EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

08 July 2014
EMA/416439/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on Guideline on core SmPC and package leaflet for (^{99}Mo/^{99m}Tc) generator (EMA/CHMP/773757/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
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General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
1	Typing error in (^{99m}Tc): 99m should be put in exponent.	Agreed.
1	Please could you confirm which word is correct : "extemporaneous" or "extemporary"? Line 224….: For instructions on extemporaneous preparation of the medicinal product before administration, see section 12.	"extemporaneous" is the correct word
1	**Line 376 : In all templates concerning section 4.6** Fertility, pregnancy and lactation The use of drugs especially radionuclides being damageable for the capacity to have children in the future and not for the children already born, the term of **fecundity** (*fertilité* in French) seems to be more appropriate than fertility (*fécondité* in French).	Disagree. The term "fertility" has been chosen.
1	**In all templates concerning radiopharmaceuticals, in section 6.6,** the term "etc" could be replaced by "biological fluids" standing for blood (bleeding or periods), sweat…. "The administration of radiopharmaceuticals creates risks for other persons from external radiation or	The guideline on Core SmPC and PL for Radiopharmaceutical uses the word "etc." Therefore, this term is acceptable.

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	contamination from spill of urine, vomiting ~~etc~~ or any other biological fluids. Radiation protection precautions in accordance with national regulations must therefore be taken."	
3	The SPC refers to the EANM dosage card for paediatric dosing. This has recently been updated (March 2014). http://www.eanm.org/publications/guidelines/art10.1007_s00259-014-2731-9.pdf	The link has been updated.
3	The SPC mentions the Ph Eur limit of 0.1% ^{99}Mo in ^{99m}Tc for radionuclidic purity. Ph Eur is currently considering lowering this limit so check what limit is in effect when the SPC is finalised.	The Ph Eur limit has been confirmed.

Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 167	3	Comment: I believe that this is an SPC specifically for the $^{99}Mo/^{99m}Tc$ radionuclide generator rather than a general SPC for any radionuclide generator. Proposed change (if any): …$^{99}Mo/^{99m}Tc$ radionuclide generator	The pharmaceutical form is expressed as "radionuclide generator". Therefore, the comment is not agreed.
Line 167	5	Comment: Activity in both GBq and mCi should be mentioned Proposed change (if any):	Not agreed. The guideline uses the international naming convention.
various	3	Comment: Inconsistent use of superscript. (^{99m}) should be superscript Proposed change (if any): Corrected	Agreed.
Line 173	2	Comment: "mean energy of 140 keV" The mean energy is typically listed as 140.5 keV or 140.51 keV, so the value is 141 keV to 3 significant figures. Proposed change (if any): "mean energy of 140.5 keV"	The change of 1 keV is not considered significant for technetium. Therefore, change is not agreed.
Line 173-174	2	Comment: "a half-life of 6.02 hours" Bureau International des Poids et Mesures gives the half-life	Agreed.

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		as 6.0067 h. This is the value in Evaluated Nuclear Structure Data Files (ENSDF) as accessed at https://www-nds.iaea.org (International Atomic Energy Association) and is consistent with a comparatively recent study (da Silvaa, Appl. Radiat. Isot., 60:301-305, 2004) and NIST (National Institute of Standards and Technology) report (Unterweger, Appl. Radiat. Isot., 56:125-130, 2002). Proposed change (if any): "a half-life of 6.01 hours"	
Line 177	5	Description of the chromatographic column should be more elaborate and should contain the information that the column is composed of Plexiglas around Alumina column	Comment not agreed.
Lines 180-185	4	Comment: It is new to add both activities from mother and daughter radionuclide. This completely theoretical approach does not provide much support for the clinicians. It seems more confusing than helpful. It may be designed to accommodate reimbursement structures in an individual country. Proposed change (if any): Mallinckrodt Medical proposes to delete this text: The ^{99}Mo on the column is in equilibrium with the formed daughter isotope ^{99m}Tc. ~~The generators are supplied with the following ^{99}Mo activity amounts at activity reference time~~	There is a need to choose one strength for mother/daughter radionuclide. This was done for clarity. The comment is not agreed.

