



imagination at work

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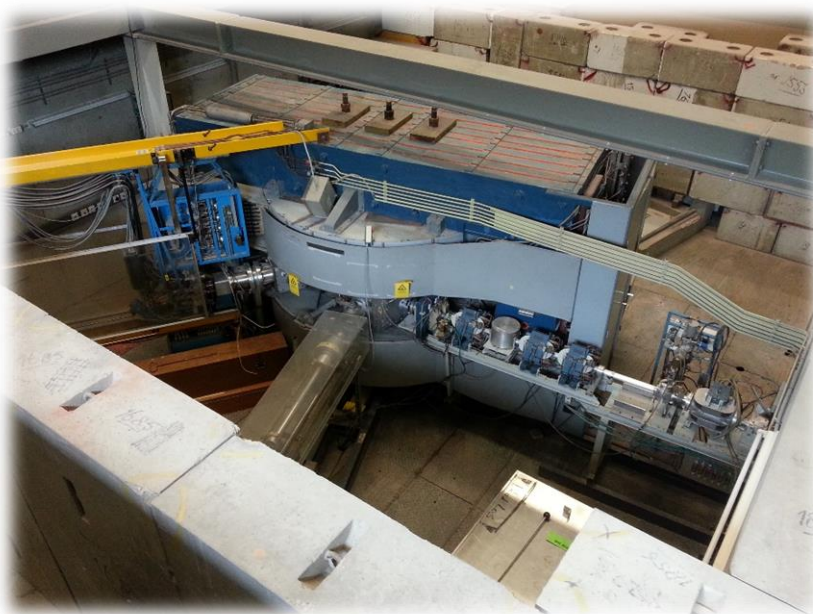
***Labelingspercentage en radionuclidische
zuiverheid van door gezuiverd H₂O¹⁸
geproduceerd 18F-FDG.***

In opdracht van General Electric Healthcare, Eindhoven

*In samenwerking met Fontys Paramedische Hogeschool,
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VOORWOORD

Deze casestudie vond plaats als afstudeeronderwerp binnen General Electric Healthcare in het kader van afstuderen bij de opleiding Medische Beeldvorming en Radiotherapeutische Technieken aan de Fontys Paramedische Hogeschool te Eindhoven. Het is voor mij een leerzame en leuke periode geweest waarbij ik achter de schermen heb kunnen kijken hoe de productie en innovatie van radioactieve tracers verloopt.

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Paul Leyzer

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SAMENVATTING

Inleiding:

Bij General Electric Healthcare (GE) te Eindhoven wordt middels een Cyclotron generator de radioactieve tracervloeistof ^{18}F -FDG geproduceerd. Voor dit productieproces wordt bij GE kostbaar verrijkt water (H_2O^{18}) gebruikt. Het H_2O^{18} kan slechts eenmalig voor productie gebruikt worden omdat er door het bestralingsproces (radionuclide) verontreinigingen in ontstaan. Om kosten te reduceren wil GE gebruik maken van gezuiverd H_2O^{18} . Bovendien dient dit door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG aan de eisen te voldoen die GE stelt. Hieruit volgt de onderzoeksvraag: *In hoeverre verschilt het ^{18}F -FDG labelingspercentage en de radionuclidische zuiverheid van ^{18}F -FDG geproduceerd uit gezuiverd H_2O^{18} in vergelijking met ^{18}F -FDG geproduceerd uit virgin H_2O^{18} ?* Tevens is onderzocht of de radionuclidische zuiverheid aan de $\geq 99\%$ eis voldoet die GE stelt.

Methode:

In dit kwantitatief experimenteel onderzoek zijn 3 batches ^{18}F -FDG door destillatie gezuiverd H_2O^{18} geproduceerd. Deze zijn gemeten op ^{18}F -FDG labelingspercentage en op radionuclidische zuiverheid. De verkregen data is vergeleken met 239 batches uit 2014 door regulier (virgin) H_2O^{18} geproduceerd ^{18}F -FDG. Voor de radionuclidische zuiverheid zijn deze vergeleken met 20 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG en gemeten middels een gammaspectrometrie opstelling. De bestralingstijd is door beperkte middelen voor de 3 batches gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG beperkt tot 1 uur. De 239 batches uit 2014 en de 20 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG hadden een variabele bestralingstijd. Om vermenging van gezuiverd H_2O^{18} met virgin H_2O^{18} te voorkomen zijn de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG op een ander target te bestralen.

Resultaten:

Het ^{18}F -FDG labelingspercentage van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG hebben een ^{18}F -FDG labelingspercentage van 65,6%, 71,0% en 68,8%. Dit is 9,03%, 3,63% en 5,83% lager dan het gemiddelde 74,63% ^{18}F -FDG labelingspercentage door virgin H_2O^{18} geproduceerd ^{18}F -FDG. De 3 batches vallen dan ook niet binnen de standaarddeviatie van 3,091%. De radionuclidische zuiverheid van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG zijn voor alle 3 de batches 100%. De 3 batches gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG scoren hoger dan het gemiddelde van $>99,99\%$ door virgin H_2O^{18} geproduceerd ^{18}F -FDG en vallen binnen de standaarddeviatie van $<0,01\%$. Tevens voldoen zij aan de radionuclidische zuiverheidseis van $\geq 99\%$ die GE stelt.

Conclusie:

Uit de resultaten van de casestudie lijkt dat het ^{18}F -FDG labelingspercentage van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG lager is dan het gemiddelde ^{18}F -FDG labeling door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Voor de radionuclidische zuiverheid van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG is er sprake van een nihil verschil in vergelijking met de radionuclidische zuiverheid van door virgin H_2O^{18} geproduceerd ^{18}F -FDG.

ABSTRACT

Preface

General Electric Healthcare Eindhoven (GE) produces the radioactive tracer fluid ^{18}F -FDG with the use of a cyclotron generator. This production uses costly enriched water (H_2O^{18}). This enriched water can only be used once because of radionuclidic impurity's being formed during the production process. To reduce costs GE wants to use purified H_2O^{18} for the production of ^{18}F -FDG. For purified H_2O^{18} to be used in the production of ^{18}F -FDG it needs to meet specific requirements set up by GE. Therefore a research question is formed: *How much does the ^{18}F -FDG labeling percentage and radionuclidic purity from purified H_2O^{18} produced ^{18}F -FDG differ from virgin H_2O^{18} produced ^{18}F -FDG?* At the same time we examined if the radionuclidic purity met the requirements of $\geq 99\%$ that GE demands.

Methods

In this quantitative experimental case study we produced 3 batches ^{18}F -FDG with the use of purified H_2O^{18} . The 3 batches were measured for ^{18}F -FDG labeling percentage and radionuclidic purity. After that they were compared with the ^{18}F -FDG labeling percentage from 239 regular produced batches from 2014. The radionuclidic purity from purified H_2O^{18} produced ^{18}F -FDG was compared with 20 batches by virgin H_2O^{18} produced ^{18}F -FDG and measured with a gamma spectrometry device. Because of limited resources the irradiation time for purified H_2O^{18} produced ^{18}F -FDG was set for 1 hour. The 239 batches and 20 batches from virgin H_2O^{18} produced ^{18}F -FDG had an irradiation time that was variable. To prevent a mixture of virgin H_2O^{18} and purified H_2O^{18} a different target was chosen to produce the 3 batches from purified H_2O^{18} produced ^{18}F -FDG.

Results

The labeling percentage of the 3 batches purified H_2O^{18} produced ^{18}F -FDG was 65,6%, 71,0% and 68,8%. This is 9,03%, 3,63% and 5,83% lower than the average of 74,63% found in virgin H_2O^{18} produced ^{18}F -FDG. Therefore the 3 batches purified H_2O^{18} produced ^{18}F -FDG did not fall within the standard deviation of 3,091%. The radionuclidic purity of the 3 batches purified H_2O^{18} produced ^{18}F -FDG was 100% for all 3 of them. They also scored higher than the average of $>99,99\%$ found in virgin H_2O^{18} produced ^{18}F -FDG and fall within the standard deviation of $<0,01\%$. Therefore they meet the requirements of $\geq 99\%$ that GE demands for radionuclidic purity.

Conclusion

From the results of the case study it seems ^{18}F -FDG labeling percentage from purified H_2O^{18} produced ^{18}F -FDG is lower than the average ^{18}F -FDG labeling percentage found in virgin H_2O^{18} produced ^{18}F -FDG. For the radionuclidic purity there is nearly a difference between purified H_2O^{18} produced ^{18}F -FDG and virgin H_2O^{18} produced ^{18}F -FDG.

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1: INLEIDING

Fludeoxyglucose (^{18}F -FDG) is het meest gebruikte radiofarmacon bij Positron Emissie Tomografie (PET) onderzoeken (1). Deze tracer vindt zijn plaats binnen de diagnostiek voor het diagnosticeren van verschillende vormen van kanker. Het nuclide dat hiervoor gebruikt wordt is Fluor-18 wat wordt geproduceerd in een cyclotrongenerator. Voor dit productieproces wordt bij General Electric Healthcare (GE) verrijkt water (H_2O^{18}) in een target geplaatst en vervolgens met protonen bestraald door een cyclotrongenerator met een spanning van 18 MeV en een stroomsterkte van maximaal 350 μA over een tijdspanne van maximaal 3 uur (2-4). Door de bestraling vindt er in het H_2O^{18} een nucleaire reactie plaats. Een H^+ proton afkomstig uit de cyclotron wordt op de kernen van ^{18}O geschoten waarna er een neutron wordt afgestoten. Hierdoor verandert het ^{18}O in ^{18}F . Nadat het H_2O^{18} is bestraald door de cyclotrongenerator wordt het ^{18}F geëxtraheerd uit het H_2O^{18} . Het H_2O^{18} wordt slechts eenmalig voor productie gebruikt omdat er door het bestralingsproces (radionuclide)verontreinigingen bestaande uit ^{109}Cd , ^{55}Co , ^{56}Co , ^{57}Co , ^{58}Co , ^{51}Cr , ^{52}Mn , ^{54}Mn , ^{57}Ni , $^{182\text{m}}\text{Re}$, ^{183}Re , ^{186}Re , ^{95}Tc , $^{95\text{m}}\text{Tc}$, ^{96}Tc , Cl , Na^+ , K^+ , Ca^{2+} tijdens de bestraling van het H_2O^{18} hier in kunnen ontstaan (1, 5). Deze (radionuclide) verontreinigingen kunnen een weg vinden naar de synthese van ^{18}F -FDG en hebben een effect op de ^{18}F -FDG productie omdat ze tijdens de synthese verbindingen aan gaan met het FDG (1, 6, 7). Hierdoor wordt er bij hergebruik minder ^{18}F -FDG gewonnen wat resulteert in een lager ^{18}F -FDG labelingspercentage (1, 6-8). Dit maakt het produceren van ^{18}F -FDG tot een kostbaar proces is doordat het H_2O^{18} voor elke bestraling maar slechts eenmalig gebruikt kan worden (1). Het H_2O^{18} wordt extern ingekocht en vormt een grote kostenpost in het productieproces van ^{18}F -FDG. Indien het H_2O^{18} gezuiverd en vervolgens hergebruikt zou kunnen worden zou dat wellicht een aanzienlijke kostenbesparing kunnen opleveren.

In de afgelopen 15 jaar is er veel onderzoek gedaan naar het hergebruik en zuivering van H_2O^{18} . Zo zijn er in de literatuur twee methoden beschreven van zuivering. De eerste door middel van destillatie, een tweede met behulp van een ionenwisselaar (6, 9). Deze twee manieren maken het mogelijk om gebruikt H_2O^{18} te hergebruiken in de productie van ^{18}F -FDG (6, 8, 9).

Asti et al. (9) heeft voor de productie van ^{18}F -FDG onderzoek gedaan naar het zuiveren en hergebruik van H_2O^{18} door middel van destillatie en ozonolyse voor het bestrijden van micro-organisme (9). In deze studie hebben zij 37 batches H_2O^{18} na bestraling in een cyclotron door middel van destillatie en ozonolyse gezuiverd. Daarnaast hebben zij 57 batches virgin H_2O^{18} op dezelfde wijze gebruikt voor de productie van ^{18}F -FDG en geanalyseerd op FDG labelingspercentage en radionuclidische zuiverheid. Virgin H_2O^{18} is nieuw H_2O^{18} wat nog niet gebruikt is in een productieproces of cyclotron generator en bevat geen radionuclidische onzuiverheden (9). Het resultaat van het onderzoek was een kleine daling in FDG labelingspercentage van gemiddeld 1.7% ($p=0.12$) in het door gezuiverd H_2O^{18} geproduceerde ^{18}F -FDG ten opzichte van productie met virgin H_2O^{18} (9). Deze daling werd verklaard door het lagere percentage ^{18}O aanwezig in het gebruikte H_2O^{18} en niet door nog aanwezige onzuiverheden (9). Het labelingspercentage van ^{18}F -FDG door productie van gezuiverd H_2O^{18} was vastgesteld op gemiddeld

65,57% (9). De aanwezigheid van radionuclidische verontreinigingen was volgens het onderzoek van Asti verwaarloosbaar klein (9).

Moon et al. (6) heeft eveneens onderzoek gedaan naar de zuivering van H_2O^{18} door middel van verschillende zuiveringsmethoden (6). Het doel was om te achterhalen wat de beste manier van zuiveren zou zijn en of de productie op deze wijze een acceptabel ^{18}F -FDG labelingspercentage zou opleveren. Voor de productie is een IBA 18/9 cyclotron genomen en zijn in totaal 182 batches gezuiverd H_2O^{18} gebruikt voor de productie van ^{18}F -FDG (6). De zuiveringsmethode die de onderzoeker Moon uiteindelijk heeft gebruikt voor de productie van deze 182 batches is een combinatie van een ionenwisselaar en een UV bestraler voor het bestrijden van micro-organisme (6). In het door middels gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG werden volgens de onderzoeker Moon nog een kleine hoeveelheid Na^+ ionen gevonden (6). Deze Na^+ ionen hadden volgens Moon et al. verder geen effect op het ^{18}F -FDG labelingspercentage wat een gemiddelde had van 49.8% (p 0.127) over 182 batches (6).

Bij GE te Eindhoven produceert men ook ^{18}F -FDG. Ook zij delen de bijzondere interesse om mogelijk kosten te reduceren door het gebruik van gezuiverd H_2O^{18} . Ondanks de positieve resultaten van Asti et al. en Moon et al. kan er niet direct gestart worden met de productie van door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. De onderzoeken van Moon et al. en Asti et al. zijn onder andere omstandigheden met andere apparatuur uitgevoerd. Zo was de gebruikte cyclotrongenerator bij de genoemde studies niet identiek en werd er met andere energieën bestraald. Tevens verschillen de synthese apparatuur en de wijze van steriliseren waardoor deze resultaten niet per definitie tot dezelfde resultaten zouden leiden wanneer GE één van deze werkwijzen zou implementeren (6-9). Ook lopen de ^{18}F -FDG labelingspercentage tussen de studies nog al uiteen en in de artikelen wordt niet gesproken over een radionuclidisch zuiverheidspercentage (6-9). GE stelt echter een eis aan de radionuclidische zuiverheid van $\geq 99\%$ die gebaseerd is op de internationale Good Manufacturing Practice (GMP) regelgeving. Om die reden kan niet met zekerheid gesteld worden of het ^{18}F -FDG verkregen uit gezuiverd H_2O^{18} daadwerkelijk aan de radionuclidische zuiverheidseis voldoet die GE stelt. Daarnaast is ook het labelingspercentage van belang voor GE. Een laag ^{18}F -FDG labelingspercentage resulteert in een lage productie van ^{18}F -FDG waardoor er meerdere keren of langer bestraald zal moeten worden. Meer en langer bestralen betekent ook hogere productiekosten. Per dag heeft GE maar 3 uur tijd om te bestralen. Als tijdens reguliere productie niet kan worden voldaan aan de gevraagde hoeveelheid ^{18}F -FDG zal dit gevolgen hebben voor de klant.

Om een wijziging in de productiemethode van ^{18}F -FDG door te voeren dient eerst onderzocht te worden of het mogelijk is om ^{18}F -FDG te produceren door middel van gezuiverd H_2O^{18} met de apparatuur die GE bezit. Bovendien dient dit door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG aan de eisen te voldoen die GE stelt, namelijk een radionuclidische zuiverheid van $\geq 99\%$ en een ^{18}F -FDG labelingspercentage wat overeenkomt met de huidige ^{18}F -FDG labelingspercentagecijfers. Omdat de kosten per batch hoog zijn zal er gestart worden met een casestudie. Als de resultaten van de casestudie positief zijn kan er vervolgonderzoek worden gestart met een groter aantal batches.

Hieruit volgt de onderzoeksvraag: In hoeverre verschilt het ^{18}F -FDG labelingspercentage en de radionuclidische zuiverheid van ^{18}F -FDG geproduceerd uit gezuiverd H_2O^{18} in vergelijking met ^{18}F -FDG geproduceerd uit virgin H_2O^{18} ? Tevens is onderzocht of de radionuclidische zuiverheid aan de $\geq 99\%$ eis voldoet die GE stelt.

2: METHODE

2.1. Onderzoeksopzet:

Deze studie is een kwantitatief experimenteel onderzoek en is uitgevoerd in de laboratoria van General Electric Healthcare te Eindhoven. In deze studie is ^{18}F -FDG bereid met gezuiverd H_2O^{18} waarna het ^{18}F -FDG labelingspercentage en radionuclidische zuiverheid is bepaald. Deze metingen zijn vervolgens vergeleken met het door virgin H_2O^{18} geproduceerde ^{18}F -FDG labelingspercentage en radionuclidische zuiverheid. Omdat het onderzoek maar een klein scala metingen bevat gaat het hier om een zogenaamde casestudy.

2.2. Instrumenten:

Voor de bestraling van gezuiverd H_2O^{18} is gebruik gemaakt van de IBA Cyclone 30 Cyclotron. Dit is een positieve ionenversneller met een maximale stroomsterkte van 350 μA en een spanning van 18-30 MeV (2). De cyclotron heeft in 2002 en 2004 aan de wettelijke vergunning voldaan en heeft drie verschillende target keuzes waarvan twee voor reguliere productie en een voor het uitvoeren van tests en experimenten (2). Voor deze casestudy is gebruik gemaakt van het target voor tests en experimenten. De synthese-unit die gebruikt werd is de FASTlab TW 130900 (zie bijlage I). Dit apparaat extraheert het ^{18}F uit het bestraalde H_2O^{18} . Vervolgens is het ^{18}F gelabeld aan FDG. Na dit proces ontstond er ^{18}F -FDG en is er door middel van de FASTlab TW 130900 het gelabelde percentage ^{18}F -FDG bepaald. Voor het afvullen en steriliseren van de 10 ml vials is gebruik gemaakt van de GEHC Global Radiopharmacy dispensing module (zie bijlage II). Dit is een module die zowel het afvullen van de vials met ^{18}F -FDG combineert met het steriliseren er van (zie bijlage II). Voor het meten van de radionuclidische zuiverheid is de CANBERRA 213230 gammaspectrometrie opstelling gebruikt. De CANBERRA maakt gebruik van een Ge-detector van 10cm hoog en is op 19 maart 2015 gekalibreerd. Voor het zuiveren van H_2O^{18} is een testopstelling gebruikt (zie bijlage III). Door middel van destillatie is het vervuilde H_2O^{18} gezuiverd. Er is voor de bestrijding van microbiologische verontreinigingen een autoclaaf gebruikt.

2.3. Dataverzameling:

De afhankelijke variabelen in dit onderzoek zijn het labelingspercentage en radionuclidische zuiverheid. Beide afhankelijke variabelen zijn van ratio meetniveau en worden uitgedrukt in procenten. De onafhankelijke variabelen in dit onderzoek zijn de bestralingstijd in minuten, het gezuiverde H_2O^{18} en het virgin H_2O^{18} .

Er is op 22 april gestart met het zuiveren van verontreinigd H_2O^{18} . Middels een 100ml flacon verontreinigd H_2O^{18} zijn door middel van destillatie vier 10ml flesjes afgevuld en in een autoclaaf geplaatst voor bestrijding van microbiologische verontreinigingen. Dit is gedaan met een testopstelling binnen GE (zie bijlage III). De flesjes gezuiverd H_2O^{18} zijn na afvullen meteen middels een rubberen sealing afgesloten van omgevingsfactoren. De sealing in combinatie met het verhitten tot 132 graden Celsius waarborgt de kwaliteit en houdbaarheid. Daarna is een van de flesje met gezuiverd H_2O^{18}

middels de CANBERRA op radionuclidische zuiverheid getest. Volgens protocol PRI4 is er op een afstand van 10cm van de Ge-detector 3000 seconden gemeten. Met deze meting is er bekend of er radionuclidische verontreinigingen in het gezuiverde H_2O^{18} aanwezig waren na zuivering. Vervolgens is een van de gezuiverde flesjes opgestuurd naar Italië voor analyse. In deze analyse is er gekeken naar het ^{18}O gehalte van het water en de aanwezige metalen en ionen zodat er voor GE meer informatie beschikbaar is over het gezuiverde H_2O^{18} . Om de mate van radionuclidische verontreiniging in ongezuiverd H_2O^{18} te meten zijn er twee 10ml flesjes gevuld uit de 100ml flacon verontreinigd H_2O^{18} . Deze 10ml flesjes verontreinigd H_2O^{18} zijn vervolgens op de CANBERRA volgens protocol PRI4 getest op radionuclidische zuiverheid zodat de mate van verontreiniging bekend is.

Voor de productie van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG zijn er op de dagen 13, 20 en 27 mei in totaal drie batches ^{18}F -FDG uit gezuiverd H_2O^{18} geproduceerd. Deze productie vond plaats met behulp van de IBA Cyclone 30 Cyclotron bij GE en bestaat uit een bestraling van 5,0 ml gezuiverd H_2O^{18} gedurende een bestralingstijd van 60 minuten onder een 21,3 MeV stralenbundel van 60 μA per batch. Deze bestraling vond plaats op het experimentele target om vermenging van gezuiverd H_2O^{18} in het reguliere productieproces te minimaliseren. Nadat de bestraling was afgrond is het bestraalde H_2O^{18} onder hoge druk door een 40 meter lange leiding getransporteerd naar de FASTlab TW 130900 synthese-unit. Daar is het ^{18}F geëxtraheerd uit het bestraalde H_2O^{18} en is verwerkt tot ^{18}F -FDG. Om het rendement van ^{18}F -FDG labeling te meten is er met de FASTlab TW 130900 het ^{18}F -FDG labelingspercentage berekend. Dit is gedaan met behulp van de volgende formule: $(\text{FDGN} / \text{FDGV}) \times 100 = \text{FDG labelingspercentage}$. Waarin FDGV de activiteit in MBq is van het ^{18}F voor het FDG labelingsproces en FDGN de activiteit in MBq is na het ^{18}F -FDG labelingsproces. Het ^{18}F -FDG labelingspercentage van de drie batches is vergeleken met het gemiddelde en de standaarddeviatie van virgin H_2O^{18} geproduceerd ^{18}F -FDG labelingspercentage van alle batches over heel 2014. Met als exclusiecriteria de batches door virgin geproduceerd H_2O^{18} over 2014 met een fout in het productie proces. Het gaat bij de door virgin H_2O^{18} geproduceerde batches over 2014 om 239 batches wat door de grote hoeveelheid recente productiedata als referentiestandaard zal worden gebruikt voor het ^{18}F -FDG labelingspercentage. Deze 239 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG zijn middels een 21,3 MeV stralenbundel van 60 μA met een variabele bestralingstijd tussen de 33 en 191 minuten geproduceerd.

