表１　体内残留放射能又は距離 1m における線量率で表した解放規準値

放射性核種	体内残留放射能		1m の距離における線量率	
	GBq	mCi	mSv/h	mrem/h
Ag-111	19	520	0.08	8
Au-198	3.5	93	0.21	21
Cr-51	4.8	130	0.02	2
Cu-64	8.4	230	0.27	27
Cu-67	14	390	0.22	22
Ga-67	8.7	240	0.18	18
I-123	6.0	160	0.26	26
I-125	0.25	7	0.01	1
I-125 刺入	0.33	9	0.01	1
I-131	1.2	33	0.07	7
In-111	2.4	64	0.2	20
Ir-192 刺入	0.074	2	0.008	0.8
P-32	**	**	**	**
Pd-103 刺入	1.5	4	0.03	3
Re-186	28	77	0.15	15
Re-188	29	79	0.20	20
Sc-47	11	31	0.17	17
Se-75	0.089	2	0.005	0.5
Sm-153	26	700	0.3	30
Sn-117m	1.1	2	0.04	4
Sr-89	**	**	**	**
Tc-99m	28	760	0.58	58
Tl-201	16	43	0.19	19
Y-90	**	**	**	**
Yb-169	0.37	1	0.02	2

** 診断又は治療の目的で通常投与される放射能量から公衆が受ける線量は極めて小さいので、この場合には、放射能又は線量率の規準はあてはまらない。

・もしペレット又はシードが出てきているのを見つけたら：
　・それを指で扱わず、スプーン又はピンセットのようなものを用いてそれをジャー又は蓋のできる他の容器に入れてください。
　・シード又はペレットを入れた容器を、人の来ない場所において下さい。
　・この注意書きに掲載されている人の１人に知らせて下さい。」

解放患者が授乳する可能性があり、授乳を継続すると乳児の線量が 1mSv を超えるおそれがあれば特別の指示を与える必要がある。この場合、外部被ばくのほか、母乳を通じての内部被ばくを考慮しなければならず、核種のほかその化学形も影響する。指針には診断・治療に広く用いられている主要薬剤についての規準値が示されている（表 2)。

授乳中断期間は、新生児の最大線量が 1mSv(0.1rem)以下となるように選ばれている。ほとんどの新生児についての実際の線量は 1mSv(0.1rem)よりもずっと低いであろう。医師はこの中断期間の増減について裁量を行ってよい。なお、計算の詳細については NUREG-1492, "Regulatory Analysis on Criteria for the Release of Patients Administered Radioactive Material"に記されている。

患者に指示を与える場合、その指示には、授乳の中断又は中止の勧告に従わなかったときの結果について患者が理解できるような情報を含めるべきである。たとえば、I-131 を用いる処置の結果として、授乳を継続すれば、子供の甲状腺に害があるかもしれない。

これらの指示については、核医学会が 1997 年に作成した指針(Guidelines for Patients Receiving Radioiodine Treatment)が参考になる。放射性ヨウ素以外の核種を用いる診断行為ではほとんど影響はないであろう。

6. 患者固有の因子に基づいた線量計算方法

5.1 に記されているように、表 1 の規準値は計算の簡単化のために、たとえば代謝を無視するなどの過大評価を行っている。規則(c)により、もっときめ細かい検討をすれば、実態により近い線量評価が可能である。

6.1 滞在係数

以下の条件のもとに 1 より小さい滞在係数 E を考慮してよい：

・E = 0.75.　物理的半減期、実効半減期、又は膀胱滞留時間のような着目期間が 1 日以下のとき。

・E = 0.25.　下記のような指示を患者に与えた場合で、実効半減期が 1 日より大きいとき。
　・少なくとも最初の 2 日間は注意深く他人との距離を保つ、
　・少なくとも最初の晩は部屋に 1 人で寝る、
　・少なくとも最初の日には航空機又は大量輸送機関で旅行しない、
　・少なくとも最初の 2 日間は他人と一緒に長時間の自動車旅行をしない、
　・少なくとも最初の 2 日間は 1 人で風呂にはいる、
　・少なくとも最初の 2 日間は多量の水分を摂る。

