EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/37394/2014

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC

Nanotop and associated names

INN of the active substance: Human albumin, denatured

Procedure no: EMEA/H/A-29/1386

Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Mutual recognition procedure (MRP) and CMD(h) 60 day procedure

ROTOP Pharmaka AG submitted an application for mutual recognition of Nanotop and associated names, 0.5 mg, kit for radiopharmaceutical preparation / lyophilisate for suspension for injection, on the basis of the marketing authorisation granted by Germany on 8 December 2011.

The application was submitted to the concerned Member States (CMS): Austria, Finland, France, Italy, Norway, Portugal, Spain, Sweden and the United Kingdom.

The mutual recognition procedure DE/H/3731/001/MR started on 7 March 2013.

On day 90, major issues on quality and efficacy, raised by Sweden, remained unsolved; hence the procedure was referred to CMDh, under Article 29, paragraph 1 of Directive 2001/83/EC, by Germany on 5 May 2013. The CMDh 60 day procedure was initiated on 29 July 2013.

Day 60 of the CMDh procedure was on 26 September 2013, and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC to the CHMP was made by Germany on 27 September 2013. Sweden raised public health objections due to the uncertainty of the impact of the observed batch variability on the efficacy of the product.

2. Scientific discussion during the referral procedure

2.1. Introduction

Nanotop is a diagnostic radiopharmaceutical kit containing denatured human serum albumin (HSA), which after radiolabelling with Sodium Pertechnetate (^{99m}Tc) solution results in Technetium (^{99m}Tc) Nanocolloid.

Technetium (^{99m}Tc) Nanocolloid is used for characterisation of the properties of the lymphatic system and in particular sentinel lymph node (SLN) detection in breast cancer and malignant melanoma.

The efficacy of a Tc-99m albumin colloid is the ability to identify the first draining SLN. Once the Tc-99m albumin colloid is administered, the passage of the tracer through the lymphatic system is recorded by imaging.

The mutual recognition marketing authorisation application (MAA) for Nanotop 0.5 mg, kit for radiopharmaceutical preparation / lyophilisate for suspension for injection was submitted on the basis of the marketing authorisation granted by Germany on 8th December 2011. The legal basis for the submitted MAA was Article 10a "well established use", relying on appropriate scientific literature data of another similar product, Nanocoll.

During the mutual recognition procedure (MRP), major concerns were raised by the member states Sweden and France, that considering the batch variability, it was not possible from a quality perspective to conclude about the comparability between Nanotop and Nanocoll. During the CMDh referral procedure that followed, no consensus could be reached as Sweden maintained their objection that the importance of the batch variability for the distribution and uptake of Nanotop in lymph nodes,

as well as its clinical implications had not been adequately addressed, as even a small difference in efficacy could represent a potential serious risk to public health. The CMDh therefore referred the matter to the CHMP through an Art 29(4) referral procedure.

2.2. Critical evaluation

Due to different views in the interpretation of the data related to particle size distribution within the defined limits relevant for efficacy, this referral was triggered to assess the importance of the batch to batch variability for the distribution and uptake of Nanotop in lymph nodes, and whether this could have an impact on efficacy, which could have major implications on public health.

Since the references included in this submission were studies conducted with Nanocoll, the MAH provided arguments that these data are relevant for Nanotop:

- *Particle size and particle size ranges for Nanotop and Nanocoll*

The composition of Nanotop and Nanocoll, and the specification are shown below.

Table 1: Qualitative and quantitative composition

Nanocoll		**Nanotop**	
Human albumin colloidal particles	0.5 mg	Human albumin colloidal particles	0.5 mg
Stannous chloride, dihydrate	0.2 mg	Stannous chloride, dihydrate	0.2 mg
Sodium phytate, anhydrous	0.25 mg	Sodium phytate, anhydrous	0.25 mg
Poloxamer 238	2 mg	Poloxamer 238	2 mg
Sodium phosphate, dibasic, anhydrous	0.5 mg	Sodium phosphate, dibasic, anhydrous	0.5 mg
Glucose, anhydrous	15 mg	Glucose, anhydrous	15 mg
Nitrogen as protective gas		Nitrogen as protective gas	