Om het product verder af te vullen is het ^{18}F -FDG via een leiding getransporteerd naar de GEHC Global Radiopharmacy dispensing module waar het is afgevuld tot 250 MBq /ml. Daarna is het 10ml flacon met behulp van een robotarm in de interne autoclaaf geplaatst. Middels een sterilisatieprocedure van 3,5 minuut onder een temperatuur van 132 graden Celsius is het product gesteriliseerd (zie bijlage II). Om het product op radionuclidische verontreinigingen te controleren is vervolgens de radionuclidische zuiverheid bepaald. Het 10ml flacon is hiervoor machinaal in een wolfram container geplaatst en na 24 tot 48 uur is er 800-900 μl in een microtube gepipetteerd. Deze microtube had hetzelfde batchnummer als het 10ml flacon en is geplaatst in de CANBERRA gammaspectrometrie-opstelling volgens protocol PRI4 op een 10 centimeter afstand van de Ge-detector. Er is volgens protocol PRI4 3000 seconden gemeten en een analyse formulier uitgedraaid

van het spectrum van geproduceerde ^{18}F -FDG. Het spectrum is beoordeeld op karakteristieke energieën van de aanwezige nucliden. De activiteit is hierbij genoteerd in Becquerel op expiratie-tijd. De aanwezigheid van andere energiepieken dan die van ^{18}F -FDG duiden op radionuclidische verontreinigingen in het product. Er is bewust gekozen om volgens protocol PRI4 24 tot 48 uur na productie de monsters te meten omdat het ^{18}F -FDG dan vervallen is. Hierdoor kunnen de radionuclidische onzuiverheden accurater worden gemeten ten opzichte van het regulier gebruikte protocol. Dit verhoogd de betrouwbaarheid van de metingen. Vervolgens is met de volgende formule de radionuclidische zuiverheid berekend: $(F/T) \times 100 = \text{Radionuclidische zuiverheid}$ uitgedrukt in een percentage. Waarbij T de totale activiteit in het monster is op expiratie-tijd gemeten in Becquerel en F de activiteit van alleen ^{18}F -FDG op expiratie-tijd gemeten in Becquerel (10). De radionuclidische zuiverheid van $\geq 99\%$ wordt bij GE volgens de GMP richtlijnen beoordeeld als een radionuclidisch zuiver product.

Voor de referentiestandaard van radionuclidische zuiverheid was bij GE geen data beschikbaar. Daarvoor zijn er in deze casestudie op 20 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG radionuclidische zuiverheidsmetingen verricht. Deze 20 batches zijn geproduceerd met een 21,3 MeV stralenbundel van 60 μA . Omdat deze metingen door beperkte middelen zijn verricht op regulier geproduceerd ^{18}F -FDG is de bestralingstijd echter variabel en ligt tussen de 110 en 180 minuten. Dit komt omdat deze batches bestemd zijn voor klanten van GE en de hoeveelheid van ^{18}F -FDG op hun behoefte wordt afgestemd. Het produceren van 20 referentiebatches met een bestralingstijd van 1 uur zouden de kosten van de casestudie onnodig opdrijven. Deze batches zijn vervolgens gemeten op radionuclidische zuiverheid conform dezelfde procedure als door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. Het gemiddelde percentage en de standaarddeviatie is hier van berekend.

Door de bestralingstijd van 1 uur zullen de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG een lagere ^{18}F activiteit behalen dan de referentiewaarde met een langere bestralingstijd (320 GBq ^{18}F voor een bestraling van 3uur met 60 μA). Echter er wordt verwacht met een bestralingstijd van 1 uur een opbrengst te behalen van 145,6 GBq ^{18}F . Dit is volgens experts binnen GE genoeg activiteit om voldoende ^{18}F -FDG te produceren. Omdat het ^{18}F -FDG labelingspercentage berekend wordt over het begin activiteit en eind activiteit van de synthese is de invloed van hoeveelheid ^{18}F daarom beperkt. Dit maakt het mogelijk een betrouwbaar onderzoek te starten.

2.4. Analyse:

De data van deze casestudie bevat ^{18}F -FDG labeling en radionuclidische zuiverheidsmetingen uitgedrukt in procenten. Omdat het om een klein scala metingen gaat is er geen statistische toets gebruikt. Het ^{18}F -FDG labelingspercentage van de drie batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG is in een Error Bar grafiek weergegeven. Om antwoord op de onderzoeksvraag te geven is deze volgens beschrijvende statistiek vergeleken met het gemiddelde en de standaarddeviatie van het labelingspercentage van 239 batches uit 2014 door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Deze data is ook weergegeven in dezelfde Error Bar grafiek. Voor de radionuclidische zuiverheid van de 20 batches virgin H_2O^{18} geproduceerd ^{18}F -FDG is het gemiddelde en de standaarddeviatie bepaald. Deze

zijn middels een Error Bar grafiek weergegeven samen met de radionuclidische zuiverheid van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. Middels beschrijvende statistiek is de radionuclidische zuiverheid van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG vergeleken met de 20 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Indirect is tevens bepaald of het door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG voldoet aan het gestelde criterium van $\geq 99\%$ radionuclidische zuiverheid.

3: RESULTATEN

3.1. Geïnccludeerde data referentiestandaard

Voor dit onderzoek is als referentiestandaard het ^{18}F -FDG labelingspercentage van 523 productiedata door virgin H_2O^{18} geproduceerd ^{18}F -FDG over 2014 gebruikt. Hiervan zijn in totaal 284 productiedata geëxcludeerd omtrent problemen in het productie proces. Dit is gedaan om afwijkingen in het ^{18}F -FDG labelingspercentage vanwege productie problemen te minimaliseren. De data die geëxcludeerd is werd aan de hand van omschreven problemen ingedeeld in de volgende factoren: Kalibratie problemen, vertraging in het bestralingsproces, problemen met afvullen of sterilisatie (Bijvoorbeeld: het verkeerd afvullen van batches), ^{18}F opbrengst problemen (Bijvoorbeeld: Een laag ^{18}F yield na bestraling door onbekende reden) en alle technische problemen (Bijvoorbeeld: Het stukgaan van modules of filters in het gehele productieproces). Het totaal aantal geïnccludeerde productiedata is 239 en had een variabele bestralingstijd van gemiddelde 154 minuten met een standaarddeviatie van 37,39 minuten over een range van 158 minuten met een minimum van 33 minuten en een maximum van 191 minuten. In tabel 1 is een overzicht van de geëxcludeerde productiedata te zien met de bijbehorende factoren.

Tabel 1: Productiedata met het aantal geëxcludeerde data per factor van virgin H_2O^{18} geproduceerd ^{18}F -FDG over 2014.

<i>Factoren</i>	<i>Aantal geëxcludeerde productiedata per factor</i>	
kalibratie problemen	19	
Vertraging in bestralingsproces	24	
Problemen met afvullen of sterilisatie	19	
^{18}F opbrengst problemen	10	
Alle technische problemen	212	
<i>Totaal aantal productiedata N=523</i>	<i>Totaal aantal geëxcludeerd productiedata N=284</i>	<i>Totaal aantal geïnccludeerd productiedata N=239</i>

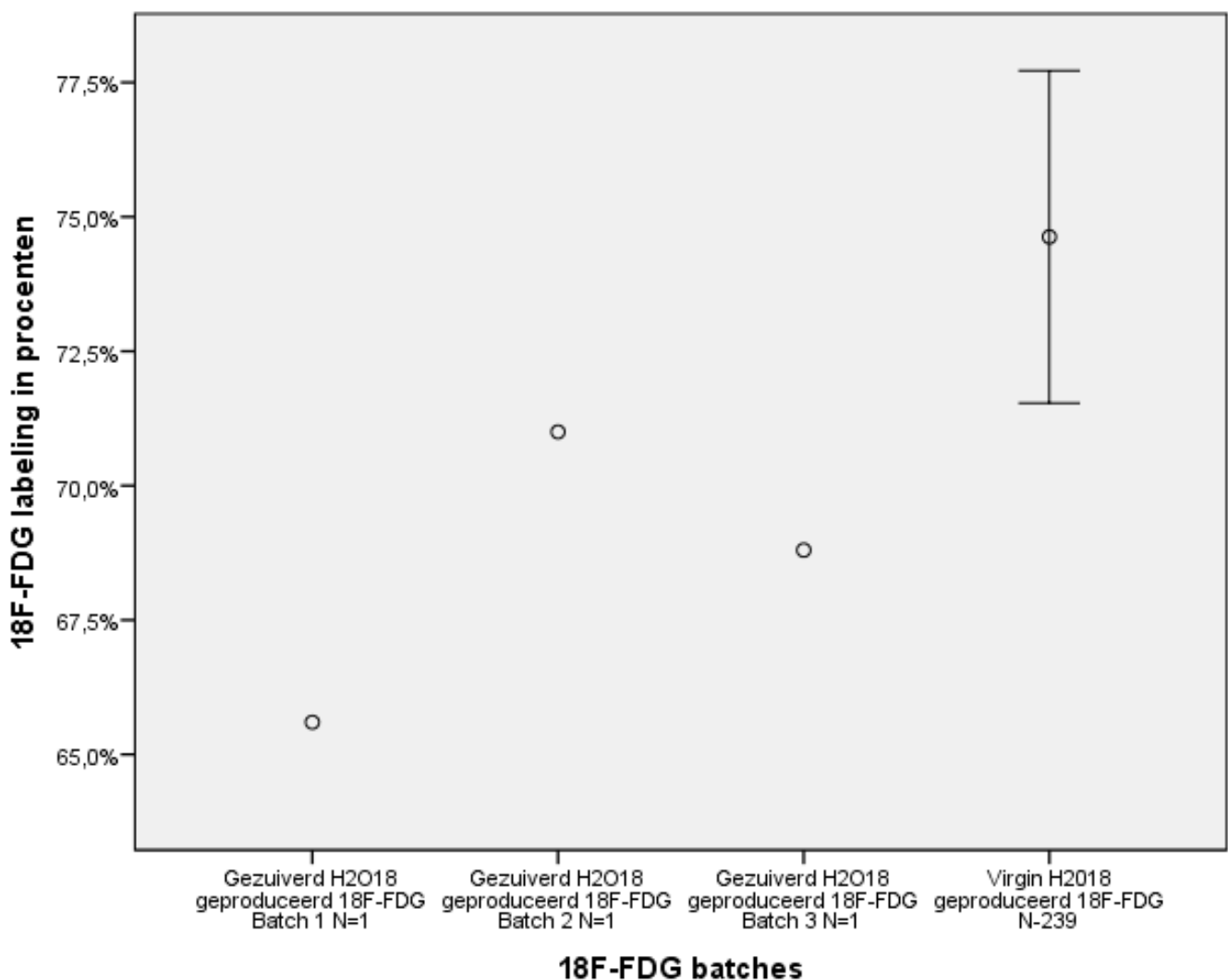
Als referentiestandaard voor de radionuclidische zuiverheid zijn 20 metingen verricht op virgin H_2O^{18} geproduceerd ^{18}F -FDG. Deze metingen zijn allen meegenomen in dit onderzoek en hadden een bestralingstijd die variabel is met een gemiddelde van 160,35 minuten en een standaarddeviatie van 21,61 minuten over een range van 70 minuten met een minimum van 110 minuten en een maximum van 180 minuten. Verder zijn er 3 batches middels gezuiverd H_2O^{18} ^{18}F -FDG geproduceerd, alle metingen hierop zijn meegenomen in dit onderzoek.

3.2. Gezuiverd H_2O^{18}

Om na zuivering van H_2O^{18} de mate van verontreiniging aan te tonen is het gezuiverde H_2O^{18} gemeten op radionuclidische verontreinigingen. Het door destillatie gezuiverde H_2O^{18} bevatte na zuivering geen radionuclidische verontreinigingen. Verder is het ^{18}O gehalte bepaald door een extern bedrijf. Het aanwezige ^{18}O gehalte in het door destillatie gezuiverde H_2O^{18} is 99,1%.

3.3. ^{18}F -FDG labelingspercentage

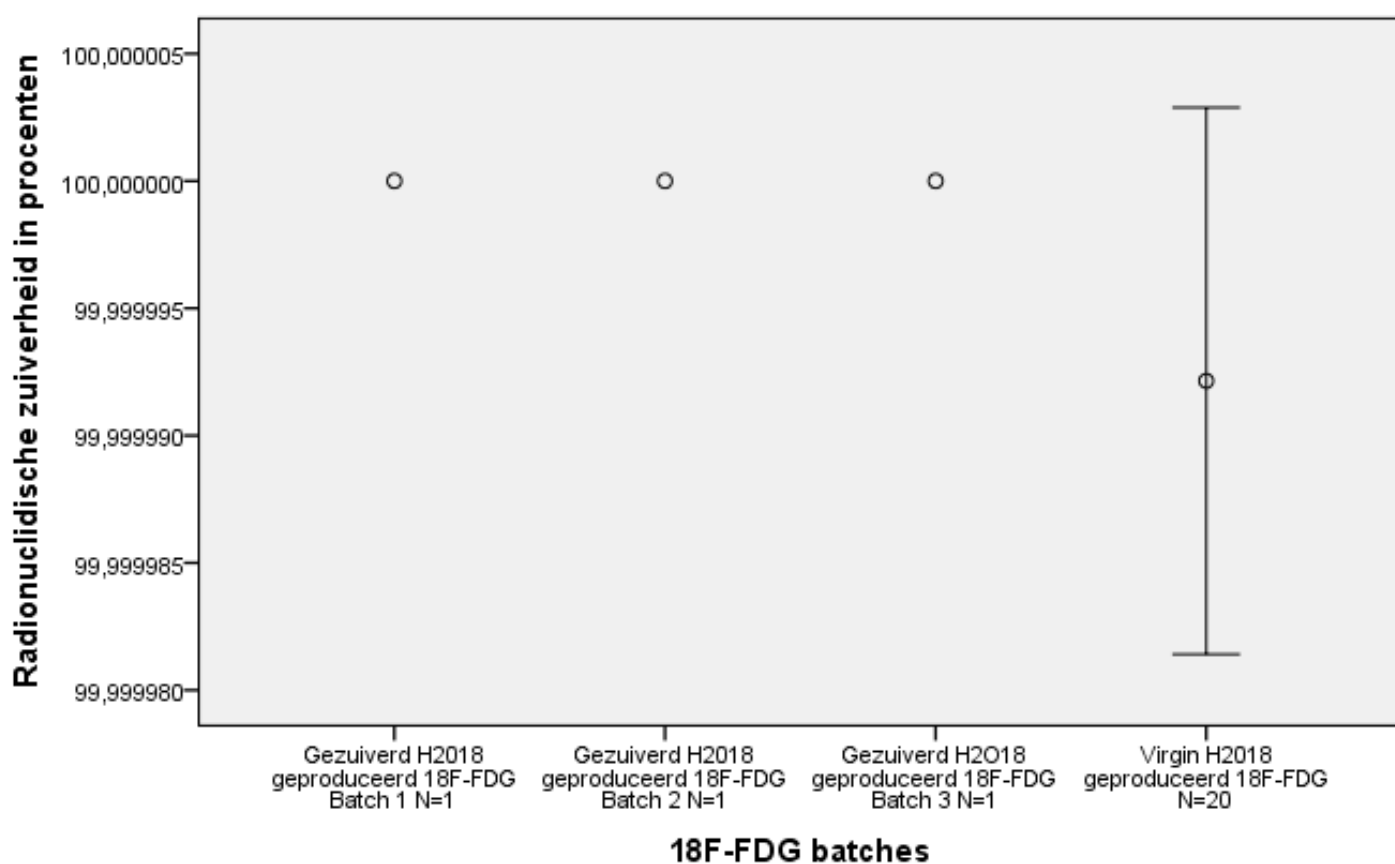
In figuur 1 is het gemiddelde ^{18}F -FDG labelingspercentage en de standaarddeviatie door virgin H_2O^{18} geproduceerd ^{18}F -FDG van 239 metingen uit 2014 weergegeven en uitgezet tegen het ^{18}F -FDG labelingspercentage van de batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. Het gemiddelde ^{18}F -FDG labelingspercentage door virgin H_2O^{18} geproduceerd ^{18}F -FDG van 239 metingen uit 2014 is 74,63% met een standaarddeviatie van 3,091%. De data van deze referentiegroep lag verspreid over een range van 27,7% en had een minimum waarde van 52,5% en een maximum van 80,2%. De drie batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG hebben een ^{18}F -FDG labelingspercentage van 65,6%, 71,0% en 68,8% en liggen daarmee respectievelijk 9,03%, 3,63% en 5,83% onder het gemiddelde van ^{18}F -FDG labelingspercentage van de referentiegroep.



Figuur 1: ^{18}F -FDG labelingspercentage uitgedrukt in procenten van 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG uitgezet tegen het gemiddelde ^{18}F -FDG labelingspercentage \pm 1 standaarddeviatie van 239 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG.

3.4. Radionuclidische zuiverheid

Als referentiestandaard voor de radionuclidische zuiverheid zijn 20 metingen verricht op virgin H_2O^{18} geproduceerd ^{18}F -FDG. De exacte waarden bevinden zich in (Bijlage IV). Het gemiddelde hiervan is $>99,99\%$ met een standaarddeviatie van $<0,01\%$. De maximum waarde van de referentiegroep is 100% en het minimum is $>99,99\%$ over een range van $<0,01\%$. Het gemiddelde en de standaarddeviatie van de radionuclidische zuiverheid door virgin H_2O^{18} geproduceerd ^{18}F -FDG is uitgezet tegen de radionuclidische zuiverheid van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG in figuur 2. Deze resultaten zijn weergegeven middels een Error Bar grafiek met op de horizontale as de gezuiverde en reguliere ^{18}F -FDG batches en op de verticale as de radionuclidische zuiverheid uitgedrukt in procenten. De 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG zijn middels 3 datapunten weergegeven en zijn allen 100% radionuclidisch zuiver.



Figuur 2: Radionuclidische zuiverheid uitgedrukt in procenten van 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG uitgezet tegen de gemiddelde radionuclidische zuiverheid uitgedrukt in procenten ± 1 standaarddeviatie van 20 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG.

4: DISCUSSIE

Het doel van deze casestudie is om aan te tonen in hoeverre het ^{18}F -FDG labelingspercentage en de radionuclidische zuiverheid van ^{18}F -FDG geproduceerd uit gezuiverd H_2O^{18} verschilt in vergelijking met ^{18}F -FDG geproduceerd uit virgin H_2O^{18} . Tevens is onderzocht of de radionuclidische zuiverheid door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG voldoet aan de $\geq 99\%$ eis die GE stelt. Het ^{18}F -FDG labelingspercentage van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG is lager dan het gemiddelde ^{18}F -FDG labelingspercentage door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Voor de radionuclidische zuiverheid van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG is er sprake van een nihil verschil in vergelijking met de radionuclidische zuiverheid van door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Er werd tevens voldaan aan de $\geq 99\%$ radionuclidische zuiverheid eis die GE stelt.

In deze casestudie zijn voor de referentiestandaard van door virgin H_2O^{18} geproduceerd ^{18}F -FDG 284 van de 523 productiedata geëxcludeerd. Dit is gedaan om afwijkingen in het ^{18}F -FDG labelingspercentage met betrekking tot productieproblemen uit te sluiten. Er is voor gekozen om elke batch waarbij een opmerking stond omtrent een technisch probleem, kalibratie probleem, vertraging in bestrahlingsproces, afvul en sterilisatie problemen of ^{18}F opbrengst problemen voor de zekerheid te excluderen. Het includeren van deze data zou een vertekend beeld kunnen geven omtrent de referentiestandaard van het ^{18}F -FDG labelingspercentage omdat het mogelijk te herleiden zou zijn naar een productieprobleem of technisch mankement.

4.1. Interpretatie van de onderzoeksresultaten

Het ^{18}F -FDG labelingspercentage van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG hebben een ^{18}F -FDG labelingspercentage van 65,6%, 71,0% en 68,8%. Dit was 9,03%, 3,63% en 5,83% lager dan het gemiddelde ^{18}F -FDG labelingspercentage door virgin H_2O^{18} geproduceerd ^{18}F -FDG 74,63%. De 3 batches vallen dan ook niet binnen de standaarddeviatie van 3,091%. Het lage labelingspercentage van batch 3 is waarschijnlijk veroorzaakt doordat er problemen waren met de transfer van het target naar de synthese-unit. Hierdoor is er activiteit weggelekt waardoor batch 3 wellicht aan externe factoren is blootgesteld. Die externe factoren kunnen volgens experts bij GE een mogelijk negatief invloed hebben op het ^{18}F -FDG labelingspercentage. Hierdoor kan batch 3 als niet betrouwbaar worden beschouwd. Een mogelijke verklaring voor het nog lagere labelingspercentage van batch 1 kan mogelijk gevonden worden in het lage gebruik van het target voor tests en experimenten. Het target heeft voor aanvang van deze casestudie lang stilgelegen. Batch 1 was de eerste bestraling sinds lange tijd. Volgens experts bij GE zou die lange stilstand verontreinigingen in het target kunnen veroorzaken die mogelijk een effect hebben op het ^{18}F -FDG labelingspercentage.

Een andere verklaring voor het lagere ^{18}F -FDG labelingspercentage is het gebruik van het target voor tests en experimenten. Van dit target was geen productiedata beschikbaar. Het is daardoor niet bekend hoe het target presteerde in een productiesetting. Echter om vermenging van gezuiverd H_2O^{18} met virgin H_2O^{18} binnen het reguliere productieproces te voorkomen, zijn de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG uitgevoerd op het derde experimentele target. De reguliere productie is

hierdoor veilig gesteld voor een mogelijke besmetting van gezuiverd H_2O^{18} . Echter de 239 referentiemetingen door virgin H_2O^{18} geproduceerd ^{18}F -FDG zijn uitgevoerd op reguliere productietargets die kunnen afwijken van het experimentele target in bundel afstelling en leeftijd van het HAVAR® folie. Dit kan volgens GE eveneens leiden tot mogelijke verschillen in ^{18}F -FDG labelingspercentage per target. Het gebruik van een ander target heeft hierdoor mogelijk geleid tot een lagere validiteit van de casestudie.

Een derde mogelijke verklaring voor het afwijken van het ^{18}F -FDG labelingspercentage kan de bestralingstijd zijn. Deze was gemiddelde 154 minuten voor de 239 batches door virgin H_2O^{18} geproduceerd ^{18}F -FDG. Voor deze casestudie is gekozen voor een bestraling van 1 uur per batch. Uit de literatuur blijkt dat een korte bestralingstijd van invloed is op de hoeveelheid kortlevende radionuclidische verontreinigingen in het bestraalde H_2O^{18} (11). Deze radionuclidische verontreinigingen nemen hierdoor toe en kunnen een binding aangaan met het ^{18}F -FDG tijdens de synthese aldus Asti en Moon et al (2007). Een langere bestralingstijd zou er voor zorgen dat deze kortlevende radionuclidische verontreinigingen eerder vervallen dan het aanwezige ^{18}F (11). Waardoor er zuiverder ^{18}F ontstaat. Dit kan resulteren in hoger ^{18}F -FDG labelingspercentage.

Tenslotte vormt een mogelijke verklaring voor het lagere labelingspercentage dat er tijdens de bestraling van gezuiverd H_2O^{18} verontreinigingen zijn ontstaan die een negatief effect hebben op het ^{18}F -FDG labelingspercentage maar in de synthese-unit zijn achtergebleven. Asti et al. en Moon et al. (2007) hebben dit effect al eerder aangetoond in hun eerdere studies.

De resultaten zeggen feitelijk dat het labelingspercentage erg laag is, echter het lijkt dat dit vele oorzaken kan hebben die eenvoudig te verhelpen zijn en desondanks veel perspectief geven om door te gaan met vervolgonderzoek.

De radionuclidische zuiverheid van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG waren voor alle 3 de batches 100%. Als referentiewaarde voor de radionuclidische zuiverheid waren 20 metingen verricht op virgin H_2O^{18} geproduceerd ^{18}F -FDG. De 3 batches gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG zitten binnen de standaarddeviatie van de referentiestandaard en scoren hoger dan het gemiddelde. De hoge radionuclidische zuiverheid en het behalen van de $\geq 99\%$ eis van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG geven goed perspectief voor verder vervolgonderzoek.

