the components</li> <li>• Specification including Testing parameter and Acceptance Criteria</li> <li>• Storage condition</li> <li>• Testing frequency</li> <li>• Primary Packaging Material</li> <li>• Shelf life</li> </ul>	3.2.P.5.1 3.2.P.5.2 3.2.P.8.1

Registration documents may contain less or abbreviated information compared to GMP-documents. For the regulatory compliance check at GRT it is essential that the site-



specific GMP-documents do not contain less information than the registration documents and do not exceed limits as given in the registration documents.

### **5.3 Discrepancies between GMP and regulatory document**

It is within the responsibility of GQPM and relevant functions e.g. QP/Responsible person as needed to take decisions in case of discrepancies between GMP and registration documents and to decide about further steps prior to approval of the document.

### **5.4 Documentation of compliance checks on GMP documents**

The GQPM signs the GMP document once the compliance check activity is finalized and the compliance between the regulatory and the GMP document is ensured.

### **5.5 Compliance check for production at CMO**

Grünenthal checks GMP documents of CMOs for compliance with registration documents according to the Technical Agreement.

The procedure for compliance check of GMP documents of CMOs is according to the one applied for the GRT documents.

## **6 Cross references**

Not applicable

### **6.1 References to standard procedural documents**

Not applicable

### **6.2 Legal references**

Not applicable

### **6.3 Other references**

Not applicable

## **7 Attachments**

Not applicable

## **8 Historical index**

First version

Version/ document no.	Description of changes	Valid from
01	First edition	See page 1