・E = 0.125.　下記のような指示を患者に与えた場合で、実効半減期が 1 日より大きい

表 2　乳幼児に授乳する患者に対して、指示及び記録を必要とする放射性医薬品の放射能

放射性医薬品	指示		記録		推奨される授乳中断期間の例
	MBq	mCi	MBq	mCi	
I-131 NaI	0.01	0.0004	0.07	0.0002	完全な中止
I-123 NaI	20	0.5	100	3	
I-123 OIH	100	4	700	20	
I-123 mIBG	70	2	400	10	370MBq(10mCi)で24h
I-125 OIH	3	0.08	10	0.4	
I-131 OIH	10	0.30	60	1.5	
Tc-99m DTPA	1000	30	6000	150	
Tc-99m MAA	50	1.3	200	6.5	150MBq(4mCi)で12.6h
Tc-99m Pertechnetate	100	3	600	15	1100MBq(30mCi)で24h 440MBq(12mCi)で12h
Tc-99m DISIDA	1000	30	6000	150	
Tc-99m Glucoheptonate	1000	30	6000	170	
Tc-99m HAM	400	10	2000	50	
Tc-99m MIBI	1000	30	6000	150	
Tc-99m MDP	1000	30	6000	150	
Tc-99m PYP	900	25	4000	120	
Tc-99m ｲﾝﾋﾞﾎﾞ赤血球標識	400	10	2000	50	740MBq(20mCi)で6h
Tc-99m ｲﾝﾋﾞﾄﾛ赤血球標識	1000	30	6000	150	
Tc-99m 硫黄コロイド	300	7	1000	35	440MBq(12mCi)で6h
Tc-99m DTPA エアロゾル	1000	30	6000	150	
Tc-99m MAG3	1000	30	6000	150	
Tc-99m 白血球	100	4	600	15	1100MBq(30mCi)で24h 440MBq(12mCi)で12h
Ga-67 Citrate	1	0.04	7	0.2	150MBq(4mCi)で1月 50MBq(1.3mCi)で2週 7MBq(0.2mCi)で1週
Cr-51 EDTA	60	1.6	300	8	
In-111 白血球	10	0.2	40	1	20MBq(0.5mCi)で1週
Tl-201 Chloride	40	1	200	5	10MBq(3mCi) で2週

とき、

・E = 0.25 に対する上記と同じ指示に従う、

・少なくとも最初の 2 日間は 1 人で生活する、

・少なくとも最初の 2 日間は家族又は友人の訪問を少なくする。

・たとえば甲状腺内成分と甲状腺外成分を用いる I-131 の取り込みの 2 成分モデルにおいて、一つの成分に関係する実効半減期が 1 日以下であるが、もう一つの成分に関係する実効半減期が 1 日を超えるならば、両成分のうち支配的な成分に関係する滞在係数を用いることがより正当化できる。

計算例 1：I-131 の 2220MBq(60mCi)を投与された患者により個人が受ける最も可能性のある線量を計算する。この患者は少なくとも最初の 2 日間注意深く他人から距離をとるよう指示されており、1 人で生活し、1 人で車で帰宅し、訪問者なしで数日間自宅にとどまっている。

解：物理学的半減期を用い、放射能がすべて減衰するまでの線量を次式から求める（排泄を考慮する場合は次節で計算する）：

$$D(\infty) = 34.6\ \Gamma\ Q_0 T_p E/r^2$$

患者は上記のような指示を受けているので、距離 1m における滞在係数として 0.125 を用いてよい。

$$D(\infty) = 34.6(2.2R\cdot cm^2/mCi\cdot h)(60mCi)(8.04d)(0.125)/(100cm)^2 = 4.59mSv(0.459rem)$$

6.2 実効半減期

個々の患者の評価においては、放射性核種の排泄を考慮し、実効半減期を用いてよいこととなっている。実効半減期は次式で定義される：

$$T_{eff} = (T_b \times T_p)/(T_b+T_p)$$

ここで、T_b = 放射性核種の生物学的半減期

T_p = 放射性核種の物理学的半減期。

I-131 の体内挙動は甲状腺外のヨウ素と甲状腺内のヨウ素の 2 成分を用いてモデル化することができる。甲状腺外成分（割合 F_1）と甲状腺内成分（割合 F_2）の実効半減期はそれぞれ次式で計算することができる。

$$T_{1eff} = (T_{b1}T_p)/(T_{b1}+T_p)$$

$$T_{2eff} = (T_{b2}T_p)/(T_{b2}+T_p)$$

ここで、T_{b1} = 甲状腺外ヨウ素の生物学的半減期

T_{b2} = 甲状腺内ヨウ素の生物学的半減期

T_p = I-131 の物理学的半減期。

しかしながら、単純な指数関数的排泄モデルでは、I-131 が胃から血液中に吸収される時間と膀胱にある尿中の I-131 のホールドアップが考慮されないので、他の人への線量の過小評価を来す可能性がある。この指針では、これらを考慮するため、投与後の最初の 8 時間に I-131 の投与量の 80 %が物理的半減期のみによる割合で体内から除去されるという保守的な近似を用いる。