4.2. Sterke punten en beperkingen

Een sterk punt van de casestudie is dat de bestralingen, syntheses en navulling van de batches door deskundig gekwalificeerd personeel is uitgevoerd. Dit zijn mensen die jarenlange ervaring hebben met de bereiding van regulier geproduceerd ^{18}F -FDG. Hierdoor is de kans zeer gering dat de resultaten van het onderzoek beïnvloed zijn door fouten die gemaakt zijn door de betrokkenen wat de betrouwbaarheid van het onderzoek negatief zou hebben beïnvloed. Verder zijn alle stappen in het bereidingsproces van de experimentele batches op de zuivering van het H_2O^{18} na met gestandaardiseerde protocollen uitgevoerd. Dit verhoogt de betrouwbaarheid van de resultaten.

Een ander sterk punt is dat het ^{18}F -FDG labelingspercentage door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG overeenkomt met wat er in de literatuur gevonden is. Asti et al. (2007) vond een ^{18}F -FDG labelingspercentage van gemiddeld 65,58% dit geeft veel perspectief om verder te gaan met vervolgonderzoek.

Het onderzoek kent ook enkele beperkingen die van invloed zijn op het ^{18}F -FDG labelingspercentage en de radionuclidische zuiverheid. Ten eerste is dat de variabele bestralingstijd van de referentiemetingen van het ^{18}F -FDG labelingspercentage en de radionuclidische zuiverheid. Deze waren variabel omdat de metingen verricht werden op monsters van batches die voor klanten bestemd waren. Dit omdat de kosten per batch hoog zijn en het specifiek produceren van referentiebatches ten behoeve van dit onderzoek hierdoor niet mogelijk was. Dit geeft een minder sterke validiteit en generaliseerbaarheid van de resultaten omdat de 3 door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG batches door beperkte middelen een bestralingstijd hadden van 1 uur.

Ten tweede is er een ander target gebruikt voor het produceren van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. Van dit target was geen productiedata bekend. De verschillen in bundelafstellingen en leeftijd van het HAVAR® folie tussen de targets kunnen volgens GE eveneens leiden tot mogelijke verschillen in ^{18}F -FDG labelingspercentage per target. Het gebruik van een ander target heeft hierdoor mogelijk geleid tot een lagere validiteit van de casestudie.

Ten derde is de destillatiemethode voor het zuiveren van gebruikt H_2O^{18} nog een testopstelling en verloopt de gehele procedure nog handmatig zonder bestaande protocollen. Dit kan effect hebben op de consistentie van de zuiverheid van het gezuiverde H_2O^{18} . Het door destillatie gezuiverde H_2O^{18} bevatte na zuivering geen radionuclidische verontreinigingen. Het is mogelijk dat er na zuivering andere niet radionuclidische verontreinigingen aanwezig waren in het gezuiverde H_2O^{18} . Dit moet nog geanalyseerd worden door een expert bij GE.

4.3. Aanbevelingen

Op basis van de huidige resultaten kan er gesteld worden dat het gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG voldoet aan het de gestelde kwaliteitseis van $\geq 99\%$ radionuclidische zuiverheid. Hierdoor is het mogelijk te gebruiken maar er is wel vervolgonderzoek vereist om te onderzoeken of het ^{18}F -FDG labelingspercentage niet verhoogd kan worden om het meer rendabel te maken. Een dergelijke onderzoek zou vormgegeven kunnen worden door te starten met een grotere groep door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG batches. Om een significante uitspraak te kunnen doen zijn er minimaal 25 batches vereist. Als de resultaten hieruit positief zijn kan het aantal batches worden opgehoogd en kunnen de resultaten stapsgewijs worden aangevuld tot dat er minimaal 25 batches zijn geproduceerd.

Het geniet de voorkeur dat deze gezuiverde H_2O^{18} geproduceerde ^{18}F -FDG batches worden geproduceerd op de twee reguliere targets in plaats van het experimentele derde target, zodat er geen afwijking in targetkeuze is tussen regulier geproduceerd ^{18}F -FDG en gezuiverd ^{18}F -FDG.

Verder wordt aangeraden om een bestralingstijd van 154 minuten te nemen in plaats van de huidige keuze van 1 uur. Dit komt beter overeen met de huidige gemiddelde reguliere bestralingstijd van door

virgin H_2O^{18} geproduceerd ^{18}F -FDG. Hierdoor zijn de parameters gelijk en verlaagt het de kans op kortlevende radionuclidische verontreinigen in het door gezuiverd H_2O^{18} geproduceerd ^{18}F (11).

Om deze alternatieve manier van ^{18}F -FDG productie in de toekomst te gaan gebruiken zal er middels chemische zuiverheidstests moeten worden onderzocht of er geen andere vervuilingen aanwezig zijn in het door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG. Daarna zal er met een kostenanalysemodel onderzocht moeten worden of het rendabel is met een lager ^{18}F -FDG labelingspercentage gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG te gaan gebruiken voor reguliere productie.

5: CONCLUSIE

Er is een lager ^{18}F -FDG labelingspercentage geconstateerd van het gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG ten opzichte van het virgin H_2O^{18} geproduceerd ^{18}F -FDG. Voor de radionuclidische zuiverheid van gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG is er sprake van een nihil verschil in vergelijking met de radionuclidische zuiverheid van door virgin H_2O^{18} geproduceerd ^{18}F -FDG. De radionuclidische zuiverheid van de 3 batches door gezuiverd H_2O^{18} geproduceerd ^{18}F -FDG voldoen aan de radionuclidische zuiverheidseis van $\geq 99\%$ die GE stelt. Op basis van de behaalde resultaten kan geconcludeerd worden dat door beperkingen in deze casestudie de resultaten feitelijk zeggen dat het labelingspercentage laag is. Echter het lijkt dat dit vele oorzaken kan hebben die eenvoudig te verhelpen zijn. Verder biedt het behalen van de gestelde radionuclidische zuiverheidseis veel perspectief om door te gaan met vervolgonderzoek.

6: LITERATUURLIJST

1. Nishijima K-i, Kuge Y, Tsukamoto E, Seki K-i, Ohkura K, Magata Y, et al. Increased [^{18}F]2-fluoro-2-deoxy- d-glucose ([^{18}F]FDG) yield with recycled target [^{18}O]water: factors affecting the [^{18}F]FDG yield. *Applied Radiation and Isotopes*. 2002;57(1):43-9.
2. Eindhoven T. Het TU/e Cyclone 30 Cyclotron. 2005:6.
3. Berridge MS, Kjellström R. Designs and use of silver [^{18}O]water targets for [^{18}F]fluoride production. *Applied Radiation and Isotopes*. 1999;50(4):699-705.
4. Berridge MS, Voelker KW, Bennington B. High-yield, low-pressure [^{18}O] water targets of titanium and niobium for F-18 production on MC-17 cyclotrons. *Applied Radiation and Isotopes*. 2002;57(3):303-8.
5. Bowden L, Vintró LL, Mitchell PI, O'Donnell RG, Seymour AM, Duffy GJ. Radionuclide impurities in proton-irradiated [^{18}O]H₂O for the production of ^{18}F :- activities and distribution in the [^{18}F]FDG synthesis process. *Applied Radiation and Isotopes : Including Data, Instrumentation and Methods for use in Agriculture, Industry and Medicine*. 2009;67(2):248-55.
6. Moon WY, Oh SJ, Cheon JH, Chae WS, Lim SJ, Cho SM, et al. Simple purification of recovered [^{18}O]H₂O by UV, ozone, and solid-phase extraction methods. *Applied Radiation and Isotopes : Including Data, Instrumentation and Methods for use in Agriculture, Industry and Medicine*. 2007;65(6):635-40.
7. Huang BX, Channing MA, Plascjak PS, Kiesewetter DO, Der M, Ma Y, et al. Routine quality control of recycled target [^{18}O]water by capillary electrophoresis and gas chromatography. *Nuclear medicine and biology*. 2003;30(7):785-90.
8. Kitano H, Magata Y, Tanaka A, Mukai T, Kuge Y, Nagatsu K, et al. Performance assessment of O-18 water purifier. *Annals of Nuclear Medicine*. 2001;15(1):75-8.
9. Asti M, Grassi E, Sghedoni R, De Pietri G, Fioroni F, Versari A, et al. Purification by ozonolysis of (^{18}O) enriched water after cyclotron irradiation and the utilization of the purified water for the production of [^{18}F]-FDG (2-deoxy-2-[^{18}F]-fluoro-d-glucose). *Applied Radiation and Isotopes : Including Data, Instrumentation and Methods for use in Agriculture, Industry and Medicine*. 2007;65(7):831.
10. Broek vd. *Nucleaire Geneeskunde*: Elsevier Gezondheidszorg; 2008. 585 p.
11. Technology BClo. PET with dedicated and DHCI cameras. PET Radionuclide and Radiotracer Production: British Columbia Institute of Technology; 2000.

BASISDOCUMENT BEREIDING STERIPET FASTLAB (¹⁸F)

Dit document is minimaal van toepassing voor functie: L02 en L03

Dit document behoort bij EIND_SOP-P21

1 ALGEMENE GEGEVENS

Product: SteriPET™, geschikt voor intravenueuze toediening,
([¹⁸F]-FDG, 2-fluoro-2-deoxy-glucose)

Batchgrootte: > 5 GBq

Activiteitsconcentratie: 250 ± 25 MBq/ml op kalibratietijdstip

Halveringstijd: 109,77 minuten

Verpakkingsgrootte: Maximaal 2,50 GBq + 10% op kalibratietijdstip

Minimaal 250 MBq + 10% op kalibratietijdstip

Kalibratietijdstip

(Referentietijd)

Ochtendbatch 10:00 uur

Middagbatch 14:00 uur

Expiratietijdstip: 10 uur na einde sterilisatie

Extensie S

2 SAMENSTELLING

Grondstoffen, benodigde hoeveelheden voor 1 synthese:

¹⁸F-targetvloeistof >5 (max 370) GBq

(EOB = end of bombardment.)

¹⁸O verrijkt water 1156041 3,8 ml

Hulpstoffen, benodigde hoeveelheden voor 1 synthese:

FASTlab cassette (incl. waterfles) 1141872 1 stuks

Bevat: 0.75 ml Eluens (0,825 ml met 50 mg Kryptofix®222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo

[8.8.8]hexacosaan), 10 mg kaliumcarbonaat in 80% acetonitril 20% water)

4 ml Acetonitril

2 ml Mannosetriflaaat 2% in acetonitril

4 ml 22,5% Fosforzuur in water

4 ml 2M Natriumhydroxide

QMA-kolom

tC₁₈-kolom

Alumina-kolom

OASIS HLB-kolom

Water voor injectie 1156122 110–120 ml

Ethanol 70 % 1155844 3 ml

Fosfaatbuffer (geproduceerd bij APL) 1155830 0 – 65 ml

3 BEREIDING

Plaats van bereiding: Fluorproductie (ruimte A0.23). GE Healthcare, Eindhoven

Benodigde apparatuur: FASTlab (TW 130900 of TW 130992) en Dispense unit (TW 130476)

Fig. 1 FASTlab opstelling

Het bereidingsproces omvat de volgende stappen:

3.1 De voorbereidingen, inclusief schoonmaken unit

3.2 Hertesten van de cassette

- 3.3 Transfer vanuit target
- 3.4 De synthese van SteriPET™
- 3.5 Het afvullen van SteriPET
- 3.6 Afsluitende werkzaamheden
- 3.7 Back to back batches
- 3.8 Bioburden
- 3.9 Enviromental monitoring

Bij de bereiding van SteriPET™ wordt altijd gebruik gemaakt van steriele hulpstoffen en hulpmiddelen.

Waar mogelijk worden de gebruikte hulpstoffen en hulpmiddelen voorzien van het batchnummer van de productiedag.

Waar mogelijk wordt de kleurcodering (groen) doorgevoerd, de bij de bereiding van SteriPET™ gebruikte voorwerpen zijn groen of als zodanig gemerkt.

Tijdens het synthese proces moet de Hot Cell deur van de synthese-unit gesloten blijven. Dit in verband met de hoge activiteit in de Hot Cell.

3.1 De voorbereidingen

3.1.1 Voorbereidende werkzaamheden

Voor aanvang van de productiedag worden op het EMS-paneel de waarden van alle ruimtes

gecontroleerd. Bij afwijkingen contact opnemen met PV-er (= productieverantwoordelijke).

Aan het begin van de productiedag wordt de Hot Cell gecontroleerd op radioactieve besmettingen. Als het stralingsniveau het toelaat (< 125 µSv/h) wordt de Hot Cell opgeruimd.

Bij een te hoog stralingsniveau wordt er contact opgenomen met EHS. De gebruikte cassette

wordt verwijderd en afgevoerd in de daarvoor bestemde HotRAS pot.

De druk van de Hot Cells wordt 1x per week gecontroleerd volgens EIND_DIV-S-FL, hoofdstuk 1.1. De waarden worden genoteerd op EIND_CBP-S-FL, blok 1

Voor de productie van SteriPET wordt gebruik gemaakt van het Charge bereidingsprotocol

(EIND_CBP-S-FL) en het Charge Dispenseprotocol (EIND_CDP-S-FL). Hierin staan alle

stappen vermeldt die moeten worden uitgevoerd.

Het oppervlak van de Hot Cell en de FASTlab wordt schoongemaakt en gedesinfecteerd met IPA.

3.1.2 Het voorbereiden van de FASTlab

Voor de werkwijze voor het aanzetten van de systemen wordt verwezen naar EIND_BOSSUS-FL §2.1

De benodigde materialen worden verzameld en klaargelegd. SAP nummers worden bij gebruik

direct genoteerd op het EIND_CBP-S-FL.

Iedere handeling wordt direct afgetekend op het EIND_CBP-S-FL.

De leiding tussen de FASTlab en de dispense unit wordt voor ieder batch gereinigd met 70%

ethanol (zie EIND-CDP-S-FL, blok 4)

De FASTlab voert zelf diverse testen uit.

- De Lab Unit test: dit is een hardware test. Hierbij wordt gekeken of het systeem voldoet

aan de gestelde eisen (zie EIND_BOS-SUS-FL §2.3)

- De cassettest. Na het plaatsen van de cassette wordt deze getest op bv. lektheid (zie

manual FASTlab en EIND_BOS-SUS-FL §2.3). Bij mislukken van de cassettest mag

deze opnieuw getest worden, zie § 3.2.

Nadat de cassettest is uitgevoerd worden de preliminary steps uitgevoerd. Tijdens deze stap

wordt de cassette geprepareerd (bv het bevochtigen van de kolommen) voor de synthese.

Wanneer de preliminary steps zijn afgerond is de unit klaar om activiteit te ontvangen waarna

de synthese gestart kan worden.

Zie voor verdere informatie Operator manual FASTlab, te vinden op de computer van de

3.1.3 Het voorbereiden van de Dispense unit

Voor de werkwijze voor het aanzetten van de systemen wordt verwezen naar EIND_BOS-DUS

De benodigde materialen worden verzameld en klaargelegd. SAP nummers worden bij gebruik

direct genoteerd op het EIND_CBP-S-FL.

Iedere handeling wordt direct afgetekend op het EIND_CDP-S-FL.

De leiding tussen de FASTlab en de dispense unit wordt voor ieder batch gereinigd met 70%

ethanol (zie EIND-CDP-S-FL, blok 4)

Voordat de dispense unit klaar is om af te vullen wordt het systeem gereinigd:

- Clean 2 bij aanvang van een productiedag

- Rinse en flush tussen twee batches is

Zie voor verdere informatie Operator manual Dispense unit, te vinden op de computer van de

Dispensing unit.

3.2 Hertesten van de FASTlab cassette

Tijdens de cassettest wordt de cassette getest op verstoppingen, lekkages ed. Dit gebeurt stap

voor stap. Wanneer er een onderdeel van de cassette niet aan de eisen voldoet volgt er direct

een foutmelding. Een cassette mag één maal opnieuw getest worden, ongeacht de foutmelding.

Bij herhaalde foutmelding wordt er een nieuwe cassette gepakt. Blijft de Fastlab foutmeldingen

geven dan contact opnemen met achterwacht voor verdere acties. Voor uitgebreidere werkwijze bij hertesten cassette zie EIND_BOS-SUS-FL §2.4.

Wanneer een cassette als failcassette wordt bestempeld wordt deze samen met het syntheserapport bewaard. Hiervoor is een box beschikbaar in ruimte 40. Als het nodig wordt geacht wordt de cassette voor onderzoek opgestuurd.

3.3 Transfer activiteit vanuit target

Aan het einde van de bestraling wordt de supportroom gereleased. Zolang de FASTlab in voorbereiding is (of zolang de hot cell van FDG1 en FDG2 niet is afgesloten), is het niet mogelijk om de activiteit over te zetten vanuit de target support room. Op de transfer computer is de "cleanroom" nog niet gereleased. CR released is rood. Wanneer de voorbereidingen aan de FASTlab zijn afgerond en de deuren zijn gesloten, kan de cleanroom gereleased worden. Op de transfercomputer met de muis de knop "Rel. CR" indrukken. Zowel in de Cleanroom als in de Targetsupport room kun je op de Transfercomputer zien dat de cleanroom in vrijgegeven, zie fig.2.

Fig. 2 Scherm van Transfercomputer, Synthese-unit FDG-2 (= 3/4 links) is vrijgegeven (CR Released is groen)

De spoeler neemt, vanuit de targetsupportroom, contact op met de fluorproductie (bv. intercom).

Het bestraalde ^{18}O water wordt overgezet naar de synthese-unit. Nadat de activiteit is overgezet

wordt de tube doorgespoeld met 1,0 ml ^{18}O verrijkt water. De gegevens van de bestraling

worden op de EIND_RNP-F en EIND_ALG-ORP ingevuld en het logboek wordt ingevuld.

3.4 De synthese van SteriPET™

Voordat de synthese wordt gestart moet er minimaal 15 minuten zijn verstreken tussen EOB

(end of bombardment) en de start van de synthese. Dit om het gevormde stikstof kwijt te raken.

Normaal gesproken is dit al verlopen na het spoelen van de targettube met $\text{O-}^{18}\text{H}_2\text{O}$.

Controleer of er activiteit in de FASTlab is ontvangen. Controleer of de activity inlet tube voor

ongeveer $\frac{3}{4}$ is gevuld en de uitlezing op het scherm nagenoeg stabiel is. Zodra alle activiteit is

ontvangen, klik op activity received. De synthese wordt gestart. Op het scherm zijn de

verschillende stappen te volgen.

Na het starten van de synthese wordt de activiteit uit de v-vial over de QMA-kolom geleid.

Hier wordt ^{18}F gescheiden van het verrijkte water. Het water wordt opgevangen in de $\text{O-}^{18}\text{H}_2\text{O}$

water vial. Het ^{18}F wordt ingevangen op de QMA-kolom. De activiteit wordt met behulp van het eluent (mengsel van kryptofix, kaliumcarbonaat, acetonitril en water) van de kolom naar de reactor gespoeld. In de reactor vindt de omzetting plaats van precursor (mannosetriflaat) naar het tussenproduct (^{18}F -FTAG). Vanuit de reactor wordt het tussenproduct op de zuiveringskolom gebracht en vervolgens gehydroliseerd tot ^{18}F -FDG. Hierna wordt het opgevangen in de rechterspuit van de cassette. Hierin wordt het eindproduct verdund tot een totaal eindvolume van ongeveer 15 ml. Als het syntheseproces is afgerond wordt het overgepompt naar de dispense unit. Wanneer de dispense klaar is voor ontvangst klik dan op Ready to transfer tracer. Het is belangrijk om zo snel mogelijk te gaan overzetten, dit voorkomt veel radiolyse en daarmee een slechtere yield. Nadat de activiteit is overgezet naar de dispensing unit wordt er gestart met de cassette rinsing. Tijdens de rinse wordt de cassette gespoeld met WFI en komen de actuators in neutrale positie te staan. Tijdens de synthese kan de trending gevolgd worden. Mochten er tijdens de synthese problemen voorkomen dan wordt de cassette rinse niet uitgevoerd (uitvinken). Het is nu mogelijk om de cassette na te meten en te kijken of de oorzaak van het probleem te vinden is. Afwijkingen tijdens het proces worden genoteerd op het EIND_CBP-S-FL en eventueel in Trackwise.

3.5 Het afvullen van SteriPET

Nadat de synthese is afgerond wordt het eindproduct overgebracht naar de collect vial van de dispense unit. Bij het bepalen van het ontvangen volume en activiteit hangt de collect vial in de activimeter. De spuit trekt 1,67 ml uit de collectvial en meet de hoeveelheid activiteit die nog in de collectvial zit (het verschil in activiteit is de activiteit van 1,67 ml). Deze stap wordt nog 2x herhaald. Aan de hand van deze gegevens wordt het volume bepaald. In het data entry veld wordt de concentratie op 250 MBq/ml gebracht. Door het buffervolume te variëren wordt de concentratie ingesteld. Alle volumes in de data entry moet juist zijn (bv een vial voor 2500 MBq moet een volume hebben van 10,00 ml). Bestellingen die niet afgevuld kunnen worden, worden verwijderd uit de data entry. Wanneer de data entry wordt goed bevonden wordt het

afvullen gestart. De eerste vial wordt door de robotarm naar de cleanroompositie gebracht en aangeprikt door de naald. De spuit heeft het juiste volume opgezogen en pompt dit vervolgens in de vial. De leiding wordt doorgeblazen met helium. De vial wordt door de robotarm naar de juiste positie in de autoclaaf gebracht. Wanneer alle vials zijn afgevuld en in de autoclaaf staan wordt de sterilisatie gestart. Na de autoclaafcyclus worden de vials één voor één, aan de hand van het referentienummer op het viallabel, uit de autoclaaf gepakt en nagemeten in de activimeter. De vial wordt naar de airlock gebracht en in de juiste wolfraampot geplaatst. Nadat alle vials zijn uitgelockt wordt het distributie rapport uitgeprint. De sterilisatiegegevens worden uitgeprint. De potten worden naar de inpak en verzend afdeling gebracht. Zie ook EIND_BOSDUS.

3.6 Afsluitende werkzaamheden

De synthese-unit blijft afgesloten. Gecontroleerd wordt of de Hot cell de juiste status heeft, als er met activiteit is gewerkt is de status “actief”, het radioactiviteits symbool op de deur moet zichtbaar zijn. Het licht in de Hot Cell wordt uitgedaan en de computer wordt afgesloten. Het synthesizerapport wordt samen met de EIND_CBP-S-FL aangeboden aan QC. Daar worden alle documenten verzameld en dan aangeboden aan de dienstdoende PV-er en VvnQP-er. Het is mogelijk om na een synthese de cassette te verwijderen en een nieuwe batch te starten. Wanneer het stralingsniveau het dan toelaat ($< 125 \mu\text{Sv/h}$) wordt de Hot Cell opgeruimd. De gebruikte cassette wordt verwijderd uit de synthese-unit en wordt afgevoerd in de daarvoor bestemde HotRAS-pot.

3.7 Back to back batches

Bij een productie dag van meer dan 2 batches of onder omstandigheden dat er maar één FASTlab unit beschikbaar is, is het mogelijk om twee batches achter elkaar op dezelfde unit uit te voeren. Voor het uitvoeren van een back-to-back run moet een actieve cassette van een vorige batch verwijderd worden. Hiervoor is door EHS toestemming gegeven omdat de cassette zeer goed wordt gespoeld en er maar weinig activiteit achterblijft in de cassette.

