PHARMACEUTICAL CONSULTANCY SERVICES (PCS)

PHASE I: Layout, QMS & process establishment/review

Explanation and steps – for manufacturers/distributors of medicinal cannabis products


CONNECTING PEOPLE
TO QUALITY

OUR MEDICINAL CANNABIS PROJECT MANAGERS

PETER VAN DOORNIK

Project Manager. Specialized in setting up Quality Management Systems (QMS) for the pharmaceutical & medicinal cannabis industries.

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Project Coordinator. Creates and adheres project planning, allocates tasks and maintains overall overview of project progress.

PCS is an established, independent international consulting group based in the Netherlands. PCS was founded on November 1st, 1990. The company provides specialised services to the pharmaceutical, medical devices and related health care industries to meet current regulatory requirements.

OUR CEO

Mr. Jaap Koster, Eng.

Jaap Koster has 38 years of experience, based in various positions (including auditing and training) within (pharmaceutical -and food-) operations in USA, Asia and Europe in bulk chemicals, (aseptic) biologics, medicinal cannabis and packaging.

NOTABLE CLIENTS

NOVARTIS	MERCK	UNIDO	SUN PHARMA	GE Healthcare
Switzerland	The Netherlands	Switzerland	India	GE Healthcare USA

For 31 years, PCS has assisted both small and large organizations in achieving EMA, FDA or WHO regulatory compliance.

INTRODUCTION

This layout & process establishment/review exercise is your first step in becoming (EU) GMP compliant.

If you don't have a layout/process yet, we will guide you to an (EU-)GMP compliant layout, process and project plan. The fundamental building blocks for (EU) GMP compliance.

If you have some documents already then we'll review them. The goal of the review is to find as many fundamental problems as possible which are hampering your journey to (EU) GMP compliance.

The four most important aspects of the (EU) GMP are;

- **Process control** – understanding what you're producing
- **Cleanability (hygiene)** – how can we prevent contamination
- **Traceability** – fixing mistakes by retracing your steps
- **Integrity of data** – recording what you're doing, when doing it

If you already have a layout or process they will be reviewed against these important criteria. Each (major) item will be scored on the following scale:

- good
- to be improved
- not in compliance

After each score, a recommendation and conclusion will be made. We describe how you should improve that part of your layout/document/process.

PHASE I COMPLETION TIME

Approx. 4 weeks

THE REVIEW/ ESTABLISHMENT

THE EUROPEAN UNION EUDRALEX - EU GMP REGULATORY REQUIREMENTS

Everything PCS does follows the EudraLex requirements.
The Eudralex is like a book, it has chapters and sub-sections.
Each chapter represents a different kind of pharmaceutical product.

Medicinal cannabis falls under Chapter 4: Medicinal Products for Human and Veterinary Use.

Are you producing oils or pills? Then you have to follow Chapter 4, sub-section 1 on finished medicinal products.

When you're manufacturing and exporting (raw) flower buds, then you have to follow a combination of sub-section 1 and sub-section 2 on active pharmaceutical ingredients.

The EU regulatory requirements apply to **each member state**.

T0: THE QUALITY MANAGEMENT SYSTEM

The (EU) GMP requires you to have a **Quality Management System**.

The Quality Management System is not the most important part of GMP, but it allows you to spot potential faults early on and to trace where things went wrong, and why so that you can correct and prevent them.

The government similarly uses your Quality Management System to see whether you do what you say, through documented evidence. Your Quality Management System is supposed to show the government that you are in control of your process, quality, efficacy and patient safety.

If you already have a Quality Management System we'll review it. If you don't, we'll lay the foundations for a (EU) GMP Quality Management System.

Points of focus (a.o.)
1. Uniform document formatting
2. Document distribution and versioning
3. Compatibility with industry formats
4. Essential GMP QMS elements
5. Training on procedures and GMP
6. Supplier assessments and follow-up
7. Internal audits and their schedule
8. Data integrity
9. Good Writing Practices (GWP)
10. Referenced regulations

T0: THE QUALITY MANAGEMENT SYSTEM (ctd.)