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		~~which deliver the following technetium (^{99m}Tc) amounts, assuming a 100% theoretical yield and 24 hours time from previous elution and taking into account that branching ratio of ^{99}Mo is about 87%: [Product specific]~~ ~~^{99m}Tc activity~~ ~~(Maximal theoretical eluable activity at calibration date, {XX} CET) i.e. 2.0 GBq~~ ~~^{99}Mo activity~~ ~~(at calibration date, {XX} CET) i.e. 2.5 GBq~~	
Line 182	2	Comment: we would suggest to specify that the document is referring to elution yield Proposed change (if any): the sentence should be as follows: “alla frase “…assuming a 100% theoretical elution yield….”	Agreed.
table between Line 184 and 185	2	Comment: the statement reported in the table for ^{99m}Tc activity (Maximal theoretical eluable activity at calibration date, {XX} CET), is in contradiction with what is previously stated at rows 180-183 (The generators are supplied with the	There is a need to know the activity to administer to patients. Therefore it is considered that both values are required in order to convert from Mo to technetium activity. This information is considered important and the comment is thus not

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		following ^{99}Mo activity amounts at activity reference time which deliver the following technetium (^{99m}Tc) amounts, assuming a 100% theoretical yield and 24 hours time from previous elution and taking into account that branching ratio of ^{99}Mo is about 87%); this may be misleading and we suggest to harmonize the above definitions with the second one, which really allows to calculate a theoretical yield value.	agreed.
Line 184	5	Comment: Activity in both GBq and mCi should be mentioned Proposed change (if any):add mCi in the table.	GBq is only mentioned as it is the international standard. Thus, comment not agreed.
Line 186-187	2	Comment: as the elution yield is depending also on the time elapsed from the previous elution, we would suggest to reword the sentence as follows: Proposed change (if any): The technetium (^{99m}Tc) amounts available by a single elution depend on the real elution yield of generator itself declared by manufacturer and approved by NCA and on the time from the last elution	This information is covered in line 182. Thus, there is no need to amend, the comment is not agreed.
Lines 186-187	1	Comment: section2: improvement of the wording.	The change is agreed except for deletion of the text which is not agreed.

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		Proposed change (if any): The technetium (^{99m}Tc) amounts available by a single elution depend on the real yields of the kind of generator used ~~itself~~, ~~declared by manufacturer and approved by NCA.~~	
Line 208	1	Comment: section 4.1: replacement of "developed and approved for radiolabelling with such solution" by "relevant" or "appropriate". Proposed change: • labelling of relevant kits for radiopharmaceutical preparation.	The change is not agreed as the kit would need to be approved by the NCA.
Lines 241-266	4	Comment: Recently an updated version of the EANM dosage card was released, if you combine this with updates in: - ECSi - EU SmPC template - EU Guideline on core SmPC… - EU Guideline on Tc Generator…. - ICRP update - etc You will end up with a mandatory variation each 6 months. Some of these guidelines must be replaced. Mallinckrodt Medical therefore prefers not to mention any specific dosage schedule.	The section was harmonised so that both tables are there for the choosing, without the tables, there would be a lack of harmonisation. Therefore the comment in not ageed.

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		Proposed change (if any): Mallinckrodt Medical BV proposes to keep only the following text: The activity to be administered to children and adolescents must be adapted and may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; ~~the activity administered to children and….~~ ……*Lacrimal duct scintigraphy*: Recommended activities apply as well for adults as for children.	
Lines 273 and282	1	Comment: section 4.2: according to the EDQM Standard Terms definition, the word "intraocular use should be used, "Ocular use is excluded". Proposed change (if any): For intravenous and intraocular use (intraocular use)	The terms "intraocular use" suggests an invasive use whereas "ocular use" suggest the form of an eye drop (instilled). Comment from QRD: The EDQM distinguishes the two routes of administration by means of the preposition, i.e. "intraocular" is administration INTO the eye, whereas "ocular" is administration UPON the eye. See official EDQM definitions below: *Intraocular use: administration of a medicinal product **into** the eye. The term 'intraocular use' is only for use when a more specific term (e.g. 'intracameral use', 'intravitreal use') does not apply. Ocular use and subconjunctival use are excluded.* *Ocular use: administration of a medicinal product **upon** the eyeball and/or conjunctiva.*

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			For ordinary eye drops, we would certainly advice the term “ocular use”.
Lines 288-289	4	Comment: Mallinckrodt Medical proposes to add ‘(Meckel Diverticulum)’ after ‘ectopic gastric mucosa’. Proposed change: Identification/location of ectopic gastric mucosa (Meckel Diverticulum): immediately after intravenous injection…..	Agreed.
Line 296	1	Comment: following information on contraindications from CSP could be added: Proposed change (if any): - when using a kit for radiopharmaceutical preparation information on contraindications should be sought in the SmPC and PIL of the kit for radiopharmaceutical preparation.	Comment not agreed. The indication is for pertechnetate solution not for labelling kit.
Line 308	1	Comment: section 4.4 : Product for diagnostic use only, therefore “therapeutic effect” should be omitted. Proposed change (if any): For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably	Agreed.