すなわち、I-131 投与患者からの線量には 3 つの成分がある。第 1 の成分は投与後の最初の 8 時間(0.33d)に対する線量で、物理的半減期と係数 0.8 を用いて計算される。第 2 の成分は甲状腺外の放射能による、最初の 8 時間後から全崩壊までの実効半減期に基づく線量である。第 3 の成分は甲状腺内の放射能による、最初の 8 時間後から全崩壊までの実効半減期に基づく線量である。総線量は次式で表される。

$$D(\infty) = 34.6\ \Gamma\ Q_0\{E_1T_p(0.8)\{1-\exp(-0.693(0.33)/T_p\} + \{\exp(-0.693(0.33)/T_p)\}E_2F_1T_{1eff} + \{\exp(-0.693(0.33)/T_p)\}E_2F_2T_{2eff}]/(100cm)^2$$

ここで、F_1 = 甲状腺外取り込み割合

F_2 = 甲状腺内取り込み割合

E_1 = 最初の 8 時間に対する滞在係数

E_2 = 8 時間後から全崩壊までの滞在係数。

計算例 2：甲状腺がん。甲状腺の残存部分及び転移部分の治療のため、7400MBq(200mCi)の I-131 を投与された患者により被ばくする個人の、最も可能性の高い線量を計算する。

解：特定の患者について取り込み割合と実効半減期の測定値があればそれを用いてよいが、そうでなければ次表の値を用いて計算する。

表 3　I-131 を用いる治療に対する取り込み割合と実効半減期

医学的状態	甲状腺外成分		甲状腺内成分	
	取り込み割合 F_1	実効半減期 T_{1eff}(d)	取り込み割合 F_2	実効半減期 T_{2eff}(d)
甲状腺機能亢進症	0.20[1]	0.32[2]	0.80[1]	5.2[1]
甲状腺がんの切除後	0.95[3]	0.32[2]	0.05[3]	7.3[2]

[1] M.G.Stabin et al., "Radiation Dosimetry for the Adult Female and Fetus from Iodine-131 Administration in Hyperthyroidism," Journal of Nuclear Medicine, Volume 32, Number 5, May 1991.

[2] International Commission on Radiological Protection (ICRP), "Radiation Dose to Patients from Radiopharmaceuticals," ICRP Publication No.53, March 1987.

[3] The thyroid uptake fraction of 0.05 was recommended by Dr. M. Pollycove as an upper limit postthyroidectomy for thyroid cancer.

甲状腺がん患者についての計算は以下のようになる。

$$D(\infty) = 34.6(2.2)(200)[(0.75)(8.04)(0.8)\{1 - \exp(-0.693(0.33)/8.04)\} + \{\exp(-0.693(0.33)/8.04)\}(0.25)(0.95)(0.32) + \{\exp(-0.693(0.33)/8.04)\}(0.25)(0.05)(7.3)]/(100cm)^2 = 4.53mSv(0.453rem)$$

上の例で、F_2 = 0.05 は甲状腺組織を除いた患者には保守的な仮定である。特定の患者について測定値があれば、それを用いてよい。

計算例 3：甲状腺機能亢進症。甲状腺機能亢進症の治療に I-131 の 2035MBq(55mCi)を投与された患者により被ばくする個人の、最も可能性の高い線量を計算する。

解：甲状腺機能亢進症についての計算は以下のようになる。

$$D(\infty) = 34.6(2.2)(55)[(0.75)(8.04)(0.8)\{1 - \exp(-0.693(0.33)/8.04)\}+ \{\exp(-0.693(0.33)/8.04)\}(0.25)(0.20)(0.32) + \{\exp(-0.693(0.33)/8.04)\}(0.25)(0.80)(52)]/(100cm)^2 = 4.86mSv(0.486rem)$$