I ALREADY HAVE A QMS

If you have a Quality Management System (QMS) based on non-EU GMP requirements or ISO standards you may already have (EU) GMP compatible elements for implementation.

For this reason, we will assess your current quality system against the (EU) GMP.

ISO quality systems have elements of management responsibilities & management involvement that can be found in the EU GMP as well.

Despite these similarities there is always a significant amount of customization needed. Copy-pasting procedures and changing their titles is not going to cut it.

DELIVERABLES

Review of current QMS

I DON'T HAVE A QMS

If you don't have a Quality Management System we'll get you started on the basics.

The basics are easier than you may think. We'll define what goes into the quality system, following which philosophy and framework.

We summarize this information in an official document called the "Quality Manual".

The Quality Manual is your first GMP document and the "Mother Plant" of your entire QMS.

DELIVERABLES

Quality Manual

A QUALITY SYSTEM IS ONLY THE TIP OF THE ICE BERG

Successful GMP implementation requires cooperation between a large number of elements

A Quality Management System is only one part of the (EU) GMP. Our approach will focus on the entire production process.

Starting with your production steps, parameters, your production philosophy, your team and finally your layout.

This exercise will provide you with a proper understanding of your (EU) GMP compliance status and what the next steps are.

T1: TEAM ASSESSMENT

Does everybody (you plan to) employ meet the basic qualifications to be allowed to work in a GMP facility?

The EU GMP has a number of requirements for personnel.

They must be frequently trained on the GMP's for example. Some key staff members need to have university degrees and a minimum amount of pharmaceutical experience.

We will examine these requirements together to determine who we'll need and who best fits those roles.

At the end of the review you'll have a solid understanding of the gap's in your team and what types of talent to attract for your project.

If you don't have a team yet we'll create a number of job descriptions and help you with the initial selection of your first staff members needed to start up the Quality Management System.

T2: BLOCK FLOW DIAGRAMS & PROCESS FLOW DIAGRAMS

Before we start looking at your layout it's important to understand your process. EU GMP inspectors don't have much time. They want to see and understand your process quickly. They expect uniform documentation and presentation methods for your process.

The commonly accepted standards in the pharmaceutical industry are;

- **Block Flow Diagrams (BFD)** – general overview of your process (the big picture)
- **Process Flow Diagrams (PFD)** – detailed overview of a process step, e.g. trimming or cutting

The first thing we'll look at is whether you have these (or similar) documents.
Subsequently we assess their quality and compliance with the (EU) GMP requirements.

Level of detail is another point of attention. Do you specify units of measurement or is everything open to interpretation?

These documents form the basis of everything; your layout, your materials, the amount of staff, staff roles, room size, room finishing, airlocks, how much waste you generate at which step and more.

This is why it's important to nail these process steps and parameters down early on in your factory establishment process.

T2: BLOCK FLOW DIAGRAMS & PROCESS FLOW DIAGRAMS (ctd.)

I ALREADY HAVE BFD'S & PFD'S

These documents can come in many forms and shapes. Some are extremely detailed, others lack any form of detail whatsoever.

The (EU) GMP requires a certain approach to your flow documents for them to be accepted as GMP documents.

We look at your flows, enter into a dialogue with your cultivation/process experts and determine how to improve the documents.

When we're done with this part of the review you will be a few steps away from GMP flows, describing your production/processing process in great detail. This allows you to have a more stable, controlled process.

DELIVERABLES

Review of current BFD's & PFD's

I DON'T HAVE BFD's & PFD's

Now that we have an idea of what your Quality Management System will look like it's time to focus on your process.

Control over your process is extremely important in GMP. It is, perhaps, the most essential GMP element. It's the first thing an inspector will look for.

How do you get in control? By knowing and understanding your process in detail. What happens where and why? This is what we will detail in flows.

These collections of flows are called Block Flow Diagrams and Process Flow Diagrams.

