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Comments

Consultation Document on the development of Good Manufacturing Practice for Advanced Therapy Medicinal Products

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General Comments

The German Pharmaceutical Industry Association (BPI) is grateful for the opportunity to comment on the above-mentioned consultation.

BPI represents the majority of Germany's industry in the field of cell-based Advanced Therapy Medicinal Products (ATMP), nearly all of these companies being SMEs. Therefore, the comments of BPI represent the voice of SMEs that are especially invited to comment on this consultation by the Commission.

In general it is seen positively that the European Commission is thinking about the development of Guidelines on Good Manufacturing Practices for ATMP. Apart from that, the question is not if those specific Guidelines should be developed or not as this is clearly demanded in Article 5 of Regulation (EC) 1394/2007. The question is therefore not "if" but "how".

In the introduction of the consultation document it is said that the described GMP requirements should apply to manufacturers of ATMP for commercial distribution in accordance with the terms of a marketing authorisation ("commercial ATMP"), as well as to manufacturers of ATMPs to be used in clinical trials ("investigational ATMPs") (lines 69-72). The wording "commercial ATMP" as a borderline to "investigational ATMP" should not be used. It would be better to use the term "authorised ATMP" instead. The reason for that is that the term "commercial" is not a regulatory term and could – especially not always having the underlying definition in mind – lead to misunderstandings that those requirements are not valid for products that are not necessarily commercalised - e.g. in a non-industrial setting - although they need to be centrally authorised. That should be avoided. For example in

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Chapter 4.2.2 in line 214/215 the following is stated: „For commercial production of ATMPs, the premises should be fully validated." We assume that it is the intention to distinguish between "investigational ATMP" and "authorised ATMP". But the sentence as it is could be misunderstood that for non-commercial production e.g. in a non-industrial setting and although a centralised marketing authorisation would be needed, full validation is not necessary.

Although the authors of the document seem to have the idea to distinguish between GMP requirements for "investigational ATMP" and "authorized ATMP" in the Introduction this distinction is not followed thoroughly when it comes to the chapters with the more detailed GMP requirements later in the paper. It would be welcomed to be a bit more precise in this regard.

Although it is understood that a future guidance cannot be applicable directly to ATMP under the hospital exemption due to legal reasons it is not seen why this is especially emphasized in the Introduction. Therefore it would be better to delete the sentence in lines 73/74.

It is described in the Introduction that early phases of research may take place in a hospital setting operating under a quality system different from the quality system typical for the pharmaceutical sector. In general it has to be said that GMP requirements as such are either important for safety reasons for all patients or not. Although the sentence describes a factual reality it would not be acceptable to misunderstand it in a way that there are two different levels of standards: one for industrial production and one for production outside the industrial field. We would like to point out that a similar discussion took place within the review of the legal requirements for clinical trials where some voices said that clinical trials in academic research should be conducted to "other" standards than it was required for with regards to industrial research. In Whereas 81 of Regulation (EU) 536/2014 it is now clearly stated: "In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors." And the German version makes it even more clear stating: "Um den wertvollen Beitrag dieser nichtkommerziellen Sponsoren optimal zu nutzen und sie zu weiterer Forschung zu animieren, sollten die Mitgliedstaaten Maßnahmen zur Förderung von klinischen Prüfungen

ergreifen, die von solchen Sponsoren durchgeführt werden; Zugeständnisse bei der Qualität der klinischen Prüfungen sollte es aber nicht geben.“

In lines 147-156 a double regulation concerning the risks of genetically modified organisms should be avoided as the provisions of the genetic engineering laws already cover these risks (e.g. Directive 2009/41: Art. 4 (2) and Annex III, Annex II Part B, Annex IV; Section 6 Gentechnikgesetz (GenTG), German Genetic Engineering Act). It should be avoided that the qualified person is also responsible for the genetically modified organism within the genetic engineering plant, if the authorized person for biological safety and the project leader are already responsible (Section 3 Nos. 8-9 GenTG).