Verder zijn de waste en de v-vial zeer goed afgeschermd. Het verwijderen van de cassette en het plaatsen van een nieuwe neemt weinig tijd in beslag. Algemeen geldt dat het stralingsniveau niet groter mag zijn dan 125 $\mu\text{Sv/h}$. Bij een te grote overschrijding contact opnemen met EHS. Tijdens de voorbereidingen van de tweede batch is het niet toegestaan om de hotcell te reinigen met IPA, of wasteflessen te legen. Let er bij het verwijderen van de cassette op dat het stikstoffilter ook wordt verwijderd. De cassette wordt afgevoerd in de hotRAS. Voor een gedetailleerde beschrijving zie EIND_CBP-S-FL vanaf §2.2a.

3.8 Bioburden

Iedere maand wordt van één van de twee FASTlabs, in combinatie met de Dispense unit, de Bioburden bepaald. Zie voor de werkwijze EIND_ALG-BBS. De synthese wordt uitgevoerd zonder activiteit, en wordt daarna overgezet naar de dispense unit. In de dispensing unit worden 2 monsters, van 5 ml, afgevuld volgens de normale procedure. Dit zijn de vials “na filtratie”. De connector van het filter wordt op een nieuwe naald geplaatst. De vials “voor filtratie” worden handmatig afgevuld. De vials worden nagemeten in de ionisatiekamer QC-FDG, gemeten waarde en tijdstip van meting worden genoteerd op EIND_ALG-BBS. De monsters worden weggezet in de koelkast (bunker I&V). Noteer de temperatuur van de koelkast op EIND_LB-TM.

:

3.9 Environmental monitoring

Binnen een periode van 2 weken wordt er in iedere hotcell gestempeld en worden er luchtmonsters genomen, de ene week “at rest” en de andere week “in production”.

De bemonstering wordt uitgevoerd door de nachtploeg. Zie voor werkwijze EIND_MVO-MICKRA

en EIND_MVO-MIC-KLM. In EIND_DIV-S-FL is een korte beschrijving opgenomen over de methode van bemonstering.

At rest:

Monsters worden genomen voordat er handelingen zijn verricht in de hotcell. In de FL en DU hotcells betekent dit dat er aan het begin van de productiedag wordt bemonsterd, voordat er handelingen zijn verricht in de hotcells.

In production:

Monsters worden genomen terwijl er handelingen worden verricht in de hotcell. In de FL

hotcells betekend dit dat er bemonsterd wordt op het moment dat de cassettest wordt

doorlopen. Voor de DU hotcell kan dit het best gebeuren tijdens het testen van de robotposities.

Een checklist, EIND_LB-MFH, wordt ingevuld om te controleren dat alle monsters zijn

genomen. Het is niet noodzakelijk dat alle hotcells tegelijkertijd worden bemonsterd.

Verdeeld

over één week moeten de drie hotcells zijn bemonsterd.

4 VEILIGHEID EN MILIEU

Algemene regels betreffende het werken met radio-actieve stoffen, de noodzakelijke dosimetrie, het handelen bij radiologische en conventionele incidenten, de afvalscheiding en –

verwerking en het radiologisch controleren en vrijgeven van de gebruikte werkruimtes staat

uitgebreid beschreven in het voorschrift produktievoorbereiding ¹⁸F-laboratorium

(EIND_DIVS-

FL-SPV).

Voor dit product gelden daarnaast geen aanvullende veiligheidsmaatregelen.

5 REFERENTIES

EIND_ALG-BBS Protocol Monsternamen Bioburden Bepaling SteriPET

EIND_BOS-SUS-FL Voorschrift Bediening, onderhoud en schoonmaak Synthese-unit

EIND_SPE-FS Specificatie Bulk- en Eindproduct FASTlab SteriPET™

EIND_DIV-S-FL-SPV Voorschrift Productievoorbereidingen ¹⁸F-laboratorium

FASTlab

EIND_CBP-S-FL Charge bereidingsprotocol FASTlab SteriPET™

EIND_CDP-S-FL Charge Dispense protocol SteriPET FASTlab

EIND_DIV-S-FL Voorschrift diverse controles FASTlab SteriPET

EIND_LB_TM Logboekvel registratie temperaturen en vochtigheid magazijn

cygne center

EIND_LB-MFH Logboekvel monsternamen afdrukcontroles en luchtmonsters

fluorproductie hotcells

EIND_MVO-MIC-KRA Methode van onderzoek kiemgehaltebepaling rodac-plaatjes

EIND_MVO-MIC-KLM Methode van onderzoek kiemgehaltebepaling luchtmonster

DOC 0856541 FASTlab Synthesizer Customer Information

Technical Publication

GE Healthcare

Direction 2373114-100

Revision 1

GE Healthcare

Manual and Operating Instructions Dispensing Unit

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Legal Notes Page 3

Legal Notes

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GE HEALTHCARE

DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT

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Revision History

Revision Date Reason for change
A 2002 Manual and Operating Instructions
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1 February 7, 2006 GE Medical System changed to GE Healthcare, several places in manual.
Ch 5, Sect 4.1; page 49 and Ch 6, page 58, text concerning supplier of ¹³⁷Cs changed.
App G, table G1 p105 new supplier added.

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Chapter 1

Preface

This manual describes operation and maintenance of the dispensing unit. Chapters 2 to 5 should be read by the operation personnel. [Chapter 2 - Overview](#) gives an overview of the dispenser including a brief sketch of the installation while [Chapter 3 - Description of the Dispenser](#) describes the dispenser. Operation instructions are given in [Chapter 4 - Operation](#). [Chapter 5 - Maintenance and Calibration](#) includes maintenance and calibration of the dispenser.

[Chapter 6 - Software Configuration](#) describes configuration of the software. The software allows to customize the dispensing and cleaning programs (**time lists**). This is described in a separate manual.

[Appendix A - Buffering FDG](#) describes buffering of FDG, which is required for sterilization. [Appendix B - Sterilization of FDG](#) discusses sterilization and is particularly useful for validation. [Appendix C - List of Alarms and Error Messages](#) explains alarms and error messages. [Appendix D - Data Format of Activimeter Calibration Check File](#) describes the data format that is used to store the activimeter check results.

NOTICE For operation and maintenance of the dispenser, and for the training of the personnel the rules of GMP / cGMP, the local laws and radiation protection instructions must be followed.

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Chapter 2

Overview

Section 1.0

The functional Modules of the Dispensing Unit

Figure 2-1 Components of the Dispenser

1. robot
2. clean room (laminar flow)
3. rotating arm
4. syringe (diluter)
5. collection vessel
6. storage tray
7. working table
8. ionization chamber (activimeter, dose calibrator)
9. dispensing pin
10. dispenser base unit
11. air velocity sensor
12. sterilizer
13. air lock

14. optional dilution vessel with stirrer
15. water supply tank
16. waste water tank
17. waste bottle
18. com server
19. control unit
20. notebook computer
21. laser printer

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Page 16 Section 2.0 - Description of Installation

Section 2.0

Description of Installation

The dispenser base unit is installed into a customized lead shielded hot cell. The hot cell is specified by the manufacturer and will only be described regarding to the dispensing unit.

A plastic insert is fitted into the ion chamber and covers the flange on the hot cell floor. This insert acts as an electrical insulator to protect from the high voltage of the ionization chamber. The ion chamber itself is located under the hot cell floor inside a lead shielded safe. The ion chamber is sealed air tight against the hot cell floor by pushing it upwards into a soft seal with a scissors jack.

On the left side of the vial tray a black cup is mounted. This cup is used as a base to park the collection vessel. This collection vessel is connected to the FDG input lines and is housed in a black cage with a knob on it. The knob is used to transport the collection vessel with the robot.

On the left wall of the hot cell a frame is mounted, that stores two bottles containing the cleaning liquids (water for injection and ethanol) and an optional third button with saline solution for dilution of the product.

A separate small lead box below the ionization chamber stores 2 waste bottles. The larger of them stores waste water from the sterilizer while the smaller one stores the waste from the cleaning cycles. If your hot cell is not equipped with this separate lead box the waste bottles must be stored in the main box. In this case the smaller waste bottle should be shielded against the operator by lead bricks.

The dispenser is electrically connected to the control unit and both are further connected to the ComServer. The Com Server communicates with the control computer via Ethernet and with the robot and control unit via RS232. Details about all connections can be found in the cabling diagram on the last page of Unit 4 in the technical documentation folder.

Electrical connections between the dispenser and outside electronics can be found underneath the top cover inside the dispenser. The connectors are located in the back half of the dispenser.

On the back left side next to the electrical connectors inside the dispenser lie the gas connectors and pressure gauges. Compressed air and helium are passed into the hot cell through separate fittings on the top of the hot cell. Cables are running through a circular cable passage.

FDG capillary lines are passed through a shielded flange. Each line connects to one FDG synthesizer. The input lines are connected to an electrical valve which allows the selection of FDG input through the control computer. The two lines connect to the dispenser with Swagelok inside the base unit (optional).

The sterilizer inside the dispenser is supplied with deionized water from a bottle on top of the dispenser. Waste water and steam from the sterilizer is running through a Teflon line through the hot cell floor on the left side into a waste water tank in a shielded compartment underneath the ion chamber.

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Both waste water tank and fresh water bottle of the dispenser require a minimum water level which is clearly marked on each container. The sterilizer is supplied with mains by a power point inside the hot cell. It can be switched on and off from outside.

In front of the sterilizer drawer is the air lock, that transfers the lead containers with the

filled vials out of the hot cell. The air lock is either a pneumatically driven lift or a simple hand driven drawer.

2.1 Hints for Workplace Arrangement

The laptop computer should be installed close to the hot cell. Transfer ways of the lead pots should be minimized by using appropriate tables or trolleys. Attention should also be paid to the radiation protection regulations.

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Chapter 3 - Description of the Dispenser Page 19

Chapter 3

Description of the Dispenser

The base unit consists out of four major components: Diluter (syringe pump), clean room, sterilizer and robot.

Each component will be described below. Additionally a brief description of the operation breakdown is given.

Section 1.0

Diluter, liquid handling

The diluter is responsible for all liquid handling. It is based on a 5 ml CAVRO XL 3000 high resolution syringe pump with a 4/2 port valve and is fitted onto the left front panel. This unit is controlled by the dispenser software and can be operated fully automatic or manually. The syringe requires conditioning before first use to prevent from air bubbles in the system.

Conditioning can be achieved by filling the syringe completely with 0.1 N NaOH for 10 minutes. Then flush with deionized water and refill with 0.1 N HCl . Flush again after 10 minutes with deionized water and repeat flushing for at least 10 times.

Seven additional valves are located behind the left front panel.

Valve V1 and V2 select the desired input line and connect via valve V3 to the collection vessel. The collection vessel is vented and this exhaust is sealed with a sterile filter to maintain a closed system. Valve V3 is connected via the main line to the syringe pump branching off three further vessels. V4 connects a waste bottle, V5 connects the cleaning liquids and V6 connects the saline input for dilution. Valve V7 is used to purge the system with helium. Helium pressure is usually set to 100 kPa.

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Figure 3-1 Dispenser Software Screen

From the syringe pump a short line runs to the dispensing pin inside the laminar flow area. It ends in a Luer connector which connects a sterile filter and needle. Only the provided filter and needle types shall be used with the system. Height and position of the filter needle combination can be adjusted to ensure, that the needle punctuates the septum in the middle.

The collection vessel is built into a black cage to be handled by the robot. To remove the vessel rotate the upper plastic spring ring until its opening allows the tubes to pass. The collection vessel is fitted with a stirrer inside the base. The stirrer is plugged into a socket on the front panel. Make sure a stirrer magnet is inside the vessel.

Section 2.0

Clean Room

For the purpose of aseptic dispensing and to keep the needle sterile the dispenser is fitted with a small horizontal laminar flow unit to provide clean room conditions. In this clean room environment the septum is pierced. No moving parts are mounted in this area to prevent particle contamination. The sterile and evacuated vials are brought into

this area by a rotating arm from outside.

Air velocity can be set and regulated by the computer and is controlled by a sensor inside the clean room area. Surfaces are kept uniform and free from holes and screws for easier sanitation and disinfection. The particle filter (H/EU 14) provides a clean room class 100 (US-Federal Standard). Laminar flow is achieved by a nylon mesh which is protected by a Stainless Steel grid.

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Chapter 3 - Description of the Dispenser Page 21

The laminar flow unit circulates the air inside the hot cell. Thus a faster recovery of the clean room environment around the dispenser can be obtained.

Section 3.0

Sterilizer

For terminal sterilization of the product inside the vial a small sterilizer is included with the dispenser.

NOTICE The integrated sterilizer is suitable for the sterilization of pharmaceuticals in the final container. It is not suitable for sterilization of medicine products.

A general view of the chamber and its elements is shown below.

Figure 3-2 Sterilizer Chamber

The sterilizer has a capacity of max. 17 vials (12 vials, former versions). It is equipped with an independent temperature sensor inside a reference vial and pressure sensor to monitor sterilization conditions. Thus sterilization conditions are continuously monitored and the Fo-value is calculated to proof sterility of the product according to the overkill method.

The sterilization cycle heats 132°C for 3.5 minutes. (In older dispensing units a German version of the sterilizer is used which uses a temperature of 135°C instead of 132°C).

CAUTION The sterilizer may only be operated while the hot cell is closed!

With the exception of the steps described in this manual, maintenance of the sterilizer may only be performed by qualified personnel!

1. drain valve and seal
2. thermocouple (chamber)
3. electrical conduit
4. tray
5. connector for pressure line
6. stopper
7. chamber
8. drawer
9. reference vial with PT 100
10. connector for PT100

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Page 22 Section 4.0 - Robot

Figure 3-3 Graphic Display of Sterilization Data

NOTICE To avoid decomposition, the FDG must be adjusted to pH = 5.5. It is important, that it does not reach pH = 6, because at this pH a considerable degradation starts. To achieve a proper pH value a buffer solution is added into the collect vessel of the synthesis module. Please, refer to [Appendix A - Buffering FDG](#) for details.

Section 4.0

Robot

All transport tasks and movements are carried out by a 3 axis robot with the following directions:

X-axis = right / left

Y-axis = forward / backward

Z-axis = up / down

The robot has its home position in the left back corner where it is initialized before operation. Attached to the Z-axis is an extension and a small pneumatic gripper. This gripper is designed to hold standard 20 mm crimping caps.

Robot positions are stored within the dispenser software and need to be reviewed regularly. Speed and acceleration for each axis can be controlled separately.

CAUTION ROBOT MOVEMENT MAY CAUSE INJURY!

The robot can cause serious injury if parts of the body are in the robot's working area during operation.

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Chapter 3 - Description of the Dispenser Page 23

NORMAL OPERATION may only be performed if the hot cell is closed.

For **CALIBRATION OPERATION**, which has to be performed with open hot cell, the operator may only start robot movements if no person is able to access the hot cell during movement. Visual inspection of the robot positions may only be performed after the movement is finished as indicated by the computer. Do not enter the hot cell, if the yellow sign "ROBOT MOVING" is shown on the screen!

MOVING THE ROBOT ARM BY HAND is only permitted, if the software is either not active or in "at rest state" (neither manual nor automatic operation is started).

In addition, the reset button of the control unit must be pressed before.

The following drawing shows a general view of the Z-axis extension and the gripper.

Figure 3-4 Robot Gripper

NOTICE The Robot arm may only be moved by hand after the reset button of the control unit has been pressed. Without "Reset" a holding current is applied to the stepper motors and moving by hand could destroy the motors.

Section 5.0

Activimeter

The dispenser is equipped with an activimeter (dose calibrator, ionization chamber) for measuring the activity of the batch the activities of the filled vials.

The activimeter has 7 amplification ranges which are switched automatically. It is calibrated with the help of a Cs-137 radiator. Range 2 is absolutely calibrated with the Cs-radiator while the other ranges are calibrated relative to each other using test currents that are provided by an internal current source.

Legend

1. Z-axis
2. zero contact cable
3. insulating block
4. extension block
5. extension rod
6. clamp
7. locking screw
8. gripper
9. finger
10. bearing
11. zero contact
12. pneumatic hose
13. pneumatic fitting

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Page 24 Section 6.0 - Software

Section 6.0

Software

The dispenser is controlled by a laptop computer. All processes (dispensing and cleaning) are controlled by "time lists" that may be customized to local demands. Usually this is done by GEHC Global Radiopharmacy personal, but it may also be performed by the customer (see [Chapter 6 - Software Configuration](#)).

Section 7.0

Operation Breakdown

The operator enters the nominal activity value and the name of the customer for each vial.

Before the hot cell is closed, lead container and vial labels are printed and the latter ones stuck onto the vials. They contain the name of the product, manufacturer, batch number, volume, activity and calibration time. For the activity the nominal value is used, that is matched by the filling process within 10%.

After receiving the active FDG solution from the FDG synthesis module the dispensing process is started either automatically or by an operator command. Total activity of the FDG stock solution is determined in a calibrated ionization chamber.

The volume of this stock solution is determined by measuring the activity before and after removing a defined volume in three steps. The measurement results are fitted into a linear function (activity against remaining volume). This function is used to calculate the total volume of the stock.

Optionally the FDG solution can be diluted with isotonic NaCl solution before dispensing into vials.

One after another vial is filled with the nominal activity.

The robot picks up the vials from the storage tray and hands it over to the rotating arm. It is then brought into the clean room by rotating it inside and lifting the vial up to pierce the septum with the sterile needle.

The syringe now picks up the calculated volume and dispenses the FDG solution into the vial.

After dispensing the vial is transferred to the integrated miniature sterilizer. If all vials are filled they are sterilized. After that the activity of each vial is checked and it is transferred to the air lock into the transport container.

After all vials have been locked out, optional labels for the lead containers are printed, which contain the same information as the preprinted labels, but the measured activity values. Alternatively each container label may be printed for each vial immediately after it is locked out with an optional single label printer.

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Chapter 4

Operation

Section 1.0

Preparation for Dispensing

Before operation please make sure the dispenser is in best conditions and all equipment is functioning to the specification.

A quick system check may prevent from fatal errors or robot crashes.

1.1 System Check

Please ensure following equipment and supplies are turned on and waste is emptied and water tank is filled.

- notebook - on
- control unit, comserver - on
- compressed air - open
- helium - open
- power outlet for sterilizer - on
- water supply for sterilizer - sufficient
- waste water tank capacity - enough space
- waste - enough space

1.2 Robot and Syringe Pump

Check, that the robot arm is in the home position. If it is not, press the reset button on the control unit and move the arm by hand into the home position.

1.3 Sterilizer, Airlock, Laminar Flow Unit

- Open and close sterilizer drawer with manual control
- Check reference vial if filled with water
- Move airlock to **IN** position
- Move airlock to **OUT** position

- Check fan on laminar flow unit
- Turn on stirrer and check function
- Move rotating arm in and out
- Test gripper

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- Open valve V7 and turn pump valve to left **bypass** position and valve V3 to position b
- Check helium pressure (100 kPa + 15%)
- Close valve V7
- Turn valve V3 back to position a and pump valve back to left **deliver** position

1.4 Customer Data Base

At the beginning we suggest you to fill the customer data base with names, addresses and all required information.

Access the customer data base by pressing the left button on the toolbar. You only have to fill in the data base once, but you can modify it whenever necessary. The last line of the customer table (beginning with a “*”) allows to add new entries.

1.5 Dispensing Data

1.5.1 Entering the Data

By pressing the second button on the toolbar the following distribution data form is opened:

Figure 4-1 Input Form for Distribution Data

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Please enter the used **program**. If you have more than one synthesizer connected to the dispenser, you will have one program for each synthesizer. They differ in the setting of the input valves. You can store distribution data for each program. If you start the dispensing cycle, the software will automatically use the distribution data according to the program that is selected in the main window (See Figure 4-2). This enables you to prepare the distribution data for 2 or more connected synthesizers ahead.

Figure 4-2 Selecting the program

The next required inputs are, **batch number**, **operator** and a **comment**. Then estimate the **available activity** and volume produced for this batch. Complete the basic information with **reference date** and time and **expiry date** and time.

Following the basic information fill in the **customers** and their ordered **activities** in the seventeen rows below. If a customer is not available in the database you can enter customer data by using the asterisk (“*”) button. Each customer may have its own reference date and time.

Select filling of given activity (with half life correction) or filling of given volume for each vial by clicking on the column headed **Fill Mode** at the right border. Clicking there switches between **Activity** mode and **Volume** mode (See Figure 4-1).

Customer's vials should be filled in **Activity** and receive at least 1 ml to reach an overall precision of $\pm 10\%$. Quality control vials should be filled in **Volume** mode. For technical reasons vial 1 will always get approx. 0.2 ml less than selected. It should be used for one of the QC samples.

NOTICE Using menu entry **CUSTOMER SETTINGS / DISTRIBUTION DATA TEMPLATE** you can store the vials for quality control etc, that are equal each day. These template vial data are automatically copied to the data of each new distribution (but they still can be changed there).

The distribution form will be presented again after measuring the actual activity of the FDG solution in the collection vessel.

1.5.2 Additional Hints

The software calculates the required volumes that are needed to achieve the selected vial activities online and checks that the total batch activity and volume is sufficient.

Additionally it is checked, that no vial is filled with more volume, than it fits. If any problems are detected, the respective values are marked with red color. As an example, if you have a total batch volume of 14 mL and try to set up 3 vials to be filled

with 5 ml, the calculated **remaining activity** will become negative and will be marked with red color. The red color will disappear, if the data are corrected. A suggested way is to select at first some arbitrary value for the total batch activity and input the vial data

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as required by your customers. Then you can check the value **used activity** in order to determine how much activity must be produced for this batch.

1.5.3 Optional Dilution of the Product

Dilution offers a good way if you produce large activity and must fill many vials. If you only fill a small number of vials, dilution is not very useful. For dilution simply insert a non zero value for **Dilution volume to add**.

NOTICE If you dilute your product, keep in mind that a too high dilution may change the pH value, because the buffer is also diluted. You should perform a test in order to determine the maximum possible amount of NaCl that may be added without changing the pH. The buffer formulation of [Appendix A - Buffering FDG](#) is suitable for adding up to 15 mL dilution volume.

1.5.4 Achieving defined Activity Concentration

Dilution may be used to achieve a defined activity concentration. Set the dilution volume to zero and adjust the total batch volume to achieve the desired activity concentration. After the total batch activity and volume has been measured the distribution data form is presented once more. Now click the button OPT. DILUTION. This will adjust the dilution volume exactly to that volume that is required to get the desired concentration that is given by the total activity and total volume values that were given before the dispensing has been started as described above.

1.6 Printing of Labels

After the distribution data have been prepared, the vial labels can be printed by clicking the according button or by selecting menu entry DISTRIBUTION / PRINT VIAL LABELS.

In a similar way you can print the container labels by clicking the according button or by selecting menu entry DISTRIBUTION / PRINT CONTAINER LABELS.

The software will always print the labels for the currently selected program, which usually belongs to a synthesis module ([See Figure 4-2 on page 27](#)). After printing of each label type you are asked whether the labels have been printed correctly. If you do not confirm, you can print them again. If you start a dispensing cycle and the labels have not yet been printed (or if you did not confirm proper printing) the software will automatically print them before the dispensing cycle is started. This behavior can be disabled in the **Misc. Settings** (See Section 5.6 in [Chapter 6 - Software Configuration](#)). If the requested labels are not printed, check the setting of the synthesis module and check the printing state in the distribution archive ([See Section 5.0 on page 35](#)). From the distribution archive you can also repeat the label printing, even after you have confirmed the printing.

If labels are not required, they can be marked as already printed in the distribution archive by clicking with the right mouse button onto the selected line.

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Chapter 4 - Operation Page 29

1.7 Consumables

Before dispensing FDG the dispenser has to be fitted with fresh consumables.

- sterile filter for dispensing (Braun Sterifix Paed)
- sterile needle - check position with a vial in manual mode
- sterile filter for ventilation
- sterile spike (Braun MiniSpike)
- water for injection for cleaning
- ethanol (70%) for cleaning
- if dilution is required: isotonic NaCl solution

Finally make sure all consumables and vials are in place and the robot is in home position.