上の例で、F_2 = 0.8 は甲状腺機能亢進症の治療を受けた患者には保守的な仮定である。特定の患者について測定値があれば、それを用いてよい。

6.3 内部線量

I-131 のようなある種の放射性核種については、解放患者による他の個人の内部線量が有意に大きくなることが懸念される。内部被ばくによる預託実効線量当量は次式によって大まかに推定できる。

$$D_i = Q(10^{-5})(DCF)$$

ここで、D_i = 患者によって被ばくする個人の、最も可能性の高い線量(rem)

Q = 患者への投与放射能(mCi)

10^{-5} = 仮定された摂取の割合

DCF = 摂取量(mCi)を内部預託実効線量当量に換算するための線量換算係数

（たとえば、K.F.Eckerman, A.B.Wolbarst, and A.C.B.Richardson, Limiting Values of Radionuclide Intake and Air Concentration and Dose Conversion Factors for Inhalation, Submersion, and Ingestion, Federal Guidance Report No.11, U.S.Environmental Protection Agency, 1988 参照）。

計算例 4：内部線量。I-131 の 1110MBq を投与された患者による個人の最大内部線量を、経口摂取の経路について計算する。ほとんどの摂取は口又は皮膚を通じてのものであるので、経口摂取の経路を選択した。

解：上記文献にある線量換算係数は 53rem/mCi であるから、計算は以下のようになる。

$$D_i = (33mCi)(10^{-5})(53rem/mCi) = 0.17mSv(0.017rem)$$

この場合、外部線量は 5mSv(0.5rem)を超えないであろうから、内部被ばくは外部被ばくのおよそ 3%である。内部線量が外部線量の 10 %以下ならば、それは外部線量の不確実性よりも十分小さいので、無視してよい。

患者解放における内部被ばくがあまり重大でないことは、NCRP の報告書にも述べられている(NCRP Commentary No.11, "Dose Limits for Individuals Who Receive Exposure from Radionuclide Therapy Patients," 1995.)。

厚生科学研究費補助金（医薬安全総合研究事業）
「医療機関における放射線利用の合理化と
新しい機器の法制面への取り入れに関する研究」

分担研究報告書

分担研究課題名　「放射性医薬品の適正で有効な利用とガイダンスレベルに関する諸外国の動向調査」

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研究要旨
現在米国で作成中の FDG を中心とした放射性医薬品の製造、管理、使用に関する GMP 草案を入手し、我が国の現状と比較検討した。その結果、細部での修正点は必要であるものの、グローバルスタンダードとして GMP に準拠した PET に関する規定の早急な整備が必要であると考えられた。

A．研究目的

先年度に実施した諸外国における FDG を中心とした放射性医薬品の取扱に関するアンケート調査の結果から、それらの製造、管理、使用に関してグローバルスタンダードとして GMP 準拠が必要であることが伺えた。今年度は引き続き諸外国の動向調査をすることを予定した。この様な背景の中、米国においても、FDA が現在 PET 製剤の使用に関して GMP 草案を作成中であり、その資料を入手することが出来たので、本資料を元に我が国における実状と将来動向に関して考察した。

B．研究方法

FDA が作成中の PET に関する GMP 草案（以下、FDA 草案と略する）は FDA のホームページから参照することが可能である。その URL は
http://www.fda.gov/ohrms/dockets/dockets/98d0266/98d0266.htm である。

C．研究結果・考察

上記資料、FDA 草案とその日本語訳を本報告書に資料として添付した。

FDA 草案の内容は、１．品質管理、２．生産管理、３．組織管理、４．配布管理、５．記録管理に大別される。各項目の詳細に関しては添付の FDA 草案を参照することとし、ここでは記載しないが、日本アイ

