GMP-Z Hoofdstuk Deel IV Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Inleiding
Onlangs is een GMP-richtlijn verschenen specifiek voor ATMP's. De titel van deze richtlijn is 'Guidelines on Good Manufacturing Practise specific to Advanced Therapy Medicinal Products'. De richtlijn is 22 november 2017 aangenomen en is per 22 mei 2018 van kracht. Er is veel overlap met de reguliere GMP. De GMP voor ATMP's geldt zowel voor geregistreerde producten als ook voor IMP's.
Op dit moment bereiden enkele ziekenhuizen ATMP's. Hierbij is de volledige richtlijn van toepassing. Het heeft geen meerwaarde om de GMP voor ATMP's toe te voegen aan de GMP-Z anders dan de vermelding dat de GMP voor ATMP's onverkort van toepassing is.

In hoofdstuk 16 'Reconstitution of product after batch release' wordt aangegeven dat dit niet onder GMP hoeft plaats te vinden. Reconstitutie wordt beschreven in het IMPD of in de SmPC. Reconstitutie mag niet worden uitbesteed en wordt alleen als reconstitutie beschouwd als het plaats vindt op de locatie van toediening.

GMP item	Gewijzigd richtsnoer GMP-Z	Toelichting
16 Reconstitution of product after batch release		
16.10. Reconstitution activities can be performed at the administration site (e.g. in hospital pharmacies) outside a GMP environment	NVT	
16.11. For the purposes of these Guidelines, the term "reconstitution" covers activities required after batch release and prior to the administration of the ATMP to the patient, and which cannot be considered as a manufacturing step. No activity that entails substantial manipulation can, however, be considered reconstitution (e.g. cultivation). Substantial manipulations should be conducted under GMP.	NVT	
16.12. The following are examples of reconstitution activities relevant for ATMPs. It is stressed that these examples cannot be extrapolated to medicinal products other than ATMPs: Thawing, washing, buffer exchange, centrifugation steps necessary to remove preservation solution (e.g. DMSO), removal of process related impurities (residual amount of preservation solution, dead cells)	NVT	

including filtering. □ (Re)suspension, dissolution or dilution with solvent/buffer, dispersion. □ Mixing the product with patient's own cells, with an adjuvant and/or with other substances added for the purposes of administration (including matrixes). However, the mixing of a gene therapy vector with autologous cells is a manufacturing activity that should be conducted under GMP. □ Splitting the product and use in separate doses, adaptation of dose (e.g. cell count). □ Loading into delivery systems/surgical devices, transfer to an infusion bag/syringe.		
16.13. The above steps can only be part of the reconstitution process if it is appropriately justified that these steps cannot be performed as part of the manufacturing process before batch release without negative impact on the product. Additionally, the above activities can only be considered "reconstitution" when they are carried out at administration site (i.e.it is not acceptable to have these steps outsourced to a third party that is not GMPcompliant).	NVT	
16.2. Obligations of the ATMP manufacturer in connection with reconstitution activities		
16.14. The manufacturer, or –as appropriate- the sponsor or marketing authorisation holdershould describe the reconstitution process, including equipment to be used and requirements at the site of administration. The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product (e.g. when the reconstitution involves thawing, the waiting period at room temperature, the rate of temperature change during thawing, use of water bath, etc. should be described).	NVT	In voorkomende gevallen kan worden beoordeeld of GMP-z voorzieningen voldoende zijn
16.15. Likewise, when the reconstitution	NVT	

requires the use of solvents and/or other materials these should be specified or, as appropriate, provided.		
16.16. In the case of authorised ATMPs, the manufacturer should validate the reconstitution processes to be followed from the point of batch release to the moment of administration to the patient; i.e. through appropriate studies it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent so that the product can be administrated without negative impact on quality/safety/efficacy profile of the ATMP.	NVT	
16.17. The compliance of the administration site with the defined reconstitution process falls outside the responsibility of the manufacturer and is also outside the scope of GMP.	NVT	