

Slide 1:

"The QP – Role & Responsibilities"
Jan Bjerrum Bach, Attorney-at-Law
WWW.JUSMEDICO.COM

Slide 2:

2 TYPES OF QPs in the EC: Regulation 726/2004 (Art. 19 (1) & 44 (1)).

- 1. Manufacturing in / Import to EC/EEA; GMP-QP
(ML: 2001/83 (Art. 41 (c) + 2004/27 (Human) & 2001/82 (Art. 45 (c) + 2004/28 (Vet.))
(Importer: Directives 2001/83 (Art. 40(3) + 2004/27 (Human) & 2001/82 (Art. 44 (3) + 2004/28 (Vet.))

- 2. Marketing in EC/EEA; Pharmacovigilance-QP
(PL: Directives 2001/83 (Art. 103) + 2004/27 (Human) & 2001/82 (Art. 74) + 2004/28 (Vet.))

(Introduction:)

As an introduction to the subject of this break-out session, the inclusion of IMP's under the scope of GMP, I believe that it will be helpful if we briefly consider the legal basis for the QP system.

To do so I have set out in this slide the basic statutory authorities for the QP-system, which operates with 2 types of QP's.

The first type is the GMP-QP and the second type is the Pharmacovigilance-QP. It may be worth noting that allocation of a QP is not required for adherence to GLP, GDP and GCP, although other professional competencies are required.

Slide 3:

GMP-QP ROLE & RESPONSIBILITIES

- **The GMP-QP Guarantees:**
 - **Import Compliance (E.g. IMPs Received)**
 - **Export Compliance (E.g. IMPs Exported)**
 - **Batch Compliance (GMP-Processes)**
 - **PSF Compliance (Clinical Testing)**
 - **PL Compliance (GMP-Processes)**
 - **Record Compliance (Traceability)**

- **Direct Report to the Authorities of Non-Compliance Issues?**

- **Personal Liability (Penal Sanctions / Authorisation Withdrawal)**

1st bullet: The paramount role of the GMP-QP is to ensure that medicinal products are of the intended quality - and that the manufacturing process cannot impact safety and efficacy in a negative fashion.

At EC level the application of GMP standards for the manufacturing, importing or exporting of medicinal products has been compulsory since 1992.

Under the 1991 directive (1991/356), inclusion of IMP's was optional for the member states, but as from 1 May 2004 directive 2003/94 requires IMP's to be manufactured in accordance with GMP.

The inclusion of IMP's under the GMP scope implies that the GMP-QP – in addition to the 1991 obligations – is now also required to check releases made for clinical trial purposes. Especially for IMP's it is important that changes during development are documented and that each and every batch released can be traced should a recall situation occur. I will get back to the release issues shortly.

2nd bullet: Before doing so, however, I believe that it is relevant to consider the difficult role of the GMP-QP. On the one hand the QP is working for and is reporting to the ML holder, and on the other hand the QP responsibilities require the QP to act as a kind of public controller. This principle I believe remains controversial, as the system requires the QP to serve 2 masters.

The question therefore arises whether the QP must report negative findings directly to the authorities and thereby possibly jeopardize her relation to the ML holder.

Well, for the pharmacovigilance-QP direct reporting is required, whereas the GMP-QP is "only" required to report findings via the ML holder, who must then in turn notify the authorities, where a defect may result in a recall or supply restriction.

However, the GMP-QP has an indirect reporting obligation vis-à-vis the authorities via the obligation to maintain, preserve and disclose release journals to the authorities.

Obviously the release criteria do not include commercial considerations so there is no doubt that the system can create moral dilemmas for the QP, who may often find herself placed between a rock and a hard place.

3rd bullet: The problem is emphasized by the member states being obliged to ensure that the QPs fulfil their duties.

The QP must be made subject to appropriate administrative measures or is required to submit to a professional code of conduct. This implies that member states can require the QP's to obtain authorisation and/or withdraw the ML if the QP identified therein is made subject to disciplinary proceedings.

Both models are seen in the EC. In Denmark, where I come from, a personal authorisation as such is not issued to the QP. In stead the QP is identified in the ML, which can be withdrawn in case of irregularities. Other countries such as France operate a system with personal authorisations, whereas QP's in England in addition to being identified in the ML as QP's (as in Denmark) are made subjects to codes of conduct.

In addition most countries, if not all, operate a penal system according to which the QP can be personally fined or even imprisoned in case of negligence or wilful misconduct. In other words the QP stands in the front line together with senior management risking personal liability.