ソトープ協会医学薬学部会サイクロトロン核医学利用専門委員会が作製した院内サイクロトロン放射性薬剤に関する指針に記載される項目と表現の方法は異なるものの、ほぼ一致している。我が国の各 PET 施設の実状を勘案しても、より詳細な基準の作製と作業のマニュアル化により十分対応可能な内容であると考えられる。ただし、品質管理項目において、品質管理部門の設置を定めており、十分なかつ独立した人員の確保を求めている。米国での一部の施設の実状を聞き取りしたところ、生産部門には教育、訓練された Radiochemist が、また品質管理部門には Radiopharmacist がそれぞれ独立的に専任で常駐している。過去に実施した本研究班におけるアンケート調査によると、我が国の PET センターの多くでは薬剤師免許を有する人員、一人が生産、品質管理を同一の部屋で実施しており、施設によってはサイクロトロンの運転も行っていたり、薬剤師免許を有する人員がいない施設もあるのが実状である（*薬剤師免許を有する人員：薬剤師免許を有していても、病院内では薬剤部に所属する薬剤師の定員数の関係から薬剤師として登録されていない人員）。この様な状況からすると、建物の構造上も、組織の構成上からも満足しうる施設は少ないものと考えられる。我が国において今回検討した FDA 草案と同様の管理を実施するとしても、我が国のみが品質管理部門と生産部門を一体化させることは不可能であるので、この点に関して、移行猶予期間の設定や何らかの指導等が必要となるものと考えられた。

この問題以外にも細かい修正点は必要であると思われるが、GMP に準拠した PET 薬剤に関する規定は FDG の保険適用を控える現状を鑑みても早急な整備が必要であると考えられた。

D．添付資料

１．Draft Outline for Positron Emission Tomography (PET) GMPs.

２．陽電子放出核種を用いる断層撮影法(PET)の GMPs 草案

Draft Outline for Positron Emission Tomography (PET) GMPs

Working Draft

Not for Implementation

February 1999

This document is a preliminary working draft prepared by the Agency as a starting point for discussions. It does not reflect the official Agency position on CGMPs for PET products and may not be used to satisfy regulatory requirements.

Table of Contents

Draft Outline for Positron Emission Tomography (PET) CGMPs

I. Scope

Minimum current good manufacturing practice for methods to be used in, and the facilities and controls used for the production, holding, or distribution of a safe and effective positron emission tomography (PET) drug intended for human use.

II. Quality System

1. Each PET Center must establish, implement and maintain a quality system that has the following features: organizational structure; defined responsibilities; and allocation of resources.

2. Review suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements and the established quality policy and objectives.

3. Dates and results of quality system reviews must be documented.

4. Quality system must include a quality control unit.

- With responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and PET drug products.
- Responsible for approving or rejecting all procedures or specifications affecting the identity, strength, quality, and purity of the drug product.
- Authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated and corrective action has been taken.
- Responsible for approving or rejecting drug products produced under contract by another company.
- Has adequate laboratory facilities available for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials,

in-process materials, and drug products.

- Responsibilities and procedures applicable to the quality control unit must be in writing; such written procedures must be followed.

5. Quality audits performed to ensure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system.

- Conduct quality audits according to pre-determined frequency.
- Conducted by individuals who do not have direct responsibility for the matters being audited.
- Corrective action(s), including a reaudit of deficient matters, must be taken when necessary.
- Report results of each quality audit, and reaudit(s) where taken, and have reports reviewed by a manager having responsibility for the matters audited.
- Manager of the PET center must certify in writing that the quality audits have been performed and documented, and must state the dates on which reviews and audits were performed and whether any required corrective action has been undertaken. Actual results need not be shown to FDA.

6. The quality system must ensure that the PET center has a sufficient number of personnel for the production, holding, storage, testing, and distribution of a safe and effective PET drug with the necessary education, background, training, and experience to enable them to perform their assigned functions correctly.

III. Laboratory Controls

1. Specifications, standards, sampling plans, test procedures, or other laboratory controls to be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

2. These requirements to be followed and documented at the time of performance. Deviations from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms must be recorded and justified.

3. Laboratory controls to include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity.

4. Each PET center ensures that all measuring gauges, recording devices and test equipment, including mechanical, automated, or electronic test equipment, is suitable for intended purposes and capable of producing valid results. Procedures to ensure that Each PET center ensures that all measuring gauges, recording equipment is routinely calibrated, inspected, checked, and maintained must be established and followed. Activities to be documented.

5. Calibration procedures to include specific directions and limits for accuracy, sensitivity, specificity, precision and reproducibility of performance.

- When limits are not met, there must be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the identity, strength, quality, and purity of the PET drug.

- Instruments and equipment not meeting established calibration criteria must not be used. Activities are to be documented.

- Calibration standards used for measuring and testing equipment must be traceable to national or international standards, if available, or to an internal reproducible standard established to maintain consistency.