Carefully check the filter and needle position with a spare vial. Adjust the needle by

opening the locking nut on the dispensing pin.

1.8 Ionization-Chamber Check

Usually local regulations require a daily brief check of the ionization chamber.

Use the RADIOACTIVITY button to automatically check the ionization chamber with its calibration source. The robot will measure the activity of the calibration source and compare it to the calibration activity. The Deviation is shown on the screen stored in a data file named CalibrationCheck.txt. Refer to [Appendix D - Data Format of Activimeter Calibration Check File](#) for a description of the data format.

1.9 Loading the Vials

Stick the labels onto the vials, avoid bubbles. Remove the protective cap and check the aluminum crimp cap. Then sort the vials into the tray.

Stick the container labels onto the lead containers or onto the tins.

Close the hot cell door and inflate seal.

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Section 2.0

Dispensing

Before you start the dispensing cycle, select the proper program ([See Figure 4-2 on page 27](#)). If you have more than one synthesizers connected to the dispenser, it depends on the synthesizer, you want to use. If there is no distribution data set for the currently selected program, you will get a warning message.

Use the green START button to start dispensing.

You will see some messages showing the required preparation steps. By clicking the OK-button of each message, you confirm, that the according preparation step has been performed. (If you click the ABORT Button the dispensing cycle will be stopped and may be started later).

After the preparation messages the software shows this message:

Figure 4-3 Message prior to tracer transfer. The exact text may vary depending on the local installation.

After you have confirmed the message you may transfer the tracer from the synthesizer. A further message will appear:

Figure 4-4 Message shown during tracer transfer. The exact text may vary depending on the local installation.

Confirm this message, after the FDG has been completely transferred. This can be noticed by observing the activity display on the screen ([See Figure 4-5](#)). Due to the autoranging feature, it may take some seconds after you see the first activity value. If the transfer has just been started you will notice at first automatic switching to higher ranges and then the first activity value. After each range change it takes some seconds, until the reading is stable. During this time the display will show **busy**, or **wait**, instead of an activity value.

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Figure 4-5 Activity Display

The transfer is finished if the activity reading does not raise any more.

After determination of activity, volume and concentration the distribution data form will return onto your screen for refinement ([See Figure 4-6](#), see also Section 1.5 on [page 26](#)).

Normally, it is not required to change any of the values. But in case of an unexpected low batch activity it is possible, that the available activity is not sufficient for the demanded fillings. In this case, you must either reduce the filling of one or more vials or delete them by setting their activity or volume value to zero.

The dispenser has a minimum and a maximum volume that it can fill into one vial.

These limits may be changed in PROGRAMMING / MISC. / TRACER AND VIALS. The software does not allow volumes below and above these limits. It will indicate exceeding these limits by turning the relevant field red. It does so too when more than the available activity is tried to dispense.

In the example of [Figure 4-6](#) vial 8 must receive a volume that is larger than the maximum volume, the vial fits (10 mL) and in addition the batch activity is too low to meet the requirements of the vial data. Hence the fields showing the remaining batch activity and the volume of vial 8 are colored red. The problem can be fixed by selecting a smaller activity for vial 8.

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Figure 4-6 Refine Distribution Data

Close the window by clicking the OK button. After this, the filling of the vials will be performed. The filled vials will be transferred to the sterilizer. The sterilization will take about 10 minutes. During sterilization temperature and pressure in the chamber are recorded by independent sensors. After the sterilization is finished the F_0 value is calculated from the recorded temperature. Details are described in [Appendix B - Sterilization of FDG](#). The software has a configured minimum F_0 value (refer to [Appendix B - Sterilization of FDG](#) for determination of this value and to Section 5.5 in [Chapter 6 - Software Configuration](#) for setting this value in the software) and will check, that the actual F_0 value is greater or equal than this minimum value.

The sterilization process ends with a short cooling down phase and the lock out cycle is started. Follow the instructions on the screen and lock out all vials in any desired order. The activity in each vial is shortly measured before placing it into the lead container. Later the measured value may be printed on an extra container label. Any automatic process (dispensing or cleaning) can be terminated with the red STOP button, but the robot will terminate its current movement. If an **IMMEDIATE** stop is required (e.g. in case of emergency) do not use this button, but the **RESET** button of the control unit.

After the dispensing cycle is finished the software asks you whether the distribution report and container labels with the measured activities (rather than the preselected activities) shall be printed. You can print additionally copies of the distribution report and the temperature monitoring data at any time from the distribution archive ([See Section 5.0 on page 35](#)).

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Section 3.0

Cleaning the Dispenser

Cleaning of the dispenser is performed in three steps by automatic procedures. At first the remaining activity is purged (**Rinse**), then the apparatus is sterilized with ethanol (**Clean 1**). Finally the ethanol is removed by rinsing with water again (**Clean 2**).

3.1 Step 1: Purging the Dispenser (Rinse)

Before a second batch is dispensed or the dispenser is cleaned, the remaining product must be purged.

It is recommended to start the rinse run immediately after the dispensing. To do so press the white RINSE button to remove all activity from the dispenser with water for injection and transfer it into the waste bottle.

During the rinse cycle two operator actions are required: Two times an empty vial has to be locked in. These vials receive the remaining FDG from the collection vial and are locked out after measuring their activity. The rinse cycle takes typically 30 minutes.

If you have 2 tray positions free, your time lists may be configured to take the rinse vials from dedicated tray positions instead of taking them from the air lock.

3.2 Step 1: Sterilization with Ethanol (Clean 1)

Click on the red CLEAN 1 button and follow the instructions on the screen. Make that only 70% Ethanol is used to clean and disinfect the unit.

During the Clean 1 run some operator actions are requested by appropriate messages on the screen. At this time the hot cell must be opened, so it is recommended, to wait until the activity, that still is in the apparatus is decayed far enough to meet the radiation protection requirements. The operator actions are:

- Remove sterile filter and needle, put a 100 mL beaker under the needle connector

in the clean room module.

- Connect the connecting tubing for water to a vented vial. (The vent should be made with a sterile filter)
- Shake the collect vial
- Remove the beaker

The typical duration of this cycle is 5 minutes. After it all tubes, the syringe and collect vial are filled with ethanol. The ethanol should stay in the apparatus until Clean 2 is started.

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3.3 Step 3: Removing the Ethanol (Clean 2)

Clean 2 is used to remove the ethanol from **Clean 1**. It is recommended to let the ethanol (**Clean 1**) stay over night in the apparatus and start **Clean 2** just before the next production (for instance, when you start irradiation).

During the **Clean 2** run you are asked to do:

- Put a fresh 100 mL beaker under the needle connector in the LF module.
- Connect new bottles with ethanol (100 mL) and aqua ad injectabilia (200 mL).
- Shake the collect vial (3 times)
- Remove the beaker, mount a fresh sterile filter and needle.

The duration of **Clean 2** depends on the allowed ethanol content of the FDG. A typical duration is 20 minutes. The European Pharmacopoeia lists ethanol as “solvent with low toxic potential”. For these solvents residual quantities of 50 mg per day are accepted without further explanatory statements. You should fix your limit accordingly.

In order to have a cleaning procedure that meets your ethanol limit but takes not a too long time, it is recommended to adjust the **Clean 2** cycle by changing the number of flushing cycles in the time list. The cleaning of the connection line between synthesizer and dispenser (described below) also influences the ethanol content of the final product. Note, that a modification of the **Clean 2** cycle may require a different amount of water than the value given above.

Replace the sterile filter for ventilation in accordance with the specifications of the filter manufacturer.

3.4 Cleaning of the Connection Lines from the synthesizer

Every day, the connection line between synthesizer and dispenser should be rinsed with ethanol. After that the line should be dried with helium and rinsed with water for injection in order to remove the remaining ethanol. For this procedure you must prepare the synthesizer to receive the ethanol and water.

In the dispenser software switch to manual operation and set valves 1 and 2 according to the synthesizer you want to clean. The rotating valve (V3) must be switched to the **WASTE** position which connects the synthesizer to the waste bottle (rather than the collect vial).

Section 4.0

Sterile Filter Check

The dispenser uses vented sterile filters. In order to perform a bubble point test, the venting whole must be closed with a rubber tape.

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Section 5.0

Archive - Recorded Data of the Dispensing Cycles

Figure 4-7 Distribution Archive

The distribution archive stores recorded data of each dispensing and cleaning cycle.

To view and maintain these data press the ARCHIVE button or select menu entry FILE / DISTRIBUTION ARCHIVE. Each cycle that has been run or scheduled is shown as one line. The column headed **Procedure** shows the used procedure, which usually is related to the synthesis module. You can perform the following tasks by clicking the

according buttons:

Search for a record of a dispensing cycle by date.

Search for a record of a dispensing cycle by batch number.

View and print distribution report or the filling data of a scheduled distribution.

View and Print sterilization data.

View and print the log of a dispensing or cleaning cycle.

Print lead container labels with the activity values that have been measured before lock out.

Delete one record.

Clicking the right mouse button over a record of the archive offers additional functions:

Export Sterilization Data to Excel (Useful for validation)

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Change Procedure You can change the procedure that will be used for the dispensing.

This is only possible if the dispensing cycle has the status **to be done**.

Change the Operation Status of a Dispensing Cycle You can set each dispensing cycle to be **done** (allows to repeat the distribution), **aborted** or **completed**.

Change the Printing Status of a Dispensing Cycle You can set the reports and labels to either **printed** or **not printed**. The latter allows to repeat the printing by selecting the according entry within the **Distribution** menu of the main window.

Section 6.0

Trouble Shooting / Crash Recovery

6.1 Pause Mode

If a robot crash or another problem is detected by the software, it will switch automatically to **Pause**. This mode of operation is similar to manual operation mode, but additionally it allows to resume the automatic operation by selecting menu entry **DISTRIBUTION / RESUME** or by pressing **CTRL-R** on the keyboard.

Pause mode may be entered intentionally by selection menu entry **DISTRIBUTION / PAUSE** or by pressing **CTRL-P**.

In case of a robot crash one or more of the 3 robot axes are blocked due to a step loss. The robot's microprocessor monitors the movement of his axes with the help of a photo sensor. Normally each motor step will cause one light sensor pulse. After each movement it is checked that the number of light sensor pulses is equal to the number of motor steps. If the number of light sensor steps is too low, a crash has happened. In this case the axis, that suffered sustained the crash is blocked. In order to resume the dispensing cycle this axis must be reinitialized and the interrupted movement must be performed with the help of the robot's **manual control**.

The recommended procedure after a robot crash is described in an example:

1. Let us assume, that the following error message is shown while the robot tried to put vial number 3 into the sterilizer:

The important information of this message is, that a crash occurred on the z axes.

So we have to reinitialize the z axes.

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2. In order to do this enter manual robot control by clicking the according button:

The following window will appear:

Figure 4-8 Manual Robot Control

3. Check, that there are no obstacles, that prohibit in the initializing movement. In case of an x-axes init, the arm must move to the left most position, in case of a y axes init it must move to the back most position (close to the dispenser) and in case of a z-axes init (which is the case in our example) the way to the upper position must be free. If this is not the case, move the arm with the help of the X, Y and Z controls to a position, where the init may be performed. These controls allow to move even, if the axis is blocked. In case of a z-crash (as shown here) in most cases no movement is required.

4. Perform the z-axes initialization by clicking the **INIT Z** button.

5. Move the arm to the destination position of the interrupted movement by selecting vial number 3 in the upper right corner of the robot control window (See Figure 4-8) and clicking the button STERIL. UNIT.

6. Resume automatic mode by pressing **CTRL-R**.

6.2 Restart Distribution

If a dispensing cycle has been interrupted after successful determination of the batch activity and volume (that means after you clicked the OK button of the **Refine Distribution Data** window) and you are not able to resume the cycle from **Pause** mode as describe above (Section 6.1), you should stop it by clicking the STOP button (shown to the left).

You can then restart the distribution without repeating the determination of batch activity and volume by selecting menu entry DISTRIBUTION / RESTART

DISTRIBUTION. The dispensing is than partly repeated beginning with **Refine Distribution Data** (See Figure 4-9).

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Here you must set the **Fill Mode** of the vials, that have already been filled to **Skip**. In the example shown in Figure 4-9), vials 1 and 2 are skipped.

In most cases dilution has been done in case of a crash, one must set the distribution volume to zero to avoid further dilution.

After you checked and corrected the distribution data, close the window to start the repeated distribution cycle.

Figure 4-9 Refine Distribution Data after Restarting

6.3 Restart Lock Out Procedure

If a crash happens during the lock out cycle the software will abort the lock out cycle.

The problem must be fixed be starting manual operation using the according button (shown to the left). After fixing the mechanical problem and initializing the axes, that suffered the crash as described in Section 6.1 on page 36 the lock out procedure can be restarted using menu entry DISTRIBUTION / RESTART LOCK OUT PROCEDURE.

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Chapter 5

Maintenance and Calibration

Section 1.0

Overview

Robot and Pump weekly monthly half-yearly yearly Instructions

Quick Check C Section 4.2, Chapter 5

Position Calibration

(see below)

C C Sections 2.2 and 2.3,

Chapter 5

Flat cable and

pneumatic hose

C C C C / R RSP 9000 Manual

Z-axis bearing C C C / R RSP 9000 Manual

Z-axis insulation block C C C R RSP 9000 Manual

X-rack, rail and belt

drive

CI CI / C RSP 9000 Manual

Pump Syringe C / R XL 3000 Manual

Pump valve, mounting

screws

C C C XL 3000 Manual

C = check, CI = clean, R = replace, F = refill

RSP 9000 and XL 3000 Operator's Manuals can be found in section 10 of the technical documentation folder.

Clean Room weekly monthly half-yearly yearly Instructions

HEPA Filter C / R Section [3.1, Chapter 5](#)

Calibration of Air Flow

Sensor

C Section [3.2, Chapter 5](#)

C = check, CI = clean, R = replace, F = refill

Activimeter weekly monthly half-yearly yearly Instructions

Quick Check C Section [1.8](#) in [Chapter](#)

[4 - Operation](#)

Calibration C Section [4.1, Chapter 5](#)

Linearity Check C Section [4.3, Chapter 5](#)

C = check / Calibrate

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Page 40 Section 1.0 - Overview

Sterilizer weekly monthly half-yearly yearly Instructions

Temp. Monitor

Calibration

Ca Ca Ca Section [5.1, Chapter 5](#)

Drain valve seal CI CI CI / R STAT/IM 900 Manual

Chamber lid seal CI CI CI / R STAT/IM 900 Manual

Vial with Monitoring

Sensor

C C C C Section [5.2, Chapter 5](#)

Cleaning of Chamber CI CI CI CI STAT/IM 900 Manual

Chamber Plastic

Insert for 17 Vials

C / R Section [5.3, Chapter 5](#)

C = check, Ca=Calibrate, CI = clean, R = replace, F = refill

The Operator's manual **STAT/IM 900 Autoclave**, can be found in section 10 of the technical documentation folder.

Other Components weekly monthly half-yearly yearly Instructions

Luer connector of

sterile filter

R Section [6.1, Chapter 5](#)

Helium Pressure

Adjustment

C C Section [6.3, Chapter 5](#)

Compressed Air

Pressure

C C Section [6.4, Chapter 5](#)

Teflon Tubes C C C / R Section [6.5, Chapter 5](#)

Valves C To be performed by

qualified personnel

Stirrer Magnet C C C Section [6.2, Chapter 5](#)

Database C [Section 7.0, Chapter 5](#)

C = check, CI = clean, R = replace, F = refill

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Section 2.0

Robot and Syringe

2.1 Quick Check

Start dispenser software

Move robot in home position

Check if syringe is empty
Select manual operation by clicking the button shown to the left.
Remove vial from tray position 1 (in case)
Select **manual robot control** by clicking the button shown in the figure to the left.

Initialize robot

Move robot to **Tray** vial 1 position
Check if position is correct
Move to **Upper Pos.** (z-move)
Insert test vial in tray position 1
Move robot again to **Tray** vial 1 position
Check if all three coordinates are correct. If coordinates are not correct all robot positions are likely to mismatch and need correction
Move back to **Initial Position**
Quit manual robot control
Initialize syringe (button on screen)
Abort manual operation

2.2 Position Calibration

Please check the robot positions regularly once a month. (In the first production month after installation or after maintenance the check should be performed once a week) The dispensing unit should be clean and free from any activity. The check is performed using **manual control**.

Ensure, that the robot is in the home position, if not turn off power and move robot slowly with your hands then switch on power again and wait 5 seconds.

NOTICE After starting MANUAL OPERATION the robot's gripper is closed. Be sure to open it before you move it to a vial position!

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For the following procedures remove all vials from trays, sterilizer, airlock and rotating arm!

Use the MANUAL OPERATION button to operate dispenser and robot from your screen.

Again ensure robot is in home position before you confirm.

Wait a few seconds for the software to switch to manual control. The software indicates operational status with coloring all valves in red and blue according their initial status.

Press the robot MANUAL CONTROL button to access the following window.

In this window you can access all **destinations** used by the robot. However some destinations are only accessible from defined starting positions (not from the home position). E.g. the **Clean Room** position may only be accessed from one of the tray positions. Thus you need to move the robot to a tray position first. Each stored position can be corrected using the X, Y and Z values and stored under the proper name using the SAVE POSITION button.

2.2.1 General Description of Tray and Sterilizer Position Alignment

For tray and sterilization unit there are 18 vial positions (in special versions up to 24 positions) which can be accessed by selection of the required vial position in the upper left corner of the computer form. Vial position **1** (stored as **back left position**) determines the positions of all other vial positions, because the other positions are calculated using position **1** and the distances between adjacent positions, that are configured elsewhere. This is described in Section [2.3](#) on [page 45](#)).

The Y coordinate of **Position 6** (stored as **back right position**) is used to calculate any angular misalignment. If no misalignment is present this Y-value should be equal to that of position 1.

Note: *The X and Z values of position 6 are not used at all. If you feel, that the X value of position 6 is not correct, you must change the X distance between the positions (see Section [2.3](#) on [page 45](#)).*

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If tray or sterilizer should be tilted in a way, that the z positions of first and last row or between first and last column are not equal, this can be corrected using the button Z

TILTING CORRECTION. This is done during installation and normally not required any more. After clicking this button the following window comes up:

In this window **Millimeters to add** means, that the given value is added to the stored Z position for the front line or the right column. An example: If position **1** of the tray has a Z value of 172.0 and **Millimeters to add for front most line** is set to 0.5, then position 13 to 18 of the tray will be accessed by the robot using a z value of 172.5.

2.2.2 Tray Positions

Make sure there is no vial in the selected position then move the robot to the **Tray** position. Set the vial position to **1** (upper left corner of the screen) and press the TRAY button. Check all three coordinates (X,Y,Z). Use a mirror for Y and Z positions. Move the robot to **Upper Position** and place test vial in the empty tray position. Then press TRAY again to move the robot down. X, Correct the X, Y and Z values if required and store the changed position as **Tray (back left)**.

Set the vial position (upper left corner of the screen) to **6**, check the Y position and correct, if required and save as **Tray (back right)**.

Finally, move to position 15 and check, whether a z tilting correction, as described above, is required.

2.2.3 Clean room Position

Move from the tray to the Clean room using the CLEAN ROOM button.

Check the three coordinates. Allow the back finger of the robot gripper a 1 mm clearance to the left and right side inside the rotating arm.

Move to **Upper Pos.** and place the test vial into rotating arm.

Move back to Clean Room to check positions again. Use the GRIPPER buttons to open and close gripper. Correct and save positions if necessary.

Make sure no vial is in any tray position.

Close gripper, move to **Tray** and open the gripper.

NOTICE The order of direction movements depends on the gripper state (closed or open) if the destination of the movement is the CLEAN ROOM. In case of closed gripper the arm will move in the order X,Z,Y, which is proper for inserting a vial into the rotating arm. If the gripper is open the order will be X,Y,Z which is proper for removing a vial from the rotating arm.

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2.2.4 Sterilizer Positions

Open the Sterilizer using the according button on the screen.

Move from clean room to **Steril. Unit**.

Again check coordinates as described above for the tray.

2.2.5 Air Lock Position

Insert an empty lead pot into the airlock and drive the lift to **in** position.

Move robot to **Air Lock** position.

Check coordinates.

Move to **Upper position** and insert test vial into lead pot.

Move back to **Air Lock**.

Correct and save airlock position if required.

2.2.6 Test Radiation Source Position

Place test source into its position.

Move robot to **Test Radiation Source** position to check coordinates.

Correct and save **Test Radiation Source** position if required

Remove ¹³⁷Cs test source and store safely.

Move the robot to the **Initial Position**.

2.2.7 Collect Vial Parking Position

Remove collection vessel.

Move robot to **Collect Vial Parking Position** and check coordinates.

Move to **Upper Position**.

Insert collection vessel into stand.

Move back to **Collect Vial Parking Position** and check coordinates again.

Correct and save collect vial parking position if required.

2.2.8 Activimeter Positions

Only the X and Y positions must be checked. The proper Z positions are determined during installation and should normally not be changed.

Move robot to **Activimeter**.

Manually insert collection vessel into the **Activimeter**.

Move robot to the measurement position for the collect vial (use COLLECT vial button under **Z positions for Activity Measurement**).

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You may pull carefully on the two Teflon lines to determine the gap in Z direction. Allow a 1 to 1.5 mm gap. Correct and save activimeter position if required.

Close gripper and Move to **Collect Vial** position.

Check coordinates, then save position.

Move back to **Collect Vial Parking Position**.

Open gripper to release collection vessel.

Move to **Initial Position**.

After all positions have been checked or reprogrammed terminate manual control by clicking the red STOP button.

2.3 Base Configuration of Tray and Sterilizer Positions

This software part is used mostly for installation purposes and only by trained professionals. It is only used if the distance between adjacent positions of tray or sterilizer must be readjusted. It is password protected and you must enable programming mode as described in [Section 1.0 in Chapter 6 - Software Configuration \(page 55\)](#).

Select COMPONENT POSITIONS and ROBOT PARAMETER from the **Programming** menu.

Figure 5-1 Base Configuration of Component Positions

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In contrast to the normal position configuration (Section [2.2 on page 41](#)) you can change the tray and sterilizer grid data:

#X = number of positions in X direction

Dist. X = distance between two X positions

#Y = number of positions in Y direction

Dist. Y = distance between two Y positions

Also, you can change the speed parameters of the robot, but it is strongly recommended not to change them.

In the lower right corner you have a field called **Manual Robot Control**. Here you can move the robot manually by entering X, Y and Z positions or by using the up and down buttons counting the given increment (mm) up and down to the selected position.

Important instructions:

Always start with the Y direction from home. In X direction you would crash with the clean room!

Always move in one direction only. Make sure the way you want to move is free of obstacles!

Never approach a position directly. Better you move in several steps.

Never initialize from any other position than home!

All dimensions are in mm. You can use decimal points for precise positioning.

Using the **Manual Robot Control** you may now approach each position. The stored positions shall only be used as guideline. After reaching the exact position you can overwrite the X, Y and Z positions in the table.

The **Default Values** are used as guidelines for installation. They are not suitable for routine operation!

Section 3.0

Clean Room

The clean room is fitted with an OEM Laminar Flow Unit. During automatic operation the fan voltage is regulated in order to achieve a constant air flow. Inside the laminar

flow unit a HEPA H14 filter is mounted. This filter needs to be replaced when:

- The fan voltage has reached its maximum of 10 V and
- The air velocity has dropped 20% below the 0.45 m/s margin

3.1 Changing HEPA Filter

Note: *The following description is not valid for some dispensers delivered before 1.1.2000, contact GEMS Global Radiopharmacy in this case).*

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For a filter change through a skilled professional please contact GEMS Global Radiopharmacy.

Turn off power from the control unit.

Remove the two acrylic side screens.

Remove the dispensing pin and the air flow sensor.

Unfasten the four screws on the aluminum frame holding the protective grid.

Remove frame and grid carefully. Do not damage the mesh on the back of the frame

Open the two locking nuts on the filter.