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		achievable to obtain the required diagnostic information.	
Lines 319-320	4	Comment: If blocking agents are given with regard to the quality of the images, then Mallinckrodt Medical agrees. If for safety reasons: the risk of giving perchlorate exceeds the risk of Tc-^{99m} and should not be recommended for this purpose. Proposed change (if any):	This issue is discussed in line 323. Therefore, no change has been implemented.
Line 328-330	1	Comment: - The information concerning the use of thyroid blocking agent could be transferred after lines 323-324 for more consistency and clarity. - According to the Compilation of QRD decisions on stylistic matters in product information, the word “should” has to be avoided to prevent from error in translation in romance languages. Proposed change (if any): Patient preparation Pre-treatment of patients with thyroid blocking medicinal products may be necessary in Meckel's diverticulum scintigraphy or lacrimal duct scintigraphy To avoid false positives or to minimise irradiation by reduction of pertechnetate accumulation in the thyroid and salivary glands, a thyroid blocking agent **must** be given prior to lacrimal duct scintigraphy or Meckel diverticulum scintigraphy.	For line 323, the sentence is already included. Specifying the indication is not considered necessary. Thus, the comment is not agreed.

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Line 332	1	According to the Compilation of QRD decisions on stylistic matters in product information, the word “should” has to be avoided. Proposed change (if any): Before the application of sodium (^{99m}Tc) pertechnetate solution for scintigraphy of Meckel’s diverticulum 332 the patient ~~should~~ must keep an empty stomach for 3 to 4 hours to reduce intestinal peristalsis.	Agreed. We try to avoid the use of the term “should” as much as possible because it tends to create problems when translating it.
Lines 339-340	4	Comment: MAH proposes to delete the time period of 12 hours, as this is depending on the activity administered and the used kit. Proposed change: Close contact with infants and pregnant women should be restricted ~~during 12 hours~~.	We acknowledge that it is difficult to have a consensus on the period of time that one should avoid contact with infants and pregnant women. However, it is felt that some guidance should be provided. Thus, the comment is not agreed.
Line 343, 351, 360, 364, 386	2	Comment: Typographical error superscript: ^{99}mTc Proposed change (if any): ^{99m}Tc	Agreed.
Lines 351-353	1	Comment: section 4.4: these 2 sentences regarding sodium content should be transferred after line 346. Proposed change (if any): Specific warnings Sodium pertechnetate (^{99m}Tc) solution for injection contains XXX mg/mL of sodium.	Agreed.

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		Depending on the time when the injection is administered, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg). This should be taken into account in patient on low sodium diet. When sodium pertechnetate (^{99m}Tc) is used for labelling of a kit, the determination of the overall sodium content must take into account the sodium derived from the eluate and the kit. Please refer to the package leaflet of the kit.	
Line 348	1	Comment: the full name should replace MR. Proposed change (if any): In salivary gland scintigraphy a lower specificity of the method should be expected compared to **magnetic resonance sialography**	Agreed.
Lines 415-418	4	Comment: Mentioning of all frequencies is superfluous, as there is only 1 frequency used. Proposed change Tabulated list of adverse reactions The frequency of undesirable effects is ~~are~~ defined as follows: ~~Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and~~ not known (cannot be estimated from the available data).	Agreed. If all ADRs fall into only one frequency category, it would be enough to define that one.

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Line 434, 937	2	Comment: This risk of hereditary defects is unduly alarming and is far too low to be relevant. The BEIR report states: "Evidence for Adverse Health Effects such as Cancer and Hereditary Disease … The latter risk is sufficiently small that it has not been detected in humans, even in thoroughly studied irradiated populations such as those of Hiroshima and Nagasaki." (National Research Council "Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2", 2006). Proposed change (if any): Remove "and a potential for development of hereditary defects" (Line 434) and "and hereditary abnormalities" (Line 937).	The deletion is not agreed.
Lines 471-473	4	Comment: As not in all countries sodium perchlorate is commercially available, MAH prefers to mention only perchlorate and leave the counter ion to the clinic. Proposed change: The uptake in the thyroid, salivary glands and the gastric mucosa can be significantly reduced when ~~sodium~~ perchlorate is given immediately after an accidentally high dose of sodium pertechnetate (^{99m}Tc) was administered.	The salt should be described appropriately, stating pertechnetate alone is not the correct way to describe it as pertechnetate is described as a salt. Thus, the deletion is not agreed.
Line 472	1	Comment:section 4.9 :is it sodium or potassium perchlorate to be used ?	Clarification that reference is made to include "sodium or potassium".