Table 2: Specifications

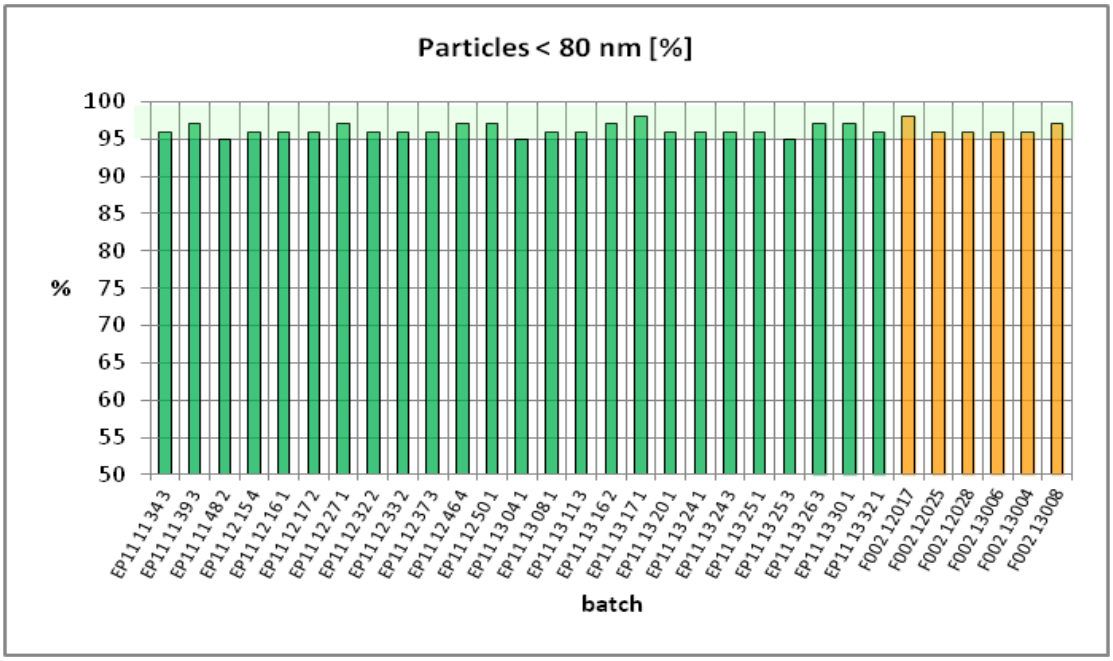
Specifications		
	Nanocoll	**Nanotop**
Particle size	≥ 95% ≤ 80 nm	≥ 95% ≤ 80 nm
free ^{99m}Tc after radiolabelling	≤ 5 %	≤ 5 %
pH after radiolabelling	7 - 8	7 - 8

The qualitative and quantitative composition of the medicinal product Nanotop was shown to be the same in comparison to the comparator product Nanocoll.

- *Particle size range comparison for Nanotop and Nanocoll (similarity)*

The figure below shows the spectrum of all 25 batches of Nanotop being produced so far including 6 batches of Nanocoll.

Figure 1: Particles of ≤ 80 nm [%], all 25 Nanotop batches (EP111-) and 6 Nanocoll batches (F002-)

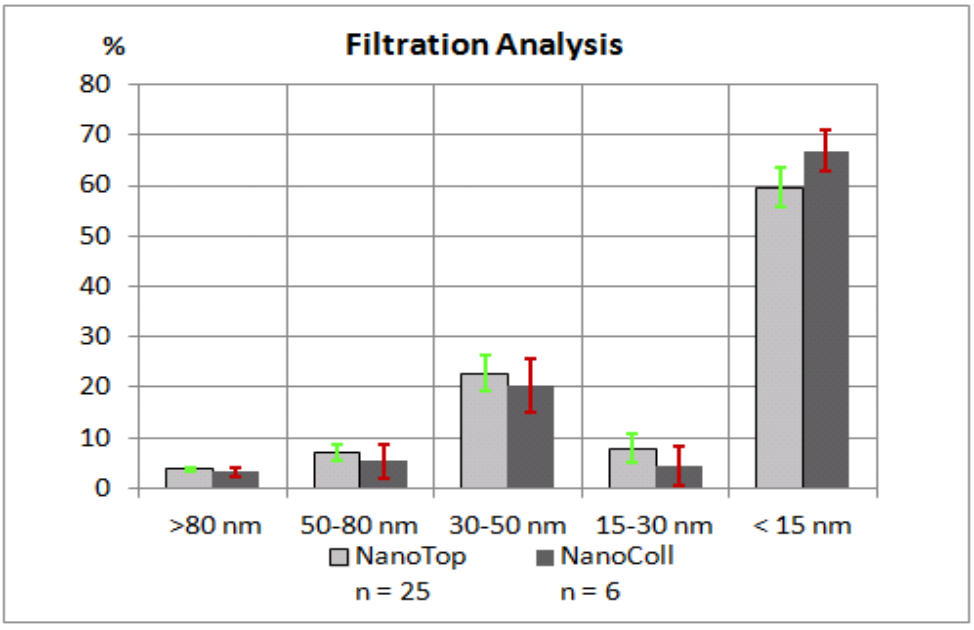


The upper particle size limits for SLN detection procedures used in Europe has been established and the acceptance criterion of at least 95% of particles having a diameter ≤ 80 nm is shown to be met by all batches of Nanotop.

During development the MAH looked into the size distribution below 80 nm and created “particle size groups”. Filters at 15 nm, 30 nm, 50 nm and 80 nm filter pore size were used.

The particle size groups for Nanotop and Nanocoll are presented in below.

Figure 2: Comparison of mean ± confidence interval of percent particle fractions of Nanotop (n=25) and Nanocoll (n=6).