DELIVERABLES

Block Flow Diagrams (v1)
Process Flow Diagrams (v2)

Now we know how you will process the raw materials it's time to look at how you'll use this process to realize a finished product.
The diagrams create an overview of what happens but doesn't provide insight into how it happens.

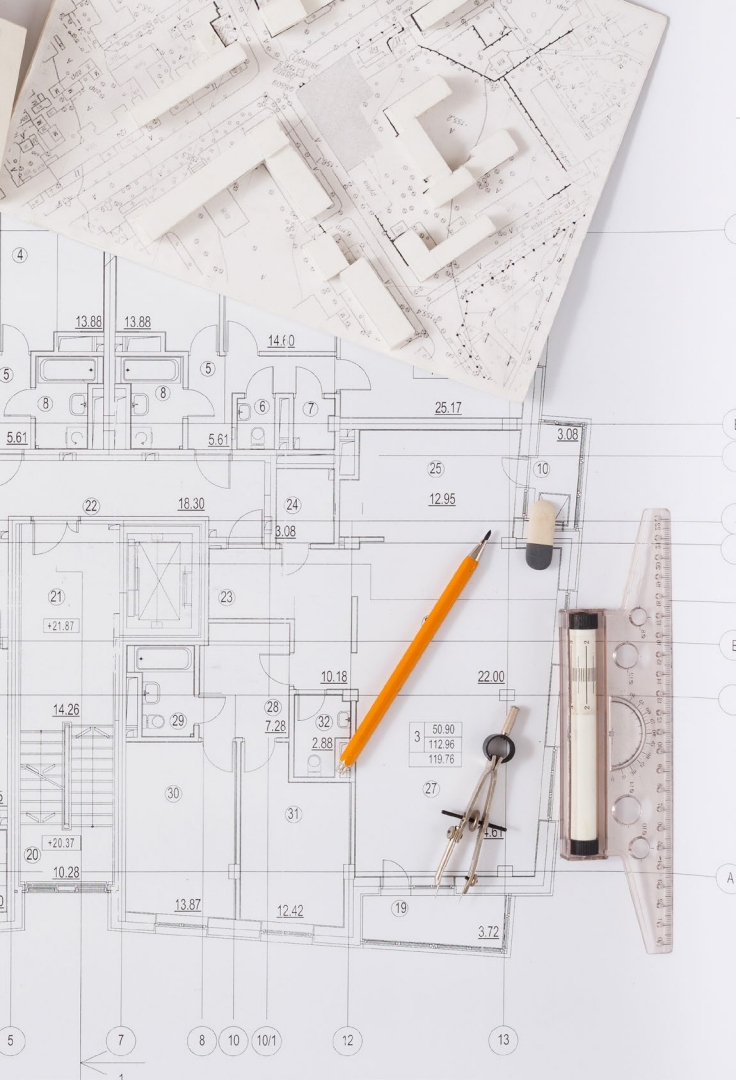
That's where the **manufacturing strategy** comes in.

The (EU) GMP expects you to think of every single factor in your process, document it and adjust your layout accordingly. As an example;

At what point in the process do we need carts to transport flowers?
How many carts do we need?
Where do we clean the carts?
How clean do the carts have to be?
Where do we store them while they're waiting to be loaded with trays?
Who picks the carts up from cleaning/storage/production? And when?

Not having answers to these questions will lead to observations from an (EU) GMP inspector.
Together we will go through your manufacturing strategy, preventing you from accidentally missing steps and the practical implications of each step.

If you don't have a manufacturing strategy yet, we'll create version 1 of your Manufacturing Strategy.



T4: LAYOUT

The (EU) GMP requires your facility to be modern, hygienic and to be fit-for-purpose.

These principles will be checked during the layout phase.

Starting construction with a GMP-approved layout reduces rework. Rework in a GMP environment increases overall costs of your facility by up to 300%.

Together with our engineering division we will review/create your layout. We cross-reference the layout with the manufacturing strategy and your process flows. If there are discrepancies we will enter into a dialogue to indicate possible failure points in your layout.