Replace filter.

Tighten the two locking nuts.

Place grid and frame in front of filter and fasten the four mounting screws.

Mount air flow sensor (opening parallel to air flow direction).

Mount dispensing pin.

Turn on power on control unit.

Recalibrate air flow sensor if necessary.

3.2 Calibration of Air Flow Sensor

After maintenance work on the laminar flow unit or a filter change the air flow sensor must be recalibrated.

You need a calibrated air flow sensor to measure the actual air flow and compare it with the air flow shown on the screen.

Air flows should be measured at fan voltages from 10V down to 3V in 0.5V steps. This should give you 15 measurements.

From the linear curve of the measurement results you get a factor F_s and an offset (MS Excel). The factor F for the bar display calculates to the formula:

To read the air velocity measured with the built in sensor you first need to change the bar display to a numeric display.

Select DEVICE CONFIGURATION from **Programming** menu. Then click on the DEVICE TEMPLATES register card.

Factor 0.00065 m / s

F_s

= -----

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Figure 5-2 Calibration of Air Flow (1)

Change the **Air Flow Display** from **Analog Input (Bar Display)** to **Analog Input (Numeric Display)**.

Figure 5-3 Calibration of Air Flow (2)

Click on the DEVICES register card and change the display size from 6 pt to 10 pt.

Figure 5-4 Calibration of Air Flow (3)

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Close the window after changing setting

Start **Manual Operation**.

Figure 5-5 Calibration of Air Flow (4)

Click with the right mouse button into the white field under the **Fan Voltage** and set the voltage to 10V for your first measurement. Confirm the entry with **Enter**.

Wait a minute to allow the fan to reach maximum speed. Then use the calibrated air flow sensor and measure the air velocity. Write down the measured and the displayed

values.

Repeat the procedure with 9.5V. Then reduce the voltage 0.5V for each following measurement.

If the measurements have been performed, calculate **offset** and **factor** as described above.

Finally insert these values into the configuration. Select DEVICE CONFIGURATION from **Programming** menu again and stay on the **Devices** register card. In the line of **Air Flow Display** insert the values into the columns for **factor** and **offset** (See Figure 5-4).

Section 4.0

Activimeter

Maintenance of the ionization chamber is mainly reduced to a regular calibration and linearity check.

4.1 Calibration

For calibration, ¹³⁷Cs is required. For information about supplier, See Table G-1

The nuclide factors, that are delivered with the dispenser are valid for the ¹³⁷Cs radiator See Table G-1. If you use another type of ¹³⁷Cs radiator, you must determine the nuclide factors.

Calibration takes approximately 20 minutes.

To start the automated calibration select ACTIVIMETER CALIBRATION from the **Maintenance** menu.

Follow instructions on the screen.

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4.2 Quick Check

For a quick check of the ionization chamber See Section 1.8 in Chapter 4 - Operation.

4.3 Linearity Check

To check the linearity of your ionization chamber you need to record the decay of a short lived isotope e.g. ¹⁸F through all ranges. Starting from range 7 a minimum activity of 30 GBq is required. Allow the activity to decay undisturbed over night.

Start **Manual operation**.

Insert activity into Ionization chamber.

Go to the Ionization chamber on your screen and click with the right mouse button onto the white field next to Nuclide.

Select the correct **nuclide** (e.g. ¹⁸F) and **range 7**.

Select **autorange** on.

Wait for the Ionization chamber to show a reliable value.

Press RECORD button.

Enter 30 (seconds) as time interval for recording.

Let the measurement run over night.

The next day you stop recording by pressing the RECORD button or STOP button.

The recorded data from the decay are written into an ASCII file in the Dispensing Unit folder named DecayCurvexxx.dat where xxx is replaced by the current date and time.

You can evaluate this data by importing them into MS Excel and calculating the error.

Calculate each measurement back to the starting activity.

If your measurements start in the second row enter following formula in the second row and third column:

=B2*EXP(LN(2)*((A2-\$A\$2)/60)/(109,8))

Copy and paste the formula for all rows.

Enter the following formula into the fourth column for reading the error in %.

=(C2/\$B\$2)-1

Copy and paste the formula for all rows.

Mark the rows and format the cells in percent (%).

You can now read the error of your Ionization chamber in percent. It is useful to display the data in a diagram.

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You may need to split your decay curve over several measurements to see all ranges. Please note that the error increases especially in the most sensitive range 1. This range is usually not used.

For measurements between range 3 and range 1 we recommend to use pure ^{18}F FDG to make sure no other nuclides influence the decay curve. For the other ranges (4 to 7) ^{18}F Fluoride is sufficient.

Section 5.0

Sterilizer

5.1 Calibration of Temperature Monitoring

The sterilization temperature is monitored by an independent Pt100 temperature sensor. This sensor meets IEC 751 class A and is independent of the sensor, that is used to control the sterilization process. It is used to calculate the F0 value. The measurement chain should be recalibrated one time a year.

To perform the calibration you must connect precision resistors (delivered with the dispenser) instead of the Pt100 sensor. The connector of the sensor is located within the drawer of the sterilizer.

The temperature reading can be checked in **manual operation mode** of the software (see Section 2.1 in [Chapter 6 - Software Configuration](#)). The required adjustments can be done by changing the values of factor and offset of **Sterilization Test Vial Temp.** within **Programming / Device Configuration** (Refer to [Chapter 6 - Software Configuration](#)).

The suggested procedure is:

1. Connect the resistor labeled **0°C**.
2. Check, that the temperature reading in **manual operation mode** is $(0 \pm 0.15)^\circ\text{C}$. If this is not the case, readjust the **offset** value in the **device configuration**.
3. Connect the resistor labeled **130.5°C**.

Figure 5-6 Calibration of Temperature Monitoring

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4. Check, that the temperature reading in **manual operation mode** is $(130.5^\circ \pm 0.15)^\circ\text{C}$.
5. If this is not the case, readjust the **factor** value in the **device configuration**.
6. Repeat steps 1 to 4 until the readings of both, 0°C and 130.5°C meet the nominal values within 0.15°C .

5.2 Check of Test Vial

If the Vial that contains the temperature monitoring sensor is less than half filled it must be refilled. This must be done by qualified personnel, contact GEMS Global Radiopharmacy for this.

5.3 Chamber Plastic Insert

The plastic insert of the sterilizer chamber must be checked at least once a year for bending that may be caused by heat. If it is bended so much, that a proper positioning of the robot is not possible, it must be exchanged. This must be done by qualified personnel, contact GEMS Global Radiopharmacy for this.

5.4 Seals

Regular replacement of the seals is described in the STAT/M 900 Manual.

5.5 Cleaning

For cleaning the chamber, please refer to the STAT/M 900 Manual.

Section 6.0

Other Components

6.1 Sterile Filter Connector

Replace the Luer connector above the sterile filter every month by a new one.

6.2 Stirrer Magnet

Check that the ceramic wrapping of the magnet is intact and clean. Exchange the magnet if necessary.

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Chapter 5 - Maintenance and Calibration Page 53

6.3 Helium Pressure Adjustment

Figure 5-7 Adjustment of Compressed Air and Helium Pressure

6.4 Compressed Air Adjustment

The helium pressure can be set with the large black knob, that can be accessed after removing the top cover of the dispenser ([See Figure 5-7](#)). Start manual operation to read the pressure on the screen. Compressed air pressure is set with the knurled screw close to the helium pressure knob and can be read on the small manometer as shown in [Figure 5-7](#).

6.5 Check of Teflon Tubes

Radioactivity may damage the teflon tubes. Two kinds of damage are observed ([See Figure 5-8](#)):

Vertical cracks

They appear at the ends of a tubing where the material is flanged for the fitting. These flanges easily crack and break off. Vertical cracks also appear at the entry hole of the reactor head. Here the tubing is always bent and held in a certain angle.

Longitudinal cracks

These cracks appear along all tubing, especially those which have to withstand vacuum and pressure.

Figure 5-8 Possible Damages of Teflon Tubes

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Page 54 Section 7.0 - Database Maintenance

Check the tubes of the collect vial for these damages. If you notice any damages all tubes should be changed. This must be performed by qualified personnel. Contact GEMS Global Radiopharmacy for this.

Section 7.0

Database Maintenance

All data about the performed and scheduled dispensing and cleaning cycles are stored in a database file named Dispensingdata.mdb. In order to avoid that this file grows too much, it is recommended to clear it once a year. This can be achieved by selecting the menu item FILE / CLEAR DISTRIBUTION DATABASE. This causes the following steps to be performed:

1. A back up copy of the current database is created. The copy has a name like DispensingData_DDMMYYYY_HHMMSS.mdb. The postfix _DDMMYYYY_HHMMSS is determined by the current date and time.

2. The original database File DispensingData is cleared.

You should store the back up copy on a save place e.G. on tape or on a CD ROM.

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Chapter 6 - Software Configuration Page 55

Chapter 6

Software Configuration

Section 1.0

Password Protection

The items that can be accessed by the submenus of **Customer Settings** are not password protected. These include the configuration of delivery notes and labels ([Section 2.0](#)) and the calibration source data ([Section 3.0](#)).

The other items and the time list editor (described in a separate manual) are accessed by the submenus of **Programming** and require the administrator password of the software. To be able to change this configuration, you must enable **Programming Mode** by selecting the menu entry FILE / ENABLE PROGRAMMING. This will enable additional menu entries and buttons after you entered the proper password. Change of the administrator password is described in a special document.

Section 2.0

Customizing Delivery Notes and Labels

In the menu select CUSTOMER SETTINGS / DELIVERY NOTES and LABELS. The following window will come up:

Figure 6-1 Data for delivery notes and labels

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Page 56 Section 2.0 - Customizing Delivery Notes and Labels

Enter the name and description of the product into the sample label in the upper left corner of the window ([Figure 6-1](#)).

NOTICE You can configure, whether documents and labels will be printed automatically when a dispensing cycle is started or only on operator demand in the miscellaneous settings as described in [Section 5.6 \(page 62\)](#).

2.1 Configuring Label Printing

If you use the fixed format labels, you must select the dimensions of the labels. Click the button FIXED LABEL TYPE. Select K&S CONTAINER LABELS for the container labels and K&S VIAL LABELS for the vial labels. For the container labels you may use labels of another manufacturer, if they have the same or slightly larger dimensions. For the vial label you should use the original K&S labels, because they withstand sterilization.

Select the desired printer and the paper source for the labels. Use the manual paper input for the labels and the magazine for the delivery notes and reports.

In case of the container labels, you can specify the number of copies, that are printed.

Preprinted copies holds for the labels, that are printed before the dispensing cycle is started while **Online Printed Copies** holds for the printing of labels with the measured activities.

Figure 6-2 Container Label Settings

As an alternative you may select CUSTOMIZED LABELS. Their layout is taken from special format files, that are designed by GEMS Global Radiopharmacy after your demands.

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Chapter 6 - Software Configuration Page 57

2.2 Configuring Delivery Notes and Reports

Figure 6-3 Settings for Delivery Notes and Reports

Enter name and address of your company and the product (tracer) name into the box

Data for Delivery Notes in the upper right corner of the window. Lay out data of the delivery notes and delivery reports are stored in format files, that may be customized by GEMS Global Radiopharmacy after your demands. If you need more delivery documents than just delivery notes (e.g. special documents for the transport), you can specify up to 10 format files after enabling VARIOUS DELIVERY DOCUMENTS, and clicking the CONFIGURE button. The required format files must be prepared by GEMS Global Radiopharmacy.

In most cases no delivery documents are required for vials that are filled in **Volume** mode (refer to [Section 1.5 in Chapter 4 - Operation](#)), because they are used for quality control only. You can prevent printing of delivery documents for these vials by enabling NO DELIVERY NOTES FOR VOLUME FILLED VIALS.

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Page 58 Section 3.0 - Specify Calibration Source and Nuclide factors

Section 3.0

Specify Calibration Source and Nuclide factors

In order to specify the data of the calibration source (Cs-137), select CUSTOMER SETTINGS / CALIBRATION SOURCE DATA in the menu.

Figure 6-4 Calibration Source Data

If you select ROBOT WILL TRANSPORT THE CALIBRATION SOURCE, a time list can be selected which automatically lets the robot transport the calibration source from the air lock into the ionization chamber and vice versa. Otherwise the operator is prompted to supply the source.

The prestored nuclide factors are related to the test radiator [See Table G-1](#).

If you use another type of Cs-137 radiator, you must determine a geometry correction factor, which can be entered here. Its effect is, that all nuclide factors are multiplied with this factor, but not the one of Cs-137 which is 1 by definition.

For changing the nuclide factors select PROGRAMMING / EDIT NUCLIDE FACTORS.

Figure 6-5 Configuration of Nuclide Factors

It is recommended to use the default nuclide factors.

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Chapter 6 - Software Configuration Page 59

Section 4.0

Device Configuration

Device Configuration allows for changing properties of the dispenser's components like valves, sensors etc. Normally there is no need to change any of them, but Device Configuration must be used for performing calibration of the sensors. Device configuration can be started by clicking on the SCREW DRIVER button.

or by selecting PROGRAMMING / DEVICE CONFIGURATION in the menu. A window will be shown, that lists all devices that are controlled or read out by the computer.

Figure 6-6 Software Configuration: Devices

Each Sensor has values for factor and offset, which serve for calibration Sensors The value displayed on the screen calculates:

display value = (raw input value + offset) x factor

This holds for all **analog input** devices but not for the activimeter, which is calibrated by an automatic procedure (see Section 4.1 in [Chapter 5 - Maintenance and Calibration](#)).

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Page 60 Section 5.0 - Miscellaneous Settings

Section 5.0

Miscellaneous Settings

5.1 Start Condition

Clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark START CONDITION allows to setup a condition for automatic start of the dispenser.

Figure 6-7 Software Configuration: Miscellaneous / Start Condition

Automatic Start is not included in the standard time lists. If you want to use it, you must include a special command in your time lists, which is described in a separate manual.

If you do so, the dispenser will start without user interaction if the activity received from the synthesis module is constant within the given limits for the given time and is greater or equal the given minimum activity.

5.2 Pump Settings

Figure 6-8 Software Configuration: Miscellaneous / Pump Settings

Clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark PUMP SETTINGS allows to set the pumps working speed and acceleration. These parameters should only be changed if explicitly recommended by GEMS Global Radiopharmacy.

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5.3 Clean Room

Figure 6-9 Software Configuration: Miscellaneous / Clean Room

Clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark CLEAN ROOM allows to setup the automatic regulation of constant air flow in the clean room module. The set point can be selected as part of full scale, which corresponds - if properly calibrated - to 0.65 m/s. The recommended value is 0.69 which results in an air speed of $0.615 \times 0.65 \text{ m/s} = 0.4 \text{ m/s}$.

Fan device and **device for monitoring the air flow** allow to select the proper components, that serve for these purposes. They should not be changed.

5.4 Tracer and Vials

Clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark TRACER AND VIALS allows to configure parameters related to the tracer and to the filling of the vials.

Figure 6-10 Software Configuration: Miscellaneous / Tracer and Vials

Total Volume Preset is used only for testing purposes and ignored in normal operation.

Volume of vial is selected to allow for checking the distribution data in order to avoid filling more volume than a vial fits. Similar to this **Smallest distributable volume** defines the smallest volume that is allowed to be filled in a vial. This avoids that the distribution data contain volumes that are too low to ensure that any activity is filled at all.

The **tracer nuclide** is selected in order to use the proper half life time for the calculations.

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The parameterized formula:

allows to apply a correction to the calculated filling volumes. **Chosen volume** is the volume that is automatically calculated from the selected activity. (Vials filled in volume mode are not effected by this). If you set , for instance a factor of 1.1 each vial will be filled with 10% more than calculated. This feature is normally not used and therefore factor should be set to 1 and offset to 0.

Undistributed remaining volume lets the software check, that the given volume remains in the collect vial. This enables to ensure that the last vial gets the required activity despite of the limited precision of the volume determination.

Number of test vials is used for testing purposes only. It does not effect the dispensing any way. It determines the number of vial test data that are used if a time list is tested by **test run of single time list**.

Allow Input of Preload Volume should not be used for normal operation and remain unchecked.

5.5 Sterilization

Figure 6-11 Software Configuration: Miscellaneous / Sterilization

Clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark STERILIZATION allows to set up sterilization monitoring.

Sterilization test vial temp and sterilization pressure allow to select the proper components, that serve for these purposes. They should not be changed.

USE STERILIZATION BY HEAT enables warning messages in case of not successfully sterilized batches. The criterion for a successful sterilization is given by the **minimum F0 value**, that must be reached. **Once this temperature is fixed in the SOP and has been validated it must never be changed.** GEMS Global Radiopharmacy recommends a value of 40 minutes. Additionally the minimum temperature can be given, above which the integration of F0 is performed.

5.6 Miscellaneous

Special Settings, that effect the software may be changed by clicking the menu entry PROGRAMMING / MISCELLANEOUS SETTINGS and then selecting tab mark MISC..

Filled Volume = <factor> × chosen volume + <offset> ml

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Figure 6-12 Software Configuration: Miscellaneous

The **Visualization Bitmap**, **Air Lock Type** and **Machine** settings should only be changed if recommended by GEMS Global Radiopharmacy. The **Simulation** settings are for testing purposes only and must be switched off for normal operation.

The user may select whether **MBq** or **mCi** shall be used as the activity unit. Note, that it may be required to change your reports files, that determine the appearance of the labels, distribution reports and delivery notes, because they determine some of the units that are actually printed - regardless the unit, that the printed values have. This holds for dispensers installed before 01.01.2002. Please contact GEMS Global Radiopharmacy, if you want to change the activity unit.

Allow manual commands during time list execution: If this is checked the operator may control the dispenser by mouse commands during time list execution.

Print Delivery Notes

Print Labels

If these are checked, labels will be printed automatically after a dispensing cycle is started and delivery notes will be printed automatically after a dispensing cycle is finished. If switched off, labels and delivery notes are only printed by the proper operator commands (See Section 1.6 in [Chapter 4 - Operation](#)).

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Page 64 Section 6.0 - Working with Different Tracers

Section 6.0

Working with Different Tracers

The dispenser software allows to use up to 9 18F based tracers. A dedicated set of data for delivery notes (See [Section 2.0](#) on [page 55](#)) and labels can be maintained for each tracer.

To enable the software to recognize, which tracer shall be used, you must create a windows **shortcut** for each of the tracers. Perform the following steps:

1. Move with the mouse on a position on the background of your **desktop screen**. Click the right mouse button.
2. From the menu that comes up, select NEW and then SHORTCUT. A new window (**Create Shortcut**) will come up. This window asks for a command line. Enter C:\Program Files\Dispensing Unit\Dispenser.exe /
TRACER1. (or /**TRACER2** etc).
3. Click on the NEXT button. You are now pleased to select a name for the shortcut. Enter the appropriate name, e.g. **Dispenser FDOPA**. Click on the FINISH button.

Each of these windows shortcuts will use different data for labels and delivery notes.

You must perform the according configuration (refer [Section 2.0](#) on [page 55](#)) for each of the shortcuts.

NOTICE Using the dispenser for different tracers requires that measures are taken to avoid cross contamination. The customer is responsible for this and should set up a validated procedure which may include a dedicated cleaning procedure to be performed before switching to another tracer.

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Appendix A - Buffering FDG Page 65

Appendix A

Buffering FDG

In order to avoid decomposition, the FDG must be adjusted to pH = 5.5. It is important, that it does not reach pH = 6, because at this pH a considerable degradation starts.

Replace the 1.2 mL 10% NaCl solution in the collect vial of the synthesizer by a NaCl / NaH₂PO₄ solution.

Add an amount of 10% NaCl solution, that results in a final concentration of 7.7 mg NaCl per mL of the buffered product.

Add an amount of 1 molar NaH₂PO₄ that depends on the cleaning cartridges. For the new cartridges (introduced in 2001) the suggested values:

- Cartridge **Set 4** (for acidic hydrolysis): 5.4 mg NaH₂PO₄ per mL of product volume
- Cartridge **Set 5** (for basic hydrolysis): 0.25 mg NaH₂PO₄ per mL of product volume

These values should be used as a starting value and may be refined after checking the pH and the osmolality in a first trial.

CALCULATION EXAMPLE FOR ACIDIC HYDROLYSIS

If nothing is lost in the cleaning cartridges, we expect the volume of the FDG solution to be equal to the water volume in vial 6, which is 14 mL. We expect the volume of the the NaCl/NaH₂PO₄ solution to be 1.9 mL, so the overall product volume will be 15.9 mL. This gives:

NaCl: 7.7 mg/mL x 15.9 mL = 122.4 mg NaCl, resp. 1.2 mL 10% NaCl solution

NaH₂PO₄: 5.4 mg/mL x 15.9 mL = 87.4 mg NaH₂PO₄ resp. 0.7 mL 1 molar solution

NOTICE It is the FDG producer's response to lay down the formulation of the product and to validate it. This must include the buffer. The buffer formulation described above is a suggestion. GEHC Global Radiopharmacy is not responsible for the validation of this formulation.

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Page 66 Appendix A - Buffering FDG

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Appendix B - Sterilization of FDG Page 67

Appendix B

Sterilization of FDG

Section 1.0

Requirement of Sterilization

According to the GMP "*Filtration alone is not considered sufficient when sterilization in the final container is possible. With regard to methods currently available, steam sterilization is to be preferred*"¹. The European Pharmacopeia recommends to sterilize a preparation in the final container. Sterile filtration is only considered, if the terminally sterilization is not possible². On the other hand, it is proved, that FDG can be sterilized³ by moist heat at temperatures below 140°C.

Because of this, the dispensing unit is designed to sterilize the FDG after dispensing into the vials with a steam sterilizer.

Section 2.0

Sterilization Concept

The dispensing unit uses steam sterilization with a sterilization temperature well below 140°C. In order to avoid decomposition of the FDG. For this purpose it is also important, that the pH value of the FDG solution is below 6 (optimum: 5.5). To achieve this, a buffer has to be added to the FDG solution before dispensing. The possible decomposition products are well known and can be detected in the chromatographic quality control.⁴ So, any decomposition that may take place in the case of malfunction of the sterilization unit or too high pH value would be detected in the quality control.

1. Good manufacturing practices. Medicinal products for human and veterinary use, The rules governing medicinal products in the European Union Vol. 4, 1998 Edition, Annex 1, No. 82

2. European Pharmacopeia, 1997, 5.1.1

3. Nebeling, B., 5. Workshop of the working group —Radiochemistry/Radiopharmaceutics of the Deutsche Gesellschaft für Nuklearmedizin, Wolfsberg, Switzerland 1997

4. Nebeling, B., to be published

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Page 68 Section 2.0 - Sterilization Concept

In order to check the proper sterilization, the F_0 value is determined for each sterilization cycle. The F_0 value has the dimension of a time and is directly proportional to the reduction of microorganisms. It is defined by:

where

D_{121} is equal to the time required at 121°C to reduce the population of the most heat resistant organism in the product by 90% (**D value**).

A is the microbial count per vial (bio burden)

B is the maximum acceptable probability of survival of microorganisms

This means, that a sterilization with an arbitrary temperature causes the same reduction of microbes than a sterilization at 121°C and a duration that is given by the F_0 value.

2.1 Required F_0 value

It is the users response to determine the required F_0 value during validation. In the following, an example is given. At first, we need to fix the values of A , B and D .

The D -value of the reference germ *B. stearothermophilus* was determined in distilled water and FDG solution. The D -value was 30% lower in the FDG solution than in water. Consequently the standard reference germ *B. stearothermophilus* can be taken as a reference germ in [18F]FDG solution as well and we use the standard D value of 1.5 minutes as a conservative estimation.