To some extent the QP is even more exposed than senior management as proving QP negligence may be easier than proving management knowledge and verbally given orders.

Disregarding inappropriate management pressure requires integrity. On a rainy day it may be worth remembering that the QP has been entrusted an important role in the safeguarding of public health, which must not be sacrificed for commercial reasons.

Slide 4:

GMP Applies to IMPs (Directive 2003/94)

IMP DEFINITION (Directive 2001/20):

- **Pharmaceutical form of API (=FP) or Placebo**
- **Used for testing or as comparator where**
 - **Authorisation not obtained for indication and/or form tested or**
 - **Additional data sought for approved form (Phase IV)**

Now, back to the IMP's.

IMP Definition: Although I believe that you are familiar with the IMP definition set out on this slide, the definition is somewhat comprehensive and at first sight it looks as if most products qualify as IMP's. Therefore it might be easier simply to define what is not an IMP.

A "not-IMP" is an approved medicinal product used in accordance with the PL. The only exception to this rule – and of course there is an exception – is that an approved product for which additional data are sought for the approved indication, is also an IMP.

Products, for which a PL has not been granted or are used in Phase IV trials, qualify as IMPs and must be treated in accordance with Annexes 13 (IMP's) and 16 (Batch Certification) to Volume IV in the EC guide on GMP. Of course Annex 16 also applies for approved products, but that is outside the scope of these comments.

The reason that special precautions have to be taken for IMP's is that during development, production routines are not yet necessarily fixed, clinical trial designs may be varied, potency and toxicity knowledge may be incomplete and the need for randomisation and blinding increases the risk of mix-up and possibly of cross-contamination. Batch certification of IMP's by the GMP-QP therefore represents a special challenge.

The challenge implies that the QP must now receive training in pharmaceutical development and processes special for clinical trials, in order to be able to release IMP's. The legislative changes imply that the QP will be working in a field where the release criteria are less stringent, as a PL has not been granted. Consequently there is greater room for discretion.

However, Annex 13 requires the QP to keep the PSF updated, i.e. the current instructions for the processing, QC testing, batch release, packaging and shipping, and sets out how the QP must handle blinding, randomisation and labelling. To make sure that the PSF reflects the CTA the QP needs unrestricted access thereto.

Slide 5:

**EC/EEA: GMP-QP IMP-Responsibilities
QP – Release Principles**

1. EC / EEA: The QP Issues BC & releases – Free circulation.
2. MRA country (E.g. CH): QP releases on basis of BC issued by "QP" in MRA country.
3. Non-MRA country (E.g. USA): QP-release only after full quality & quantity (API) control of PL compliance.

As our topic today includes free circulation, it is relevant to take a look at the IMP origin.

1. EC/EEA: Before releasing IMP's for clinical testing, the QP must certify that the batch has been manufactured and controlled in accordance with GMP (directive 2003/94), that the current PSF requirements are met and that the IMP is in accordance with the information included in the CTA submitted to the authorities.

If the IMP has been sourced from the open market in the EEA, the duties of QP are limited to checking compliance with the CTA and PSF trial related elements.

Once checked, the IMP's may circulate freely in those EEA countries, which have approved the CTA, only accompanied by a control report signed by the ML holder's QP.

2. MRA partner countries comprise Australia, Canada, New Zealand and Switzerland. The Mutual Recognition Agreements imply mutual recognition of ML's, conclusions of inspections of manufacturers, and batch certification without re-control at import.

Apart from ensuring that the provisions on certification on batch release as set out in Annex 16 to Volume IV are fulfilled, the QP may rely on the batch certification received.

3. Third Countries: If the IMP has been imported from a third country, i.e. a country outside the EEA and a country which has not entered into an MRA, then the QP must repeat all control tests prior to certification and must – possibly subject to auditing the manufacturer's quality systems - certify that the manufacturing standards applied are not inferior to the EEA standards.

If the IMP is a comparator product from a third country from which such documentation cannot be obtained, the QP must ensure that each production batch has undergone all relevant analyses, tests and checks to ensure compliance with the CTA submitted.

Having fulfilled these requirements, the QP may sign the release certificate and the batch may now freely circulate in the EC CTA member states without undergoing any further checks.