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		Proposed change (if any): The uptake in the thyroid, salivary glands and the gastric mucosa can be significantly reduced when ~~sodium~~ perchlorate is given immediately after an accidentally high dose of sodium pertechnetate (^{99m}Tc) was administered.	
Line 472	5	Comment: sodium perchlorate administration method should be mentioned: I.V., P.O. Proposed change (if any):	There is no need to specify the route of administration. The comment is not agreed.
Line 569	2	Comment: could it be useful to better specify what is intended with “accessories”?	Comment not agreed. The term “accessories” is a generic term which is easy to understand.
line 575-576	2	Comment: propose to add the GMP requirement of the lab where the elution takes place (currently only mentioning of radation protection). consider also advice to check/monitor the eluate microbiologic as the generator is generally used during a whole week	The preparation of the solution is done by a physician in a lab which may not have GMP facilities. Therefore, it is not agreed to add GMP requirements of the lab where the elution takes place. In addition, national regulations are different and thus no recommendation on the check/monitor of the eluate microbiological contamination can be made.
Line 585	2	Comment:	Agreed. Text has been amended.

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		in our opinion, a row dedicated to physiological saline solution ("solution for elution") shelf-life should be added, as it is on the other hand indicated at line 579.	
line 612	2	Comment: typing error: creats should be creates	Agreed.
Line 613	1	Comment: section 6.6, the term "etc" could be replaced by "biological fluids" standing for blood (bleeding or periods), sweat…. Typing error on vomiting. Proposed change (if any): The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, **vomiting or any other biological fluids**. Radiation protection precautions in accordance with national regulations must therefore be taken.	As the text is included in the core SmPC and PL from Radiopharmaceutical guideline, the statement should remain. Typo has been corrected.
Line 650	1	Comment: section 11: dosimetry data with pre-treatment with a blocking agent is missing Proposed change (if any):	There should be two tables, one with blocking agent, the other without blocking agents. Yanna will provide the table.
Lines 661-663	4	Comment: This section is not useful. These statements can only be based on the molybdenum on the column and as	Agreed to delete.

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		such would require a separate text for each activity. Molybdenum on the column is however not relevant, most of the radiation of a generator in use does not originate from the molybdenum on the column, but from the technetium in the tubing and needles which are outside the shielding during and after elution. In Europe each hospital must have a competent person who is able to measure and control the radiation in the specific setting in which the generator is used, taking into account the radiation during use. Proposed change: deletion of this text. ~~External radiation exposure~~ ~~^{99}Mo-^{99m}Tc dose rate on the surface of generator (mGy/h/GBq)~~ ~~^{99}Mo-^{99m}Tc dose rate at 1 m distance from the generator (mGy/h/GBq)~~ ~~Shielding with … mm lead … …~~	
Line 664-665	2	Comment: the meaning of the sentence is not clear	The sentence has been reworded for clarity.
Lines 670-673	4	Comment: Generators are intended to be used according to the instructions of the supplier that guarantees these	Not agreed. It is normal to check that quality of the preparation is ok. It is standard and

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		specifications in the industrial products. Different from the radiolabeling of kits the hospital does not perform critical steps that influence these specifications. They remain the responsibility of the manufacturer of the generator. If a hospital choses to retest these specifications the outcomes from the manufacturer remain decisive as the manufacturer cannot audit and accredit hospital laboratories. Sections with mandatory rechecks by hospitals of company released generators should be deleted as this is not helpful from a quality perspective and could lead to legal ambiguity. The only item that is influenced by the hospital and that actually should be checked on each eluate is the activity and that measurement is missing in the proposed text.	routine. NCAs evaluate all quality control data in the dossier, but sodium pertechnetate solution needs to be checked before administration as stated by cGRPP-guidelines, version2 March 2007 EANM Radiopharmacy Committee and Moreover, it is legally binding in Italy, the Norme di Buona Preparazione in Medicina Nucleare states that: *Quality control parameters of the eluates of technetium-99m generators:* *- Molybdenum-99 breakthrough on the first eluate from each technetium-99m generator* *- Elution activity must be measured on each eluate.*
Line 674	5	**It should be noted that saline for elution should be** Saline bubbled with nitrogen for better labelling	Not agreed. This is not routine practice.
line 670-679	2	Comment: no mentioning of remarks/advice regarding microbiology/sterility/GMP: p.e. does the generator contain an in-line filter thus sterile eluate can be expected?	Agreed. This is a quality requirement that eluate must be sterile but it does not need to be stated in the SmPC.
Lines 684-686	4	Comment: These instructions are applicable to radiopharmaceutical kits labelled in hospital. Only radioactivity has to be checked. For the generators the other	Partially agreed with the comment, see comment above. Deleted “clarity of the solution and pH”, but not molybdenum (99Mo)

