New EU GMP for ATMPs vs existing GMPs – pros and cons

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Rapid implementation

- The EC adopted GMP requirements for ATMPs 22 NOV 2017
- Comes into operation 22 May 2018
- Part IV of EudraLex Volume 4

These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines.
Structure (and what it is a bit like)

Section 1 – quality systems (Chapter 1)
Section 2 – Risk Based Approach; not in Part I or annexes, not similar to ICH Q9 (Part III)
Section 3 – Personnel (Chapter 2)
Section 4 – Premises (Chapter 3 and Annexes 1 and 2)
Section 5 – Equipment (Chapters 3 and 6, and Annex 1)
Section 6 – Documentation (Chapter 4, Annexes 2 and 11)
Section 7 – Materials (Chapters 5 and 4, Annex 2, Part II)
Section 8 – Seed lots (Annex 2)
Section 9 – Production (Chapter 5 and Annex 1)
Section 10 – Validation (Annexes 11, 13 and 15)
Section 11 – QP (Chapter 2, Annexes 2, 13 and 16)
Section 12 – QC (Chapter 6, Annex 19)
Section 13 – Outsourced activities (Chapter 7)
Section 14 – Defects & Recalls (Chapter 8, Annex 2 and 13)
Not in part IV – Self Inspection (Chapter 9)
Section 15 – GMOs (Annex 2)
Section 16 – Reconstitution (Annex 13)
Section 17 – Automation (not like anything)
Those in both may vary too. Much of Part I and Annexes not included in the review.

Total standards: Facilities Utilities, equipment, Production, Qualification, Reconstitution, computers/automated
Part IV = 315
Part I & Annexes = 645
Issues with disharmony

• Difficult to understand what has actually change or remained
• Revisions to Part I-III and Annexes will not apply to ATMPs
• No longer equivalent to PIC/S guide (see letter 24 FEB 2017 next slide)
• Will our GMP inspectors even use it?
• Making both standard drugs and ATMPs – which to follow?
• Will ATMPs made in EU be excluded from MRAs?
• After Brexit, will UK GMP go back to the previous system?
  • And if so could UK-ATMPs remain in MRAs?
The PIC/S Committee is unanimously concerned about the impact on public health and for the safety of patients that the ATMP GMP Guideline will cause. By lowering the GMP requirements for ATMPs, the European Commission is not only exposing patients to an increased risk to their health; it is also engaging its individual and collective responsibility for any health incident (and related court action) that lower ATMP standards may occasion. We would like you to duly ponder this aspect.
Are the GMP requirements really *lower*?

- Need a side-by-side comparison (has anyone done this? PIC/S?)
- What have we lost?
- What have we gained?
- What has remained but changed grossly?
The pros and cons

I apologise that the remainder of this presentation is very very dry, and has just a few highlighted examples of the changes. I will share my comparison file but each time I look at it I find more issues
Section 1 - PQS

Pros
• None

Cons
• Nobody ultimately responsible for PQS (e.g. senior management)
• Does not refer to ICH Q10
• Poor/no guidance on: RCA; knowledge retention; PQR; GDP; management review; QC; sampling
1.25 – Self-inspection (as in Chapter 9)

Pros

• None

Cons

• No list of topics to include in the schedule
• No need for independence of review
Section 2 – RBA (QRM in Part Q9)

**Pros**
- Water simulation for particulates – filter liquids
- Extra validation emphasis for two-stage certification

**Cons**
- For IMPs documentation can be informal and lack detail
- No RA tools
- Not always appropriate to assess risks formally
- A over C for IMPs (exceptionally unlikely)
- RBA in MA can be trumped by GMP inspection
Section 3 – Personnel

**Pros**
- New obligation for knowledge of the product in training
- For GM – new role for biosafety appointed by senior management

**Cons**
- No senior management responsibilities
- *Discard garments before leaving containment area* [technically challenging]
- No requirement for organisation chart; JDs; PQS training; medical examination; visitor supervision;
Section 4 – Premises

Pros

• Grade D particle limits must be set (previously ‘not defined’)
• Adopted PIC/S Grade A micro-ID requirement
• No poison production
• Segregate replication competent viruses

Cons

• [multi-product/batch] Separated expulsion of exhausted air from the incubator
• Lost guidance on; beta-lactam; clean-up period; radius-of-bend; pressure monitoring
• Flawed assumption of low risk for non-viral vectors
• Lost RCR/RCL test requirement
Section 5 – Equipment

Pros
• New guidance on decontamination of moved production equipment

Cons
• Lost some cleaning and maintenance standards
Section 6 – Documentation

Pros
• SEC-DI on final label
• 30 y traceability for xenogeneic starting cells [not in 1394/2007]
• New video format for documents
• Clear guidance on blinding instructions
• Line clearance recorded in BMR

Cons
• Lost ‘clear, legible, indelible, alterations permitting reading of the original’
• Much of Annex 11 electronic data integrity guidance lost
• No printed materials guidance
• BMR standards watered down
• No mention of packaging record
• PSF contents omitted
• No SOP for: receipt; tech-transfer
Section 7 – Starting / Raw materials