Slide 6:

**EC/EEA: GMP-QP IMP-Responsibilities
APIs / FPs / Placebo: Release Scenarios**

- **API inventor has no GMP facility, and no QP**
- **Engages CMO to do scale up and API for IMP-production for clinical trials – GMP / QP release required?**
- **API sent to neighbouring CMO for formulation – GMP / QP release required?**
- **IMP sent back to Inventor/sponsor who will send it to CRO for clinical testing – GMP / QP release required?**

The longer the supply chain is the more planning is required. Amongst criteria to consider are:

1. Which countries or regions are involved?
2. Origin of API's.
3. Which manufacturing steps take place in each country / region?
4. Which facilities and staff are involved in each country / region?
5. Which standards are applied in each country / region?

Slide 7:

**EC/EEA: GMP-QP IMP-Responsibilities
APIs / FPs / Placebo: Case**

- API inventor in the USA (3rd country) has no GMP facility, and no QP
- Engages CMO in England (EC) to do scale up and API for IMP-production for clinical trials – GMP / QP release required?
- Exported to new CMO in Switzerland (MRA country) for formulation – GMP / QP release required?
- IMP exported to EC / EEA for clinical testing by CRO – GMP / QP release required?

1st step: Today USA is a third country. If a US based inventor wishes to avail himself of the free circulation advantages in Europe, it is important that he plans his development with due consideration to the EEA, MRA and third country-regime implications. Otherwise he may soon jeopardize cost and time advantages otherwise obtainable by using the system correctly.

In our scenario the inventor has no GMP facility. Without such facility he has to rely on Annex 18, which will not include API's under the GMP scope until 30 October 2005. Only by restraining his supplies to comprise active ingredients (and other starting materials) his FP will be able eventually to comply with GMP.

Had he chosen to ship e.g. granulated product, he would not be in a position to obtain GMP-certification for the FP and consequently clinical trials in EEA would not be possible.

2nd step: To do the up-scaling, our inventor engages a CMO in England, which is the holder of a ML. For the up-scaling steps the CMO is required to adhere to GMP-standards. To release the final work product, the CMO's QP must issue a batch certificate documenting GMP-compliance, in this case in order to release the batch for shipment to CH for formulation.

3rd step: CH is an MRA country. Consequently CH will recognise the CMO's ML and the GMP certificate issued without the Swiss CMO being required to carry out any further re-control.

The Swiss CMO, which also must have an ML, formulates the IMP, which, subject to the Swiss QP certifying and releasing the batch, can then be re-exported to a CRO as FP for clinical testing without being re-analysed.

The CRO receives the IMP's as FP's. The distribution and free circulation of IMP's in the EEA may now take place in those countries, where a CTA has been approved.

Slide 8:

Conclusions

QP Responsibilities / Clinical Trials

IMP Compliance with:

- **GMP (or equivalent)**
- **Clinical Trial Application**
- **Product Specification File**

QP negligence may lead to loss of authorisation & penal sanctions

In conclusion your responsibility is to ensure GMP compliance for all products having been subject to manufacturing steps.

With respect to intermediates imported to the EEA, you will be responsible for securing that the quality is equivalent to EC GMP-standards by repeating all control tests prior to certification.

As the free circulation principles only apply for those member states in which the authorities and an ethical committee have approved the clinical trial, it is also necessary for you to verify that the product complies with the data contained in the CTA.

Finally it is necessary to ensure that the PSF has been updated to reflect the procedures eventually applied.

Slide 9:

Matthew 6:24

No man can serve two masters: for either he will hate the one, and love the other; or else he will hold to the one, and despise the other. Ye cannot serve God and mammon.

A principle for legislators to consider?

Future: No doubt that the future will hold a further streamlining of the regulatory environment for research and development activities, including quality standards.

Although I welcome this trend it is not likely to reduce the QP workload a lot.

On the contrary the pressure on the QP, who has a duty not only to her employer, but also to the relevant authorities, will remain, because the standardising advantages will be outweighed by an increase in responsibilities.

One initiative leading to a more effective release process could be relieving the QP from serving more than one master.

In a position paper from January 2004, EMEA indicated that a QP could only release an affected batch (out of specifications) subject to approval by a supervisory authority having granted the ML. However, only a very few member states have the resources to render such service, and for those which have, an answer can seldom be given within a reasonable time frame, which for commercial reasons should be no more than 2-3 working days.

Thank you for your attention.

Slide 10:

List of Abbreviations

- **API: Active Pharmaceutical Ingredient**
- **BC: Batch Certificate / Certification**
- **CMO: Contract Manufacturing Organisation**
- **CTA: Clinical Trial Application**
- **FP: Finished Product**
- **IMP: Investigational Medicinal Product**
- **ML: Manufacturer's License**
- **MRA-country: Mutual Recognition Agreement country**
- **PL: Product License (=Marketing Authorisation)**
- **PSF: Product Specification File**