- The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date must be documented. These records must be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

6. Laboratory records to include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of the sample received for testing with identification of the source (that is, the location where the sample was obtained), quantity, lot number or other distinctive code, time and date sample was taken, and time and date the sample was received

for testing.

- A statement of each method used in the testing of the sample to indicate the location of data establishing that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested.

- The suitability of all testing methods used must be verified under actual conditions of use.

7. A statement of the weight or measure of the sample used for each test.

8. A complete record of all data obtained in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product for each lot tested.

9. A record of all calculations performed in connection with each test, including units of measure, conversion factors, and equivalency factors.

10. A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

11. The initials or signature of the person who performs each test and the date(s) the tests were performed. Documentation showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

12. Complete records must be maintained of any modification of an established method employed in testing. Records to include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

13. Complete records must be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

IV. Production and Process Controls

1. Each PET center to ensure that key process parameters that could affect product quality are controlled and monitored. Develop and follow written production and process control procedures. The PET center to document that key process

parameters were controlled in accordance with procedures at the time of performance. Deviations from the written procedures to be recorded and justified.

2. Each PET center to establish, maintain, and follow procedures for changes to a specification, method, process, or procedure. Changes to be validated before implementation, and activities documented.

3. Each PET center to establish, maintain, and follow procedures to adequately control environmental conditions, where necessary. Environmental control system(s) must be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. Activities to be documented and reviewed.

4. Each PET center to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances or personnel that could reasonably be expected to have an adverse effect on product quality.

5. PET production facilities to be of suitable design and contain sufficient space to perform necessary operations, prevent mixups, and assure orderly handling of materials and equipment.

6. Each PET center must ensure that all equipment used in the production process is appropriately designed, constructed, placed, and installed for its intended use. Equipment must be constructed so that surfaces that contact components, in-process materials, or drug products are not reactive, additive, or absorptive so as to alter the quality of the drug product beyond the official or other established requirements.

7. Each PET center to establish, maintain, and follow appropriate schedules for the adjustment, cleaning, and other maintenance of equipment to ensure proper functioning of equipment. Maintenance activities, including the date and individual(s) performing the activities, must be documented.

8. Computers or automated data processing systems used as part of production must be validated for their intended use according to an established protocol. Automated data processing system changes must be reviewed to determine the need for revalidation before approval and issuance. Validation activities and results to be documented.

9. Actual yields and percentages of theoretical yield must be determined at the conclusion of each appropriate phase of production or holding of a PET drug.

10. The manufacturing process must be validated according to established procedures, and the quality control unit must approve the validation. The validation activities and results, including the date and signature(s) of the individual(s) approving the

validation, the monitoring and control methods and data, and the major equipment qualified, must be documented.

11. When changes or process deviations occur, the PET center must review and evaluate the changed process and perform revalidation. Activities to be documented.

12. Each PET center must establish, maintain, and follow written procedures that will assure that the complete history of the production and distribution of PET drugs can be determined. This may be done by identifying with a control number each batch or portion of a batch of PET drugs and documenting this number in the batch production and control record. The procedures must facilitate corrective action in the event that defective product quality is identified.

13. Batch production and control records must be prepared for each batch of drug product produced and must include complete information relating to the production and control of each batch. These records must include:

- An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

- Documentation that each significant step in the production or holding of the batch was accomplished, including:

    1. Dates

    2. Identity of individual and major equipment used;

    3. Specific identification of each batch of component or in-process material used;

    4. Weights and measures of components used in the course of production;

    5. In-process and laboratory control results;

    6. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

    7. Specimens or copies of all labeling used;

    8. A description of drug product containers and closures;

    9. Any sampling performed;

10. Names of persons performing and directly supervising or checking each significant step in the operation;

11. Any investigation made into the failure of a batch or any of its components to meet any of its specifications.

14. All drug product production and control records, including those for packaging and labeling, must be reviewed and approved to determine compliance with all established, approved written procedures before a batch is released for administration to a patient. This review and approval must be documented.

15. Any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications must be thoroughly investigated, whether or not the batch has already been distributed. The investigation must extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation must be made and maintained and must include the conclusions, follow-up, and a description of any corrective action.