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		specifications are guaranteed by the generator supplier. Proposed change: Quality control ~~Clarity of the solution, pH,~~ radioactivity ~~and the molybdenum (^{99}Mo) break-through~~ must be checked before administration.	break through as requested by EANM guideline.
Line 692-694	2	Comment: for the sake of clarity, we would reword the sentence as follows: “The first eluate obtained from this generator can be normally used, unless otherwise specified. Eluates even eluted later than 24 hours from the last elution can be used for kit labelling, unless it is excluded by the specifications of the relevant kit SmPC.	Agreed.
Line 696	1	Comment: ^{99m}Tc generators are registered under national registration procedure. Therefore the template to be used is the one intended for Mutual-recognition, decentralised and referral procedures instead of the one for Centralised Procedure. Proposed change (if any): The sentence “Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu” should be replaced by :	Agreed to add it as optional.

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		"<Detailed information on this medicinal product is available on the website of {name of MS/Agency}>	
PIL Line 725-727	1	Comment: should be deleted since there is no additional monitoring for Tc^{99m} generator Proposed change (if any):	Not Agreed. It is stated in the SmPC as optional and therefore should also be included as optional in case there is a need.
Line 793	1	Comment: to be added since potentially administered to a patient Proposed change (if any): In certain indications, a pretreatment with thyroid-blocking agents may be necessary.	Not agreed. This is information about another agent and it is based on a clinical decison. It may also cause undue concerns to patients.
Line 833	1	Comment: to be deleted because replaced by "Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines" in QRD 9 Template Proposed change (if any):	Agreed.
Line 848	1	Comment: replacement of "specialist in Nuclear Medicine " by "nuclear medicine doctor" for consistency. Proposed change (if any): Resuming breast-feeding should be in agreement with the ~~specialist in Nuclear Medicine~~ nuclear medicine doctor who will supervise the	Agreed.

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		procedure.	
Line 884	1	Comment: replacement of 24 hours by 30 minutes, maximal period of time for images acquisition according to SPC section 4.2. Proposed change (if any): Scans can be performed at any time, between the time of injection and for up to ~~24 hours~~ 30 minutes after the administration, depending on the type of examination.	Not agreed. Scans can be acquired at regular intervals up to 24 hours.
Line 903	1	Comment: omission Proposed change (if any): Should you have any further questions on the use of this product, please ask your nuclear medicine doctor who 903 supervises the procedure.	Agreed.
940	1	Proposed change (if any): Reporting of side effects If you get any side effects, talk to your < nuclear medicine doctor or doctor> <or> <,> <pharmacist> <~~or nurse~~ >. This includes any possible side effects not listed in this leaflet.	Not agreed. The term “doctor” also includes the “nuclear medicine doctor”, therefore there is no need to specify. The term “nurse” is included according to the current QRD template.
Line 954 -959	1	Comment: information intended for specialist should be deleted since useless/unnecessary for the patient and redundant with the information given elsewhere. Indeed as written in the leaflet "The complete SmPC of {(Invented)	Not agreed. This is part of the current QRD template.

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		name} is provided <as a separate document> <as a tear-off section at the end of the printed leaflet> in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical. " Proposed change (if any): deletion	
Lines 988-998	1	Comment: deletion because not appropriate for “old products “	Not agreed. This is part of the current QRD template.
Lines 1002-1005	1	Comment: ^{99m}Tc generators are registered under national registration procedure. Therefore the template to be used is the one intended for Mutual-recognition, decentralised and referral procedures instead of the one for Centralised Procedure. Proposed change (if any):<Detailed information on this medicine is available on the website of {MS/Agency}>	Agreed to add this sentence as optional.