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Answers concerning the given questions

Question 1: Yes.

Question 2: No. As there is a specific Guidance available regarding this topic redundancies should be avoided.

Question 3: No answer. Concerning the JACIE accreditation system it can be said that this system provides a very detailed set of standards that are independently audited and maintain the quality of the tissues and cells and so should be recognised as a suitable standard to help assess for safety and reproducibly processing and testing cellular products. It would be down to the manufacturer to determine if suitable based on their requirements.

Question 4: Yes.

Question 5: In general yes. But in line 231 there is a reference to ISO 14644, however there is no reference to Annex 1 EU GMP for microbiological limits and definition of grades. Apart from that the information in line 232 is vague as it implies early stage trials can be performed in a different environment. It is not always known upfront if a trial will be a pivotal study or not. In general there should be some reference to the potential use of isolator technology as this is an area of interest for the manufacture of ATMP's from both an aseptic and containment perspective. Apart from that in line 234 a definition for large scale should be given.

Question 6: In general no, but a universal definition of open, closed and functionally closed system would be useful.

Question 7: No.

Question 8: No, we do not think the background for grade A should be downgraded from B to either C or D for early phases. It should be noted however that functionally closed systems can be operated in clean room areas grade C or D, irrespective of the product's lifecycle stage.

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Question 9: Yes.

Question 10: In general yes. But concerning line 316 the term “Product Information” could be misleading as it is widely used for the documents accompanying the product upon shipment. The statement in lines 337 to 339 is welcomed. In lines 417-419 the note is unclear. And in line 438 we have the question why the 30 year traceability requirement is only applicable to cell based products.

Question 11: No.

Question 12: The requirement for a contract and quality agreement for each biological raw material in a less defined process is too stringent. This should at least be risk based.

Question 13: In general yes. But in line 452 this should read "5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS" currently in draft. In lines 466 and following. the acceptance of licensed establishments without an audit requirement is fully endorsed. And in lines 481-484 we are not sure why this is specific to cell-based products. It should apply to any ATMP where sterilization is not possible.

Question 14: Yes. In lines 530-532 evidence of stability may occur concurrently for investigational ATMPs.

Question 15: In general yes.
But in line 611 'preferably is a standard format throughout the facility' should be deleted. There is evidence to show that changing the style and appearance of different labels can reduce errors.
In line 618 the sentence "Mix-ups of dedicated (autologous) materials should be prevented" should be changed to materials for individual patients or equivalent. Mix-ups of all materials should be prevented but just as important for an allogenic product for a specific patient. Not always autologous.

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In line 628 ‘separation in place’ is somewhat vague. Allowances should be made where certain product stages require incubation of products in the same space. It may not be feasible to separate each lot of a given product, particularly for small scale individualised patient production. Some degree of risk assessment should be performed e.g. depending on whether the incubation is performed in an open or closed state. Add to the separation requirement "unless completely closed processing is applied".
In line 648 cleaning validation is not appropriate to be conducted between every batch of a cell-based product where individualised patient products are made using single use disposable items of equipment. This should apply to all ATMPs not just cell-based ones.
In line 652 we do not believe this is true if closed vessels are used for centrifugation.

Question 16: In general yes, but in line 724 it should be clarified that in line with the expectation that investigational ATMPs will not be validated to the same extent as authorised ATMPs the same applies to changes made.

Question 17: Agreed. A pragmatic approach must be applied. For early stage development prospective validation may only be possible using simulated starting material or that from healthy donors and this may be different from starting material used to manufacture products for clinical use. A concurrent validation approach may be more applicable with regular reviews of data from the manufacture of clinical lots.

Question 18: Yes.