V. Control of Components and Drug Product Containers and Closures

1. Each PET center must establish, maintain, and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures.

2. Components and drug product containers and closures must be handled and stored at all times in a manner to prevent contamination and/or deterioration. Containers and closures includes the dispensing and administration assemblies.

3. Each component and container or grouping of containers and closures for the drug product must be uniquely identified for each lot in each shipment received. This identifier must be used to trace the disposition of each lot. Each lot must be appropriately marked to reflect its status (i.e., quarantined, approved, or rejected).

4. Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures must be examined visually for appropriate labeling as to contents, container damage, broken seals, and contamination.

5. Components, drug product containers, and closures must

be stored under quarantine until they have been tested or examined, as appropriate, and released.

6. Each lot of components, drug product containers, and closures must be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

7. Representative samples of each shipment of each lot must be collected for testing or examination. Samples must be collected in a manner to prevent contamination of either the component or the sample. Samples must be examined and tested as follows:

- At least one test must be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, must be used.

- Each component must be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the PET center, and provided that the PET center establishes the reliability of the supplier's analyses.

- Containers and closures must be tested for conformance with specifications. In lieu of such testing by the PET center, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the PET center and provided that the PET center establishes the reliability of the supplier's test results.

- Each lot of a component, drug product container, or closure that is susceptible to objectionable microbiological contamination must be examined against established specifications for such contamination.

8. Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity may be approved and released for use. Any lot of such material that does not meet such specifications must be rejected.

9. Components, drug product containers, and closures may be retested or reexamined for identity, strength, quality, and purity as necessary, e.g., after storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the component, drug product container, or

closure, if the PET center wants to use the components, drug product containers, or closures. After retesting or reexamination, the components, drug product containers, and closures must be approved or rejected by the quality control unit.

10. Rejected components, drug product containers, and closures must be discarded.

11. Drug product containers and closures must not be reactive, additive, or absorptive, and must be sterile, pyrogen-free, and protect the drug product so as to preserve its established safety, identity, strength, quality, and purity.

12. Records for components, drug product containers, and closures must include the following:

- The identity and quantity of each shipment of each lot of components, drug product containers, and closures; the name of the supplier; the supplier's lot number(s) if known; the unique identifier for that lot; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, must be listed if known.

- The results of any test or examination performed and resulting actions.

- The disposition of rejected components, drug product containers, and closures.

VI. In-Process and Finished Product Acceptance Activities

1. Each PET center must establish, maintain, and follow procedures for acceptance activities including inspections, tests, or other verification activities. These procedures must be established, maintained, and followed.

2. Each PET center must ensure that specified requirements for in-process materials are established, maintained, and followed. Procedures must ensure that in-process materials are controlled until the required tests or other verification activities have been completed, or necessary approvals are received, and are documented.

3. Each PET center must ensure that each PET drug product batch meets the established acceptance criteria.

4. PET drug products must be held in quarantine or otherwise adequately controlled until released and must not be released for distribution until the following occur:

- Associated data and documentation are reviewed;
- Release is authorized by the signature(s) of a designated individual(s); and
- Authorization is dated.

5. Each PET center must document acceptance activities. Records must include: acceptance activities performed; dates the activities are performed; the results; the signature(s) of the individual(s) conducting the acceptance activities; and the equipment used. These records must be part of the Historical Record.

6. Each PET center must identify by suitable means the acceptance status of the PET drug product, i.e., its conformance or nonconformance with acceptance criteria. The identification of acceptance status must be maintained throughout production of the product to ensure that only a product that has passed the required acceptance activities is distributed or used.

7. For each batch of drug product, there must be appropriate laboratory determination of satisfactory conformance to acceptance criteria for the drug product, including its identity, strength, quality, and purity, prior to administration to the patient. This does not include sterility testing, which does not need to be completed before administration to the patient but should be completed as soon as possible after filtration.

8. When the product is distributed prior to completion of testing, there must be a mechanism to inform the receiving facility of final product test results before the drug is administered to the patient. Such communication with the receiving facility must be documented. If the product fails the sterility tests, these results must be communicated to the receiving facility.

9. Any sampling and testing plans must be described and conducted in accordance with written procedures.

10. The accuracy, sensitivity, specificity, and reproducibility of test methods must be established and documented.

11. Drug products failing to meet established standards or specifications and any other relevant quality control criteria must be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

VII. Nonconforming PET Drug Product and Corrective and