If you are already building it is important to only build the “outer shell” of the building. Leave the interior empty while your layout is under review/being made.

Besides the layout PCS assesses environmental factors which may affect patient health.

T4: LAYOUT

I ALREADY HAVE A LAYOUT

It's great to have a baseline on how you want your facility to look. In almost all cases we will need to add/change/remove rooms/corridors or other aspects as they conflict with the GMP requirements.

Man, material, waste and product flows have to be unidirectional and prevent cross-contamination for example.

If your layout allows for the criss-cross movement of product types, we're not EU GMP compliant.

During the review we'll provide practical pointers on how you can improve your layout.

DELIVERABLES

Review of layout against EU GMP requirements.

I DON'T HAVE A LAYOUT

So far we've checked off your QMS, process and manufacturing strategy.

These are the key ingredients to an EU GMP compliant layout.

Together with our engineering team we will produce a layout based on your unique process, plot dimensions and wishes.

There will be several iterations of the layout. This iteration will be sufficient to ask a contractor for a ROM budget. In Phase II we will finetune your layout even further.

DELIVERABLES

EU GMP compliant layout draft 1

T4: LAYOUT

Points of focus (a.o.)
1. Man/material/product/waste flows
2. Cleanroom zoning
3. Placement of sanitary facilities
4. Personnel air lock placement
5. Material air lock placement
6. Cross-contamination avoidance
7. Storage room for production materials
8. Warehouse quarantine area
9. HVAC placement and capacities
10. Water installation requirements

Failure modes (a.o.)
Product types crossing in corridors
Insufficient space in airlocks
Incompatible zoning (unclassified next to cleanrooms)
Sanitary facilities next to/in proximity to clean zones
Incompatible air rate changes between rooms
Possibilities for unauthorized access to production rooms
Insufficient storage space for production (and related) materials
Insufficient room for cleaning production (and related) materials
No designated quarantine area
Insufficient HVAC capacity for clean air

GMP requirements (a.o.)
No airborne contaminants by heavy industries/agriculture in surrounding environment
Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

WHERE DO WE START?

THE FIVE INITIAL STEPS

FIRST STEP	SECOND STEP	THIRD STEP	FOURTH STEP	FIFTH STEP
PCS provides a tailor-made quotation for the review	Starting the project requires signatures of both parties on the offer	Non-disclosure agreement will be signed between the parties	Planning for the first activities start, remote or on-site	Documents are exchanged for review or the consultant is on-site to jointly review/discuss in person

Completion of the review/establishment project (PHASE I):

Upon completion of the project you will have practical points to work on/a number of baseline documents to start your EU GMP journey.

The baseline documents;

- Quality Manual (QM) v1
- Job Descriptions v1
- Block Flow Diagram (BFD) set v1
- Process Flow Diagram (PFD) set v2
- Manufacturing Strategy v1
- Layout for ROM budgeting (draft v1)

If we've reviewed documents it's up to you to implement these suggestions, but remember that there is always room for differences in interpretation. PCS delivers an advice which you are free to follow in whichever way you like to.

If you would want continued support then we can create an offer for PHASE II.

NEXT STEPS

What happens in PHASE II?

PHASE II follows PHASE I

PHASE I is designed to get you acquainted with GMP requirements and to establish a baseline in documentation.

In PHASE II we will expand the existing documentation and GMP understanding so you can start ordering equipment, hire QA staff and begin building the interior of the facility.

PHASE II deliverables (include, not limited to);
- 2 Hour GMP training on Phase II for management, senior team members, including training certificate - Quality Manual (v2) GMP document - Validation Master Plan (v1) GMP document - Set of starting SOP's (approx. 5 SOP's) GMP documents - Manufacturing Strategy (v2) GMP document - Process Flow Diagram Set (v2) GMP documents - Block Flow Diagram Set (v2) GMP documents - Process Description (v1) GMP document - Layout 2nd Draft (v2) GMP document - GANTT project chart for project planning (v1) GMP document

PHARMACEUTICAL
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SERVICES

THANK YOU

FOR YOUR ATTENTION

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