The bioburden (A) is expected to be low, because the FDG is produced from sterile initial products, sterile filtered and filled into sterile vials. It is not higher than approx. 10-100 germs/vial and we assume conservatively as the worst case 1.000 germs/vial. The maximum acceptable probability of survival of microorganisms (B) is determined by the requirement of a security assurance level (SAL) of at least 10^{-6} (*sterile* criterion of EN 566). So we set B to 10^{-6} .

With these values we can calculate the F_0 value, that is required to achieve the SAL value of 10^{-6} :

For security reasons, we increase the required F_0 value in order to meet the requirement of the overkill procedure, which is a 10^{12} reduction of microorganisms. So our final sterilization criterion is:

$$F_0 = D_{121} \cdot (\log A - \log B)$$

5. "Validation of Steam Sterilization Cycles," Technical Monograph No. 1, Parenteral Drug Association, Inc., Philadelphia, PA.

$$F_0 = 1.5 \text{ min} \cdot (3 + 6) = 13.5 \text{ min}$$

$$F_0 \geq 18 \text{ min}$$

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Appendix B - Sterilization of FDG Page 69

This must hold even in the coldest vial. For taking into account any measurement uncertainty, it is recommended to add a safety factor to this value. The sterilizer reaches at least $F_0 = 30$ minutes.

2.2 Check of Successful Sterilization

For the measurement of the F_0 value, that is achieved during a sterilization cycle, the temperature is monitored by an independent temperature sensor (See [Chapter 3 - Description of the Dispenser](#)). Then the F_0 value is calculated by:

where

t_1 is the time at which a temperature of 130°C is reached during heating up

t_2 is the time at which the temperature falls below 130°C during cooling down

T_0 is the temperature to which the F_0 value is related. It is fixed to 121°C

$T(t)$ is the time depended temperature in the sterilization unit

z is the temperature difference in °C that causes an increase of the D value by a factor of 10

Δt is the time interval of the periodically temperature measurements. It is equal or less than 2 seconds.

In order to take into account for limited temperature measurement precision, it is recommended to check for an F_0 value that is larger than the required F_0 value of 18 minutes. **A suggested value is 30 minutes.** For illustration here is an example of the effect of a wrong temperature measurement: If you achieve an F_0 value of 46 minutes with a temperature reading that is 1°C too high, the real F_0 value would be 36 minutes.

$F_0 10$ $(T_0 - T(t))$ z $\frac{1}{z}$ $\cdot \Delta t$ t_1 t_2 $= \sum$

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Page 70 Section 3.0 - Description of the Sterilization Unit

Section 3.0

Description of the Sterilization Unit

The sterilization unit is a customized version of a sterilizer that is manufactured by SciCan (STAT /M 900). The unit has a build-in microprocessor that controls the sterilization cycle including steam preparation and the transfer of the steam into the chamber. In order to monitor the sterilization and to measure the F_0 value, the sterilizer is equipped with an independent temperature sensor.

This sensor is a Pt 100 resistance thermometer (according to IEC 751 class A), and is mounted into a test vial that is filled with 10 mL of isotonic sodium chloride solution, which has the same heat capacity and heat conduction as the FDG. This sensor and its electronic measurement chain is completely independent of the sterilizer. It's signal is recorded periodically in steps of 2.5s by the computer during the sterilization. The computer does not control the sterilizer, it only starts the sterilizer by closing a contact. The sterilization process is controlled by its build in microprocessor with is independent of the computer. So controlling and monitoring of the sterilization are completely independent.

Section 4.0

Validation Hints

The sterilization relies on the physical temperature/time relation of the sterilization cycle as measured by the F_0 value. According to EN 554 this means, that no microbiological tests are required for validation.

The sterilization process does not operate with plateau-time but it follows the F_0 value concept. Validation must show, that the F_0 value that is determined by the dispenser is correct. Because the F_0 value is directly proportional to the microorganism reduction and a proper value of F_0 guarantees, that the **sterile** criterion of EN 566 is fulfilled, it is not necessary, to check the holding time of the sterilizer.

4.1 Recording of a Sterilization Cycle in *Manual Operation* of the Software

For Validation purposes it is helpful to perform sterilization cycles without a complete dispensing cycle. This can be done by using the **manual operation mode** of the software.

Start **manual operation mode** by clicking the menu entry MAINTENANCE / MANUAL OPERATION or the yellow HAND-button. After the initialization is finished (the valves are colored blue or red) one can start a sterilization cycle by clicking the START-button of the sterilization unit. After the sterilization cycle is finished (the drawer opens)

manual operation mode should be terminated by clicking the red 0-button. If you start a second sterilization without previous termination and restart of **manual operation**, the recorded data would be mixed.

In contrast to the normal dispensing runs, the recorded temperature and pressure recording data are overwritten by each subsequent **manual operation** run.

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Appendix B - Sterilization of FDG Page 71

Consequently the recording data should be exported to excel files immediately after the sterilization run (See below).

To be able to compare time vs. temperature curves, validation measurements must

have the same start time as the monitor measurement, which has $t=0$ just after the drawer is closed. For software versions equal or later than 1.5.4 $t=0$ is additionally indicated by a beep of the computer.

4.2 Export of the Monitoring Data to Excel files

After the sterilization cycle is finished (the drawer opens) stop the **manual operation mode** by clicking the red 0-button. Go to the **distribution archive** by clicking menu entry FILE DISTRIBUTION ARCHIVE or the BOOKSHELF-button. In the list of distribution cycles select the line -LAST TEST RUN OF SINGLE TIME LIST - by clicking with the left mouse button. Then click with the right mouse button on it. A menu will show up, in which the entry EXPORT STERILIZATION DATA TO EXCEL must be selected. If you want to see the data together with the F_0 value on the screen, click the STERILIZATION DATA button.

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Page 72 Section 4.0 - Validation Hints

4.3 Connecting Temperature Sensors for Validation

In dispensing units installed after 4/2001 the drawer of the sterilization unit has a spare hole for connecting up to 4 additional sensors. For older machines a special validation drawer can be lent from GEMS Global Radiopharmacy or the drawer can be exchanged by a new one.

The drawer of the sterilization unit has a spare feed through for connecting independent thermocouples in order to validate the sterilizer. The following pictures show, how the wires of additional thermocouples (or other sensors) can be connected. The feed through is designed for up to 4 wires of 0.5 mm diameter, while the pictures show thicker wires for better visibility.

Figure B-1 Mounting Validation Sensors into the Sterilizer

a: Mounted for normal operation

b: Mounted for connecting validation sensors

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Appendix B - Sterilization of FDG Page 73

4.3.1 Removing the Front Panel

In most cases the thermocouple wires will easily fit through the gap between the dispenser front panel and the white front panel of the drawer. This gap stays even with closed drawer. In some cases it may be required to remove the front panel of the drawer.

In order to do this, open the three screws that serve to fix the front panel on the drawer.

One of these screws is indicated by a red arrow in the picture shown below. The other two screws are located below the drawer's bottom (not visible in the picture).

Additionally open the three screws that fix the stainless steel duct at the drawer's front panel (also marked with a red arrow).

Figure B-2 Removing the Front Panel of the Sterilizer Drawer

4.4 Pressure Sensor does not need to be Validated

Usually the pressure in a steam sterilization chamber for medical instruments or for clothes is monitored in order to check the condition of saturated steam, which is important to avoid air bubbles within the chamber. In the case of the dispenser we sterilize liquids in closed vials, so that the air bubble problem does not exist.

Nevertheless the unit the pressure is monitored, but this only for information and to make diagnosis easier in case of a fault (e.g. defect seal). For this reason, the pressure monitoring needs not to be validated.

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Appendix C - List of Alarms and Error Messages Page 75

Appendix C

List of Alarms and Error Messages

Section 1.0

List of Alarms and Error Messages

All messages numbers begin either with **U** or with **E**. The messages of the **U** type are caused by malfunction, configuration errors or operator errors or they inform the operator about a special situation. Two special **U** messages (U2055 and U2056) are related to the robot or to the pump of the dispenser. They contain an additional error code and message, which are explained in [Table C-2](#) and [Table C-3](#) in [Section 3.0 - Robot and Pump Error Messages](#).

Messages of the **E** type are internal software errors and should be reported to GEHC Global Radiopharmacy. They are not listed here. Some of the explanations in the following lists refer to the **configuration database**. This is a database file, that stores the configuration of the machine and the time lists. For the dispenser the filename is dispenser.mdb and for the synthesizer it is synthesizer.mdb.

Messages that occur in standard situations, need no further explanations and have no message number, are not listed.

Section 2.0

“U”-Messages

Table C-1 U-Messages

Message

Number

Message Text Explanation

U1001 Calibration check could not be done.

An error happened during the initialization of the control unit prior to activimeter calibration. Possibly, the control unit has a malfunction. Check the control unit in **manual operation**.

U1002 Calibration could not be done.

See U1001.

U1004 Please configure the 'Clean' 1 time list!

An attempt has been made to start the **clean 1** cycle, but no time list has been assigned to this task.

Assign a proper time list for **clean 1**.

U1005 Please configure the 'Clean 2' time list!

See U1004.

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Page 76 Section 2.0 - “U”-Messages

U1006 Time List <name>. not found in the database.

The time list with this name could not be accessed within the configuration database. Restore the back up copy of your configuration database. Contact technical support if the problem remains.

U1007 The Database contains no

time list set!

Restore the back up copy of your configuration database.

U1008 The configuration of the control unit has not yet been stored on this computer
(...) Do You want to save this configuration?

Answer the question with YES if this is the first software start after a fresh installation. If this message occurs in other cases contact the technical support.

U1009 Control unit configuration mismatch: (...)

The configuration that is actually reported by the control unit does not match the original configuration. Close the software and start **manual operation**. If the message comes again, contact technical support.

U1010 Control unit configuration mismatch: (...)

See U1009.

In this case more components than originally installed were detected.

If you did not install new components of the control unit, contact technical support.

U1011 Please configure the Rinse time list!

See U1004.

U1012 WARNING: Vials are NOT sterile!

The required F_0 value was not achieved during the sterilization. Check the sterilizer (power, water and waste bottles). If sterilization has been performed check the recorded temperature data.

U1013 The time list set is not properly configured: There is no time list for step 1.

An attempt has been made to start a dispensing cycle, but no time list has been assigned to the mentioned step. Assign a proper time list for this step. Dispensing programs, that use sterilization, require 3 steps, programs for aseptic dispensing require 2 steps. Restore the back up copy of your configuration database. Contact technical support if the problem remains.

Message

Number

Message Text Explanation

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U1014 Time list can't be started,
because there are errors in
device or template
definitions!

There is an error in at least one of
the visualization parts of the device
or template definitions. Contact
technical support.

U1015 Manual operation not
possible, because there are
errors in device/device
template definitions!

See U1014.

U1016 Can't find process bitmap
<file name>.

Check, whether the bitmap file for
the visualization is installed in the
folder of the software. This file is
selected within the **misc. settings**.

U1017 Can't find <file name>. The configuration database could
not be accessed. Check, whether it
is installed in the folder of the
software. If you have a network,
check whether the database is
accessed by an other computer.

U1018 The database file < file
name> is read only. Please
make all files in this
directory writeable and
restart this software!

The configuration database was
found to be **read only** .Follow the
instructions in the message.

U1019 <software name> is already
active!

The software has been started
twice. If you cannot find the
window of the previously started
software, restart the operating
system and retry.

U1020 The configuration database
contains no process data!

Restore the back up copy of your
configuration database. Contact
technical support if the problem
remains.

U1021 Time list can't be edited
now, because there are
errors in device/device
template definitions!

There is an error in at least one of
the visualization parts of the device
or template definitions. Restore the
back up copy of your configuration
database. Contact technical
support if the problem remains.

U1022 There is no distribution
which has status 'aborted'

and has a total activity
measurement not older than
24 hours!

You tried to restart a distribution,
but no distribution data record
which is suitable could be found.

Message

Number

Message Text Explanation

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Page 78 Section 2.0 - "U"-Messages

U1023 No separate lock out step is
defined in the time list
set!

You tried to restart a lock out
procedure, but no suitable time list
could be found. Restore the back
up copy of your configuration
database. Contact technical
support if the problem remains.

U1024 There is no distribution
which is ready to lock out.

You tried to restart a lock out
procedure, but no distribution data
record with at least one vial, that is
not locked out, could be found.

U1025 The Lock Out procedure can't
be resumed. Please use
'Distribution / Restart Lock
Out Procedure' instead!

Click the ABORT button (red 0)
and follow the instructions of the
message.

U1026 Time List can't be started,
because there are errors in
device/device template
definitions!

There is an error in at least one of
the visualization parts of the device
or template definitions. Restore the
back up copy of your configuration
database. Contact technical
support if the problem remains.

U1027 There are no distribution
data for <program name>.

"Enter Distribution Data or
select an other procedure
than <program name>.

Follow the instructions in the
message. Note that each
distribution data record is
connected to one of the programs
(typically named **FDG1** and
FDG2), that is selected in the
upper left part of the main window.
You can only start a distribution
that belongs to the currently
selected program.

U1028 The time intervall must be

within 30 s ...3600 s.

After starting activity recording (suitable for testing purposes, not used during normal operation), you entered an improper time interval. Select a time between 30s and 3600s.

U1029 <different text> The software discovered an improper version of the Com Server driver software or it was not able to determine the version of the Com Server. The message may be shown after updating the software. You will find a proper Com Server driver on the software CD. Please call technical support for instructions to install it.

Message

Number

Message Text Explanation

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Appendix C - List of Alarms and Error Messages Page 79

U1030 You cannot import from the currently active Database!

(Use the 'save as' button in the time list editor to double a time list within the database.)

Follow the instructions of the message.

U1031 The file <filename> is no dispenser hardware database! The configuration database is damaged. Restore the back up copy of your configuration database. Contact technical support if the problem remains.

U1032 No match for <text>. You tried to import configuration data from a file that is not suitable for this.

U1033 You cannot import from the currently active Database!

(Use the 'save as' button in the time list editor to double a time list within the database.)

Follow the instructions of the message.

U1043 The file <filename> is no dispenser hardware database! You tried to import configuration data from a file that is not suitable for this.

U1044 The imported time list is stored under the name <name>

It contains <count> time list commands, that have no corresponding device!

You have imported a time list, that

has references to devices that are not included in your configuration database.

U1045 <Different text>. You have not completed one of the preparation steps.

U1046 This software needs 24 hours time format. Please set this in control panel / country settings / time! The time format should be: 'HH:mm:ss' Your operating system is not properly configured. Follow the instructions of the message.

U1047 Please configure the 'Clean' time list! (Menu: Programming / Time List / Time List Set).

An attempt has been made to start the clean cycle, but no time list has been assigned to this task. Assign a proper time list for the clean cycle.

U1048 File MSINFO32.EXE not found. SYSTEM INFO was invoked from the ABOUT box, but the system info software was not found on the hard disk.

Message

Number

Message Text Explanation

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U2000 'Simulated Activity' is selected, but the file <file name> does not exist! Deselect 'Simulated Activity' or create the file!

The file, that contains values for the **simulated activity** feature could not be found.

U2001 Warning: <different text>

You can change this in 'Programming / Misc'.

At least one of the simulation features is enabled.

U2002 No I/O Channel has been defined for the activimeter signal.

The configuration is not proper. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

U2003 No I/O Channel has been defined for the activimeter control.

See U2003.

U2004 No Counter Channel has been assigned to the activimeter!

See U2003.
 U2005 Missing device definition
 for the activimeter signal.
 See U2003.
 U2006 Missing device definition
 for the activimeter control.
 See U2003.
 U2007 Missing device definition
 for the air lock control.
 See U2003.
 U2008 Missing device definition
 for the gripper.
 See U2003.
 U2009 Missing device definition
 for the robot.
 See U2003.
 U2010 Missing device definition
 for the sterilizer control.
 See U2003.
 U2011 Missing device definition
 for the autoclav status.
 See U2003.
 U2012 Missing device definition
 for the autoclav temperature
 of test vials.
 See U2003.
 U2013 Missing device definition
 for the autoclav pressure.
 See U2003.
 U2014 Missing device definition
 for the helium pressure.
 See U2003.
 U2015 Missing device definition
 for the clean room fan.
 See U2003.
 U2016 Missing device definition
 for the clean room air flow.
 See U2003.

Message

Number

Message Text Explanation

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U2017 For this software the system
 must be rebooted at least
 one time a week. The reboot
 is now necessary, please
 shut down the system and
 reboot!
 Switch the computer off and start
 again.
 U2018 Port for data acquisition
 module not configured!
 The configuration is not proper. If
 you changed it intentionally,
 correct it. Otherwise restore the
 back up copy of your configuration
 database. Contact technical
 support if the problem remains.

U2019 I2C Bus control module not configured!

See U2018

U2020 Port for robot not configured! Check device list and I/O channel list!

See U2019

U2021 I2C Bus Control Module at COM <port number> not responding!

Terminate the software, reset the control unit and start again. If the error stays, check the power and connection cables of the control unit and the cable between the ComServer and the hot cell. If you cannot fix the problem, contact technical support.

U2022 Robot not responding! See U2021

U2023 Digital pump not responding! See U2021

U2024 Configuration error: Robot has no com port.

See U2019

U2025 Air lock error: <different texts>

Check the airlock. If you cannot fix the problem, contact technical support.

U2026 The time list is empty! The currently selected time list has no entries. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

U2027 to

U2039

Error in time list:

<different texts>

The currently selected time is erroneous. If you changed it intentionally, correct it using the hints in the error message.

Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

Message

Number

Message Text Explanation

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U2040 The hardware does not provide a high precision counter, which is required by this software!

This computer is unsuitable for the dispenser and synthesizer software.

U2041 Dummy version without hardware drivers!

You have started a demonstration version of the software.

U2042 Firmware file <file name> not found!

Check, that the mentioned file is present in the folder of the software.

U2043 No counter channel has been assigned to the activimeter!

The configuration is not proper. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains

U2044 The number of tray positions is too large!

Check the tray or sterilizer data.

Click PROGRAMMING / COMPONENT POSITIONS AND ROBOT PARAMETER.

U2045 Too large X distance or number of positions for the tray!

See U2044

U2046 Too large Y distance or number of positions for the tray!

See U2044

U2047 The number of sterilizer positions is too large!

See U2044

U2048 Too large X distance or number of positions for the sterilizer!

See U2044

U2049 Too large Y distance or number of positions for the sterilizer

See U2044

U2050 Port for robot not configured!

See U2019

U2051 Illegal component position data: Number of tray and autoclav vials must be >0!

Check the position data in Click PROGRAMMING / COMPONENT POSITIONS AND ROBOT PARAMETER or in manual operation mode.

U2052 Inconsistent tray coordinates!

See U2051

U2053 Inconsistent sterilizer coordinates!

See U2051

Message

Number**Message Text Explanation****GE HEALTHCARE****DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT*****Appendix C - List of Alarms and Error Messages Page 83***

U2054 Robot movements will only be simulated!

The software is currently switched to **simulated robot**. You can change this by clicking PROGRAMMING / MISC. SETTINGS / MISC.

U2055 Robot error <additional text>

or

Pump error <additional text>

The robot microprocessor reported an error, which is described in the message. For details see [Table C-2](#) and [Table C-3](#) in [Section 3.0 - Robot and Pump Error Messages](#).

U2056 <Robot or pump not initialized error with different text>

The pump or the robot is not initialized. It cannot be operated until it is initialized. The pump can be initialized using the INITIALIZE button on the visualization screen, the robot is initialized automatically a dispensing cycle or manual operation mode is started.

U2057 See U2055

U2058 See U2055

U2059 Inconsistent tray coordinates!

Check the position data belonging to the tray.

U2060 Inconsistent sterilizer coordinates!

Check the position data belonging to the sterilizer

U2061 Device <name> has as visualization problem (bad size or position). Check visualization the command(s) of this device, which includes 'AUTOFILL' !

The configuration is not proper. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

U2061 Please terminate the software and start again!

The time list has been aborted while it was waiting. For technical reasons this requires a restart of the software.

U2061 Time out reading
activimeter!
Check the activimeter in **manual
operation.**

U2064 Sterilizer door does not
open!
Check the sterilizer in **manual
operation.**

U2065 Sterilizer door does not
close!
Check the sterilizer in **manual
operation.**

U2066 Sterilizer reports an error!
(See sterilizer LCD display
for error code)
Check the sterilizer in **manual
operation.**

U2067 Error: Sterilizer did not
sign 'ready' after <N>
minutes.
Check the sterilizer in **manual
operation.**

Message

Number

Message Text Explanation

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U2068 See U2065

U2069 See U2065

U2070 The measured activity of <N>
MBq is too low!
The amount of activity is too low for
a dispensing or the
ionizationchamber or the
electronics is defect.

U2071 The measured reduced
activity is not smaller than
the total activity!" (...)

Unexpected activities were
obtained during the volume
determination

U2072 Device for Pump Volume
Preset not found!

Incorrect device configuration.

U2073 See U2072

U2074 Temperature <N> reports an
error!

Check temperature channel N of
the control unit.

U2075 <Different text> The robot arm is not in the proper
starting position for the submitted
command. This is most probably
caused by an error in the time list,
or - if in **manual operation** by an
improper command.

U2076 Pump cannot pick up this
volume! <different text>

You tried to suck more volume
than the pump fits.

U2077 See U2076

U2078 Before the total volume is calculated, there must be measuring points of 'reduced volume' in the time list!

The time list is not correct

U2079 <different text> The program has been aborted due to a software error. Please contact GEHC Global Radiopharmacy.

U3000 Error copying <file name 1> to " <file name 2>

Check, whether the file number 1 is present in the folder of the software.

U3001 There are no data! A filling precision statistics can currently not be prepared, because no data of dispensing cycles are stored in the database.

U3002 The dispenser database <file name> could not be found!

Check, whether the mentioned file is present in the folder of the software.

U3003 to

U3005

<value> is not a valid number"

For the mentioned value an invalid number was entered. This is most probably caused by including spaces or more than one point in the input.

Message

Number

Message Text Explanation

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U3006 to

U3008

<value> must be > 0! Enter a value that is greater than zero.

U3009 to

U3010

Please, enter a valid Batch Number!

Dispensing data must have a batch number. The batch number field may not be left empty.

U3011 The Batch Number <text> is already assigned to another synthesis. Please select another!

Two syntheses are not allowed to have equal batch numbers.

U3012 Please enter a valid date!

<different texts>

The date, that was entered, is not in the proper form and could not be

recognized by the software.

U3013 Please enter a valid time!

<different texts>

The time, that was entered, is not in the proper form and could not be recognized by the software.

U3014 Time difference between

customer ref. date <date and

time> and synthesis date

<date and time> is too

large!

The date difference is so large, that it is not possible to calculate a proper activity.

U3015 The measured total activity

of <value> is too small!

The measured activity was lower than 1 kBq. Check, that the activity has been transferred to the collect vial. Check the activimeter.

U3016 The measured total active

volume of <value> is to

small!

The measured activity was lower than 0.001 mL. Check, that the activity has been transferred to the collect vial.

U3017 Please enter a batch number! See U3009

U3018 Please enter a valid date!

<different texts>

See U3012

U3019 Please enter a valid time!

<different texts>

See U3013

U3020 Please enter a valid date!

<different texts>

See U3012

U3021 Please enter a valid time!

<different texts>

See U3013

U3022 Vial <name> has no activity!"

Either enter an activity greater than zero, or delete the entry for this vial.

U3023 Activity for vial <name> is

too small (too small

volume)! Do you want to

correct the error?"

The entered activity leads to a volume that is lower than the configured minimum. It is recommended to answer with YES and enter a higher activity for this vial.

Message

Number

Message Text Explanation

GE HEALTHCARE

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U3024 Activity for vial <name> is too large (too large volume for vial)!

The entered activity leads to a volume that is more than the vial fits. Enter a lower activity for this vial.

U3025 Vial <name> has no volume! Either enter a volume greater than zero, or delete the entry for this vial.

U3026 Volume for vial <name> is too small! Do you want to correct the error?