Question 19: No.
In Line 895 there may be a need for some flexibility around the total independence of QC and production in the case of very small scale manufacturing for investigational ATMPs. QC activities must be performed by a trained individual independent of that specific production activity.
In line 924 some guidance is needed for the manufacturing of individualised patient products where a single or very few units are produced. The retention and reference samples cannot always be fully representative in that for an individual patient product only one unit may be manufactured.

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In line 928 the retention of primary packaging and some expensive (non-biological) reagents ordered and made on demand is a huge burden and of very limited value and due to sampling constraints (one item only) rarely helpful in quality defect investigations.
In line 938 it is not practical to retain samples of biological starting materials for individualised patient products.
In line 957 in the same way processes may not be fully validated for investigational ATMPs the same should apply to test methods. Those concerned with safety should be at all stages. Other tests may be performed for information only and may not be validated at this stage of product development.
In line 985 it is stated that trending is not required for investigational ATMPs however this should be performed at all stages to determine what is important to product quality and what may not be.
In line 1000 there should be guidance on stability expectations for investigational ATMPs.

Question 20: Yes.

Question 21: Yes.

Question 22: Yes.

Question 23: Yes, for both ATMPs and ATIMPs.

Question 24: Reconstitution may encompass: dissolution or dilution with solvent; thawing, transfer to infusion bag, syringe; but not buffer exchange.

Question 25: The automated production raises a lot of questions. It would therefore be useful to have a scientific discussion about that topic separately.

The development of automated single-use technologies does not only affect ATMP-development and –manufacturing, it also impacts the premises. Together with the automated closed-systems “ballroom” facilities are evolving as an alternative concept to classical plants.

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Since automated single-use closed systems protect the product and the process from the environment, ballroom plants need less segregation and less classified containment to manufacture different products simultaneously – the final products are mostly patient-specific without need for upstream and downstream processing. High control of contamination/cross-contamination through the closed system is the main driver of this concept.

Together with these novel multipurpose ballrooms and automation as quality improver per se, manufacturers have greater flexibilities in responding to frequent product changes which are not unusual for complex esp. investigational ATMPs, so premises and manufacturing could “follow the biology” faster and more easily. Innovative therapies need these favorable smart environments and automated systems to contribute to smaller footprints, reduced costs and faster start-ups, thus ultimately enabling promising therapies for patients more quickly than conventional concepts.

In general, there should be no objections against a closed-system manufacturing in Class C or D with remaining (theoretically or formally) open steps handled A in C or D, as long as the process has been validated, risk-assessed and media-fill-tested. Even point-of-care models in less classified but controlled environments should be regarded as valid future concepts for ATMPs.

Such devices should be installed by qualified personnel from the supplier incl. IQ/OQ documentation where possible. An annual service and/or calibration should be performed which, alongside in process controls and strict quality specifications, should ensure correct performance of the device.

However, the process must be thoroughly assessed for risks especially remaining open processes that could affect the closed system status - the linchpin of the whole concept - must be addressed carefully (e.g. due to IPC/QC sampling, preparation of buffer/media, buffer/media exchange during processing, final formulation etc.).

A sophisticated barcode-label-documentation system or equivalent to prevent mix up of materials (starting and raw materials, excipients, final product) including IPC-, QC- and backup-sample handling is also required. National blood banks could be a reference for this.

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An important issue that also has to be addressed for automated ATMP-manufacturing is the question of who has the ultimate responsibility for the quality of the drug product in case of failures. Where possible, certified medical devices can be used, in which case liability of all non-variable and site unspecific performance is obligated to the supplier under the Medical Device certification but any variable or adapted element of the device or supplied protocol would necessitate the transfer of responsibility to the ATMP Manufacturer and a risk-based approach. For EU member states the Qualified Person who certifies and releases the batch is one important responsibility partner. Other important players are manufacturers, marketing authorisation holders, sponsors of clinical trials and of course the tool providers themselves who are enabling closed automated production. Especially attention has to be given to automated systems including software that has been designed specifically for the individual user. A responsibility split should clearly provide transparency for all the partners within this multi-edge figure.

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