**Pros**

- New guidance on research-grade materials
- TE processing steps acceptable to make the cells available (washing/preservation)
- New guidance on *critical* [not defined*] raw materials
- Emphasis on TSE and mycoplasma

* e.g. sera, growth factors, enzymes (e.g. trypsin), cytokines

**Cons**

- No audits of / agreements with / approval and maintenance of suppliers
- No procedure guidance for raw material receipts/checks
- No mention of records for materials
Section 8 – Seed lots / cell banks

Pros

• Extra stability data guidance
• Cell stock changes require *authorisation* as well as validation

Cons

• Testing into compliance for banks made before 1394/2007 (needs authorisation)
Section 9 – Production

Pros

• Deviation investigation must involve QP
• WFI is appropriate
• Gasses must be pharmacopoeial
• Some nice new guidance on PSTs taken from PI-007
• Cross refs Annex 1 (sterilisation)
• Cross refs Annex 12 (ionizing radiation)
• Inform CA if ATIMP reprocessing

Cons

• Technical/organisational measures watered down
• Confusing guidance on closed systems (e.g. bags)
• Use in-line pre-tested filters for adding aseptic liquids
• No controlled format for labels
• GMP in an operating theatre?
• PST start-up lost 6-week window
• No reconciliations / yields / limits
• No premises access restriction
Section 10 – Qualification / Validation

**Pros**
- Surrogate materials for process validation
- Premises revalidation for new products

**Cons**
- QbD principles and hybrid approach omitted
- No mention of VMP
- No LLOD or LLOQ
- No concurrent validation guidance
- No guidance on: PQR; packaging; utilities; change control
- No carryover – toxicological evaluation
Section 11 – Qualified Person

**Pros**
- New guidance on decentralised production including ‘central site’
- New guidance on third-country testing of starting materials

**Cons**
- Routine duties reduced from 21 to 14, omits: supply-chain doc; API requirements; records complete; OOT/OOS resolved; complaints; technical agreements
- No check that MIA permits certification
- Bad guidance on releasing OOS products
- Lost requirements for CPD
- Lacks guidance on audits of outsourced production
- Nothing on parallel imports
- No example certificates
Section 12 – Quality Control

**Pros**

• Reference samples may be stored differently from product to maximise stability/retesting
• Label copies/photos for (autologous) retention samples
• Practical guidance on samples of starting materials
• Surrogate batches for ongoing stability
• Define critical raw materials and keep samples

**Cons**

• No independence-of-function requirement
• No OOS/OOT LIR guidance
• Diluted guidance on reference samples and retest-capability, and no Ann13 storage time (2y after end of trial)
• Documentation requirements absent
• No QC reagent management guidance (e.g. GPT for media)
Section 13 – Outsourced Activities

Pros
• New guidance on contracts clearly stating responsibilities for quality defects and traceability

Cons
• GMP-certificate not needed (exceptionally) for QC contract acceptor
• No obligation to review CA performance
• Poor subcontract guidance
• ‘The Contract’ guidance omitted
Section 14 – Defects and Recalls

Pros

• Recall procedures to be in technical agreements with CMOs
• Action plan for defects found post-administration

For IMPs, the responsibility for unblinding only the minimum amount has been transferred from the Sponsor to the manufacturer

Cons

• Inferior SOP and report guidance for complaints
• No guidance on adverse events (i.e. not a quality defect)
• Mock recalls not appropriate if time to administration is short
• No longer obliged to contact CA when a defective batch is not actually recalled (e.g. short shelf life)
• Complaints staffing obligations omitted
• No guidance on centralised complaints department
• No guidance to avoid human-error root cause
Section 15 – Containment for GMOs

Pros

• New requirement for GM risk assessment (e.g. HSE)
• New guidance on containment measures in Risk Management Plan (authorised ATMPs)

Cons

• No guidance on traceability from plasmid to DP
Section 16 – Reconstitution

**Pros**

- New guidance extends to thawing, washing, removal of DMSO and filtering
- Guidance on reconstitution process validation
- Reconstitution advice applies to both ATIMPs and authorised ATMPs

**Cons**

- No longer states that reconstitution has to be undertaken as soon as practicable before administration
Section 17 – Automation

**Pros**

- All new guidance
- CE mark is no substitute for validation
- Maintenance under technical agreement
- Media simulation

**Cons**

- Fails to cross reference Good Automated Manufacturing Practices (GAMP 5 Guide)
No sections for...

• Part II – APIs – probably not applicable anyway
• Part III – SMF/MRA QP certificate/IMP release templates, Q9, Q10, excipients, exposure limits...
• Annexes that are not necessarily applicable: radiopharma, veterinary, gases, herbals, liquids creams ointments, aerosols, ionising radiation, blood products, parametric release
Does Part IV contain lower standards?

• Yes – at least less guidance, and fewer requirements
• There are fewer pros than cons
• Some new guidance is poor and technically unintelligible

• PIC/S concerns are valid