The volume that was entered is smaller than the configured minimum. It is recommended to answer with YES and enter a higher volume for this vial

U3027 Volume for vial <name> is too large.

The entered volume is more than the vial fits. Enter a lower activity for this vial.

U3028 The sum of the activities over all customers is greater than the total activity (minus undistributable remaining activity of <value>. Please correct the distribution data! Do you want to correct the error?

It is recommended, to correct the distribution data by deleting at least one vial or reducing the activities or volumes, that have to be filled into the vials.

U3029 No activity is distributed! At least one vial must receive a volume above the configured minimum.

U3030 Do you really want to proceed without correcting the error?"

You answered message U3026 or 3028 with NO.

U3031 See U3012 See U3012

U3032 See U3013 See U3013

U3033 Required volume is zero, can't calculate!

The optimum dilution volume cannot be calculated.

U3034 Batch volume is zero, can't calculate!

See U3033

U3035 Current concentration is smaller than the required concentration!

See U3033

U3036 Warning: Resulting NaCl

volume is unusual high!
Calculation of the optimum dilution
volume leads to an unusual high
NaCl volume. Check the entered
data.

Message

Number

Message Text Explanation

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U3037 Calculation Error:

<description>. Data cannot
be saved. You can proceed
without saving the data or
you can correct the data Do
you want to correct the
data?

Check the entered distribution
data.

U3038 See U3012 See U3012

U3039 See U3003 See U3003

U3040 See U3013 See U3013

U3041 See U3012 See U3012

U3042 to

U3043

See U3003 See U3003

U3044 See U3013 See U3013

U3045 Please enter a customer #! A customer record must include a
customer number.

U3046 This customer # is already
in use, please choose
another!

Customer numbers must be
unique.

U3047 This Record can't be
deleted, because it is used!

Customer records, that are
referenced in at least one
distribution record, cannot be
deleted.

U3048 Currently there is no record
selected!

Click with a mouse on the
customer, that you want to delete!

U3049 The size of the selected
label sheets is greater than
the paper size currently
selected for the Printer.

Please choose an other paper
size in the printer set up of
Windows

Follow the instructions of the
message.

U3050 Batch number must be greater
than 0!

For the starting batch number
enter a value greater than zero.

U3051 The database is empty! No distribution records could be
found in the database.

U3052 All Delivery Notes and Reports have already been printed!

The documents can only be printed if they are marked as **not printed**. You can change the printing status of a distribution by clicking FILE / DISTRIBUTION ARCHIVE and clicking with the right mouse button over the desired dispensing record.

Message

Number

Message Text Explanation

GE HEALTHCARE

DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT

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U3053 There are no data for this period!

You tried to print the delivery statistics, but no delivery data have been stored for the selected period.

U3054 Please enter a valid date! You did not enter a valid date for the delivery statistics.

U3055 The second date must be after the first date!

You entered an invalid period for the delivery statistics.

U4000 Invalid Value: <different text>

You entered an invalid time value in the time list editor.

U4001 This entry can't be deleted because is in use.

Time lists, that are referenced in at least one time list set cannot be deleted.

U4002 No values are defined for this device template

In the time list editor you tried to use an improperly defined device. Check the device template on which this device is based!

U4003 This time list cannot be deleted, because it is used by one of the time list sets!"

See U4001

U5000 I2C bus control module not found!

Terminate the software, reset the control unit and start again. If the error stays, check the power and connection cables of the control unit and the cable between the ComServer and the hot cell. If you cannot fix the problem, contact technical support.

U5001 Data acquisition module not

found!

See U5000

U5002 Robot not found! See U5000

Can't connect to control

unit / data acquisition

module

U6001 No 'analog input' device is

defined. You need it to

measure the helium pressure

and air flow. Until you have

not defined a device for

measuring the helium

pressure, You cannot set all

parameters!

Define the analog input devices.

Select menu entry

PROGRAMMING / DEVICE

CONFIGURATION.

U6001 Number of test customers

must be a valid number

between 1 and 24!

Select a number between 1 and

24.

Message

Number

Message Text Explanation

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U6003 Syringe volume must be a

valid number greater than 0!

Select a volume > 0.

U6004 Smallest distributable

volume must a valid number

be greater than 0!

Select a volume >0.

U6005 Vial volume must be a valid

number greater than 0!

U6006 Change of the sterilisation

option requires termination

and new starting the

software!

U6007 Change of the Air Lock Type

requires termination and new

starting the software!

U8000 The hardware does not

provide a high precision

counter, which is required

by this software!

See U2040

U8001 Currently the operation

system's decimal separation

character is <character> It

should be either ',' or '!'.

Please check control panel /

country settings!

Follow the instructions of the

message.

U8002 Can't open file <file name> The file containing the label format

data could not be opened.

U9000 Various messages with “Error in visualisation command” in the header bar.

The configuration is not proper. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

U10000
to 10030

<Different text> This group of messages is caused by the hardware driver, that connect the dispenser software to the I2C microprocessor in the control unit.

Contact technical support if the problem does not disappear.

U12000 Please select timelists for the transport of the calibration source!

The configuration is not proper. If you changed it intentionally, correct it. Otherwise restore the back up copy of your configuration database. Contact technical support if the problem remains.

Message

Number

Message Text Explanation

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Page 90 Section 2.0 - “U”-Messages

U12001 Please set the values for the test source (customer settings/test source data) and restart the calibration!

Calibration of the activimeter can not be performed, because the data of the calibration radiator have not been entered. Do this according to the instruction in the message.

U12002 Can't connect to control unit / data acquisition module

See U5000

U12003 Minimum activity of test source is not reached!

Either the activity of the test source is too small, or the test source is not in the ionization chamber or there is a failure in the activimeter, control unit or cabling.

U12004 Cannot find proper range for the test source

During calibration no proper amplification range could be found for measuring the test source.

Either the activity of the test source

is too small or too large, or the test source is not in the ionization chamber or there is a failure in the activimeter, control unit or cabling.

U12005 See U12002 See U12002

U12006 See U12000 See U12000

U12007 See U12001 See U12001

U12008 Warning: The ionization chamber is not calibrated!

Calibrate the activimeter.

U14000 Couldn't find printer

<name>. Trying to print on standard printer

Check whether the printer, that is selected in this software still exists in the printer folder of the operating system.

U14001 See U14000 See U14000

U14002 Warning: Region <name> is not defined!

A region was defined in the time list, but not in PROGRAMMING / EVALUATION OF RECORDED DATA.

U14003 Cannot find file <name> A file, that is required for the export of recorded synthesis data to Excel could not be found.

U15001 There are not enough free channels for a <N> bit

device. There must be <N-1> free channels following.

Define a device with less bits

U15006 To define a <N> bit device at this position, you must free the the following <N-1> bits!"

Message

Number

Message Text Explanation

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Appendix C - List of Alarms and Error Messages Page 91

U15007 You must define device templates before You can define devices!

Define templates!

U15008 No Values are defined for this device template

Define values!

U15009 <Text> is not a valid format string!

U15010 A Device of this type is already present. More than one device of this type is not possible!

U15011 For this device a 'Digital In' channel with <N> bits is needed!

U15012 For this device a 'Digital Out' channel with <N> bits

is needed!
 U15013 This device needs an 'Analog In', 'Temp. In' or 'Counter' channel!
 U15014 This device needs an 'Analog Out' channel!
 U150015 For this device a 'Digital Out' channel with 13 bits is needed!
 U15016 For this device a 'Digital Out' channel with <N> bits is needed!
 U15017 For this device a 'Digital In' channel with bits is needed!
 U15018 For this device a 'Digital Out' channel with 3 bits is needed!
 U15019 For this device a 'Digital Out' channel with 2 bits is needed!
 U15020 This device needs a COM Port connected to a Cavro Robot!
 U15021 For this device template at least one device state must be created
 U15022 For this device template more than one states have the same I/O value!

**Message
Number**

Message Text Explanation

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Page 92 Section 3.0 - Robot and Pump Error Messages

Section 3.0

Robot and Pump Error Messages

The messages listed in [Table C-2](#) and [Table C-3](#) occur within the messages U2055 and U2056. They inform more detailed about errors and special situations that are related to the robot or to the pump.

U15023 Pulsable devices may have only two states!

U15024 Max. <N> states are possible!

U15025 This combination of device function and operator action is not allowed!

U15026 Pulsable devices may have only two states!

U15026 For discrete devices display size must be set in 'Device template configuration' (if applicable).

**Message
Number**

Message Text Explanation

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Appendix C - List of Alarms and Error Messages Page 93

3.1 Errors of the Pump

Table C-2 Errors of the Pump

Message

Number

Message Text Explanation

1 Initialization
error"

This error occurs when the pump fails to initialize. Check for blockages and loose connections before attempting to reinitialize. The pump will not accept commands before it has been successfully initialized.

2 invalid command This error occurs, when an incorrect command is used. Inform technical support about this.

3 invalid operand This error occurs, when an incorrect parameter is given with a command. Inform technical support.

4 invalid command
sequence

This error occurs, when the communication between the computer and the robot is incorrect. Inform technical support.

7 device not
initialized

The pump was not initialized. It cannot be operated until it is initialized. The pump can be initialized using the INITIALIZE button.

9 Plunger overload This error occurs, when the syringe plunger loses too many steps. The pump must be reinitialized before normal operation can resume. Inform technical support.

10 Valve overload This error occurs, when the valve drive loses too many steps. Continual valve overload errors are an indication, that the valve should be replaced. The pump must be reinitialized before normal operation can resume. Inform technical support.

11 Plunger move not
allowed

When the valve of the pump is in one of the bypass positions (no open connection to the pump), plunger movement commands are not allowed Switch the valve into a position, where there is an open connection to the pump is.

15 Command overflow This error occurs, when the communication between the software and the robot firmware is incorrect. Inform technical support.

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Page 94 Section 3.0 - Robot and Pump Error Messages

3.2 Errors of the Robot

Table C-3 Errors of the Robot

Message

Number

Message Text Explanation

1 initialization
error

The robot failed to initialize. Check the flex cable

and movement mechanism for obstructions. If this does not help, a check of the fuses and the electronic board of the robot is required. Call technical support for this.

2 invalid command This error occurs, when an incorrect command is used. Inform technical support about this.

3 invalid operand This error occurs, when an incorrect parameter is given with a command. Inform technical support.

4 invalid command sequence

This error occurs, when the communication between the computer and the robot is incorrect. Inform technical support.

5 device not implemented

Check power supply and cables. Call technical support for this.

6 time out error This error occurs, when the communication between the computer and the robot failed.

Inform technical support.

7 device not initialized

The robot was not initialized. It cannot be operated until it is initialized. Restart the software and try again. The robot is automatically initialized when a dispensing cycle is started. In manual operation it must be initialized using the button within the **manual robot control** window. This error may occur if the power supply of the robot was interrupted or the control unit was resetted. In both cases an initialization of the robot is required.

8 command overflow This error occurs, when the communication between the computer and the robot is incorrect. Inform technical support.

10 entered move for Z-axis out of range

One of the programmed positions is out of the range of the robot. Call technical support.

20 step loss detected on X-axis

Most probably a crash is the reason. Try to find the reason and to fix the problem. Check the programmed positions. Other causes are broken cable connections or a defective robot. If the problem stays, call technical support.

21 step loss detected on Y-axis

See 20

22 step loss detected on Z-axis

See 20

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Section 4.0

“E”-Messages

Messages of the “E” type are internal software errors and may have different numbers after the “E”. They indicate software problems or errors and should be reported to GEHC Global Radiopharmacy.

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Page 96 Section 4.0 - “E”-Messages

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Appendix D - Data Format of Activimeter Calibration Check File Page 97

Appendix D

Data Format of Activimeter Calibration Check File

The data are stored in ASCII format in a file named **CalibrationCheck.txt**. Each measurement is stored in one line which contains separated by tab characters (ASCII 9):

1. Date of measurement
2. Time of measurement
3. Measured activity in MBq
4. Calibration activity (half life corrected) in MBq
5. Background activity in MBq

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Page 98 Appendix D - Data Format of Activimeter Calibration Check File

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Appendix E - Dismantling Instructions Page 99

Appendix E

Dismantling Instructions

If it is required to remove the dispenser out of the hot cell, the following steps must be performed. Ensure, that there is no radioactivity within the device.

1. Switch off the control unit. Close external valves for helium and compressed air.
2. Disconnect cables and lines from the top of the dispenser. Remove the top lid of the dispenser before. It can simply be lift-off without removing any screws.
 - 4 signal lines (DB25 connectors)
 - 24V power line for the robot (2 wires connect to terminal strip)
 - Tubes for FDG (up to 4)
 - Tube for compressed air
 - Tube for Helium
 - Tube for sterilizer water
3. Disconnect cables and lines from the back side of the dispenser.
 - Power line of the sterilizer (back side of sterilizer)
 - Waste water tube for sterilizer (back side of sterilizer)
 - Power line of the sterilizer (connector at the back of the sterilizer)
4. Disconnect tubes from the front of the dispenser
 - 2 Waste tubes
 - Ethanol tube
 - Water for injection tube
 - NaCl tube
5. Carefully take the dispenser out of the hot cell. Take into account, that the unit is rather heavy (approx. 70 kg)
6. If it is required to remove the control unit, disconnect all cables from the back side and, if installed, the optional reset cable from the front.

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Appendix F

Specifications

Table F-1 Electrical

Table F-2 Electrical Safety and Suppression

Table F-3 Operational Data

Input voltage and frequency

Control unit and dispenser

110-115 V AC / 220-240 V AC

switchable

47-63 Hz

Input voltage and frequency

Com Server

220-240 V AC 50 Hz

Input voltage and frequency

Sterilizer

220-240 V AC 50 Hz

Output voltage and current of Control
Unit

to supply robot (RSP 9651), syringe
pump (XL 3000),

Laminar flow module, ionization
chamber and remaining valves and
transducers

24 V DC \pm 2 V

+ 12-15 V DC

- 12-15 V DC

5 V DC

5 A

2 A

0.5A

6 A

Power consumption of dispenser max. 250 W

Power consumption Sterilizer max. 1380 W

Dielectric strength according to VDE

0806 / EN 60950

Primary - Secondary

Primary - Earth

Secondary - Earth

3.0 kVRMS

1.5 kVRMS

0.5 kVRMS

Class of Protection I to VDE 0100 Male connector with projecting
earth contact

Suppressed to EN 55022 150 kHz -
30 MHz

Ambient temperature 15°C to 40°C

Humidity 30% to 85% Non condensating

Storage temperature 0°C to 60°C

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Table F-6 Performance

Compressed air input pressure, tube size
400 to 800 kPa Ø6 mm
Helium input pressure, tube size 200 to 1000 kPa Ø1/8 inch
Over all dimensions width = 770 mm
depth = 735 mm
height = 780 mm (Z=840mm)
(780 with plate)
Corpus dimensions width = 770 mm
depth = 370 mm
height = 520 mm
Weight approx. 70 kg
Volume Collection vessel
Dilution vessel (optional)
~100 ml
~350 ml
Number of dispensed vials per cycle max. 17
Dispensable volume per 10 ml vial 0.25 - 8 ml
Type of dispensing: A. aseptic
B. with terminal sterilization
(including aseptic)
Inaccuracy of dispensed volume
Inaccuracy of dispensed activity
± 5%
± 10%
for volumes of at least 1 mL
First vial gets approx. 0.2 mL
less than selected
Automatic CIP (Cleaning in Place)
procedure: duration, agent
Not specified yet 70 % ethanol
Automatic rinse/flush cycle: duration,
agent
Not specified yet water for
injection

GE HEALTHCARE**DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT*****Appendix F - Specifications Page 103*****Table F-7 Sterilizer****Table F-8 Ionization chamber****Table F-9 Laminar Flow Unit**

Supply water conductivity 2-10 µS/cm
Supply tank capacity 2 l
Minimum water level 200 ml
Water consumption per cycle ~150 ml
Waste water tank capacity 5 l
Dimensions of sterilization chamber length = 190 mm
width = 90 mm
height = 53 mm
Volume of sterilization chamber 0.9 l
Maximum pressure 340 kPa
Maximum steam temperature 142°C
Sterilizing time 3.5 min
5 min
± 15 s
± 15 s
Sterilizing temperature 132°C / 135°C ± 2°C
Min F0 value 30 minutes

Range 18F
 Range 137Cs
 100 kBq to 300 GBq
 100 kBq to 500 GBq
 Energy range for gamma rays 25 keV to 3 MeV
 Measurement time (with change of
 ranges - autorange)
 2-90 s
 Measurement time (without change of
 range)
 1-15 s
 Absolute error < 5%
 Linearity error < 1%
 Dimensions Ø140 x 385 mm
 Fan Voltage: 24 V DC supply
 0..10 V DC control
 Nominal horizontal air velocity 0.45 m/s ± 20%
 Filter class according prEN 1822 HEPA H14
 Clean room Class (certified) US-Federal Standard 209D Class 100
 Dimensions clean room area width = 253 mm
 depth = 110 mm
 height = 176 mm

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Page 104 Appendix F - Specifications

Table F-10 Syringe Pump

Table F-11 Computer and Printer

Syringe size 5 ml
 Valve 4-way / 2 port (90°)
 Plunger drive High resolution 3000 / 24000
 steps
 Travel: 60
 mm
 Imprecision (according to OEM
 manufacturer)
 0.05% CV within run at full
 stroke
 Inaccuracy (according to OEM
 manufacturer)
 < 1% at full stroke

Material

Barrel:

Plunger:

Seal:

Borosilicate Glass

Stainless Steel

Virgin Teflon

Control Computer see computer manual

Printer see printer manual

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Appendix G - Consumables and Chemicals Page 105

Appendix G

Consumables and Chemicals

Table G-1 Consumables and Chemicals

Supplier Specifications,

Order No.

No. per cycle No. per box

Vials GEMS Global
 Radiopharmacy
 (ACILA)
 10 ml, evacuated 12 80
 Sterile filter B.Braun Sterifix Paed, 0.2 µm
 Ref No. 0409 9354
 1 50
 Needle B.Braun Sterican Gr.12, 0.70 x
 30 mm
 22G x 1 ¼"
 Ref No. 0465 7624
 1 100
 Filter for
 ventilation
 B.Braun
 Millipore, etc.
 1
 Dispensing
 Pin
 B.Braun Mini-Spike Plus 5µm
 Ref No. 0455 0234
 1 50
 NaCl
 solution
 0.9%, e.g. 100 ml bag
 or bottle
 1
 Ethanol 70%, for cleaning and
 disinfection
 ~20 ml
 Sterilizing
 Tissues
 B.Braun For surface
 disinfection of
 Laminar-flow unit
 Meliseptol
 Ref No. 0932 1608
 1 90
 Water for
 sterilizer
 Double distilled
 water, Conductivity 2-
 10 µS/cm
 Radiator
 for
 calibration
 www.nuklearmedizintechnik.
 de
 137Cs

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Appendix H - Spare parts Page 107

Appendix H

Spare parts

Table H-1 Spare parts

Supplier Specifications

HEPA filter GEHC Global Radiopharmacy
(Freudenberg)

H 14 (see dimensions on
label)

Robot cable GEHC Global Radiopharmacy
(CAVRO)

Flat moving cable for y-rack
on robot

Robot Z-axis
insulation block

GEHC Global Radiopharmacy
(CAVRO)

Pump syringe GEHC Global Radiopharmacy
(CAVRO)

Valves GEHC Global Radiopharmacy
(Bürkert / VICI)

Teflon tubes GEHC Global Radiopharmacy
Chamber Plastic

Insert for 17 vials

GEHC Global Radiopharmacy

Vial with Monitoring

Sensor

GEHC Global Radiopharmacy

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DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT

Page 108 Appendix H - Spare parts

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DIRECTION 2373114-100 REVISION 1 MANUAL AND OPERATING INSTRUCTIONS DISPENSING UNIT

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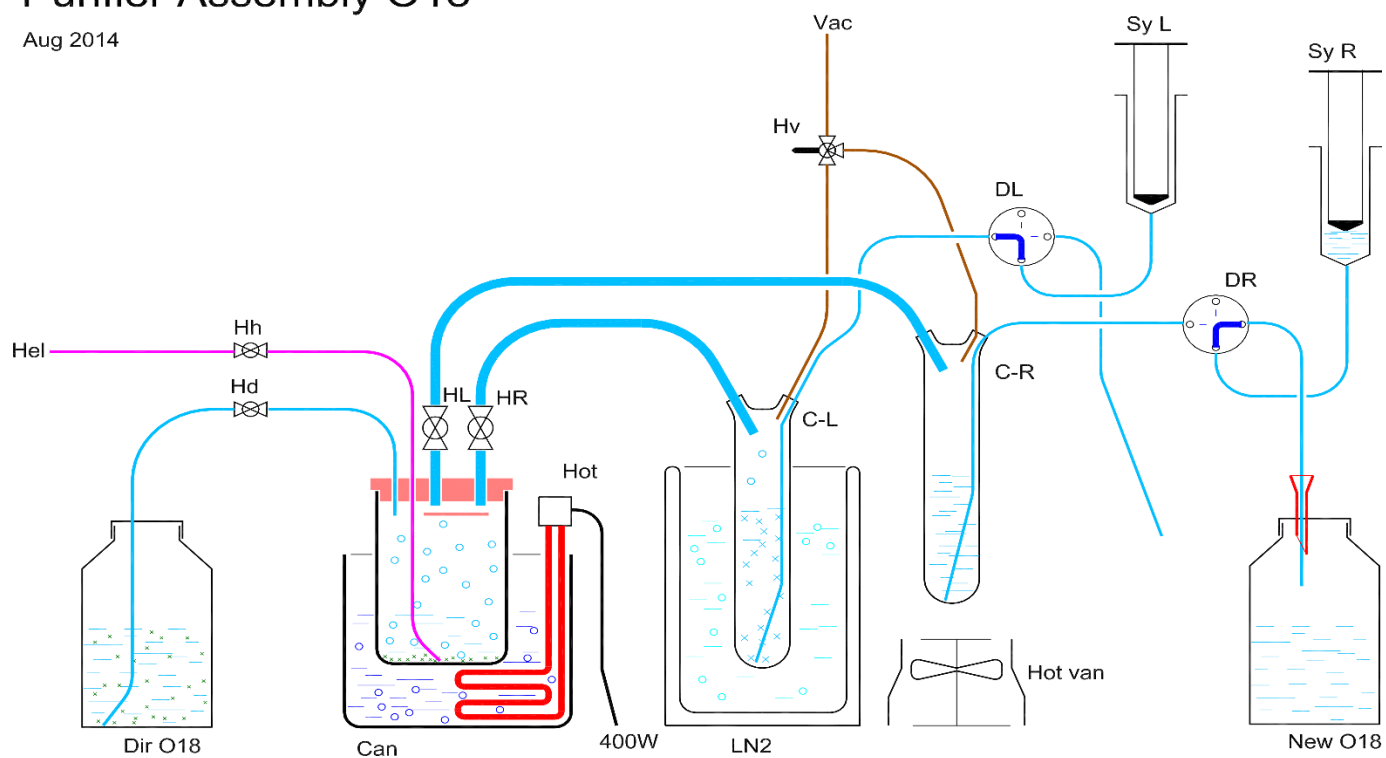
GE Healthcare-Europe: Fax 33.1.40.93.33.33

Paris, France

BIJLAGE III OVERZICHT DESTILATIE OPSTELLING

Purifier Assembly O18

Aug 2014



BIJLAGE IV OVERZICHT DATA RADIONUCLIDISCHE ZUIVERHEID

Als referentiewaarde voor de radionuclidische zuiverheid zijn 20 metingen verricht op virgin H_2O^{18} geproduceerd ^{18}F -FDG. Het gemiddelde hiervan is >99,99% (99,9999921485%) met een standaarddeviatie van <0,01% (0,000010738158%). De maximum waarde van de referentiegroep is 100% en het minimum is >99,99% (99,9999649208%) over een range van <0,01% (0,00035079101%).