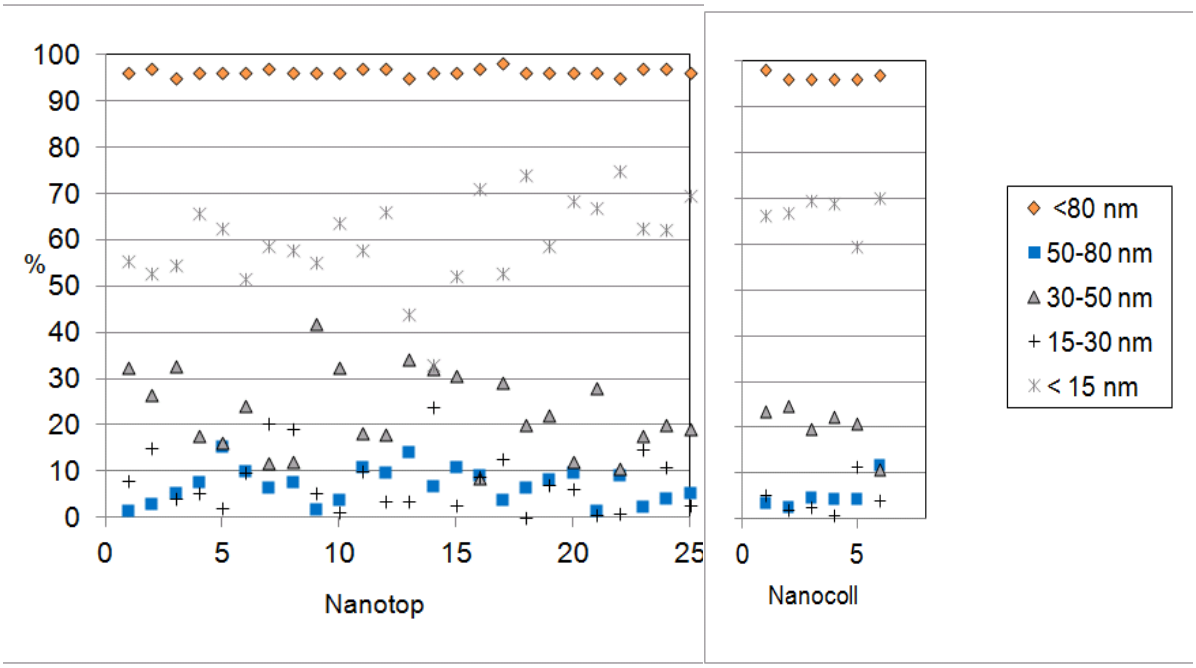


From these data it appears evident that Nanotop and Nanocoll are comparable in terms of particle size groups. The “fluctuation” in particle size distribution is reflected by the error bars (confidence interval)

for each particle size group. It is highlighted by the MAH that these "deviations" occur within the release criteria (≤80 nm).

In response to the objection that there is a difference in the data fluctuation between Nanotop and Nanocoll, the following figure has been presented by the MAH to show that the fluctuations observed are comparable and that particle size group distribution is comparable between Nanotop and Nanocoll.

Figure 3: Single data points of Nanotop size groups (25 batches) and Nanocoll (6 batches)



The MAH argues that the fluctuations per se are not clinically relevant and therefore differences between such fluctuations are not likely to pose a risk to public health.

In addition the MAH has provided data on Nanocoll and Nanotop batches that were analysed on four days (Figure 4), and on the same day (Figure 5). The fluctuation seen for both products is reduced as shown in the figures below.

Figure 4: Single data points of Nanotop and Nanocoll size groups (six batches each)

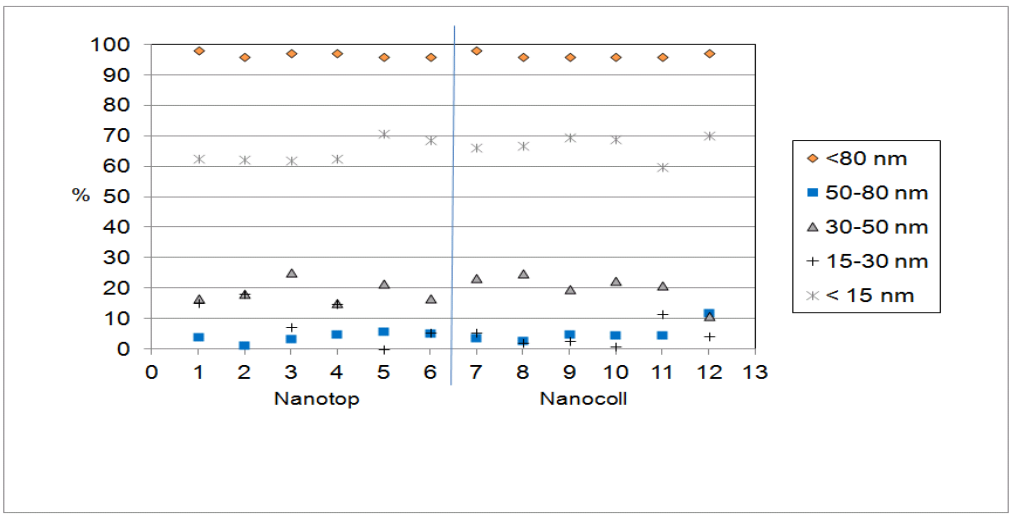
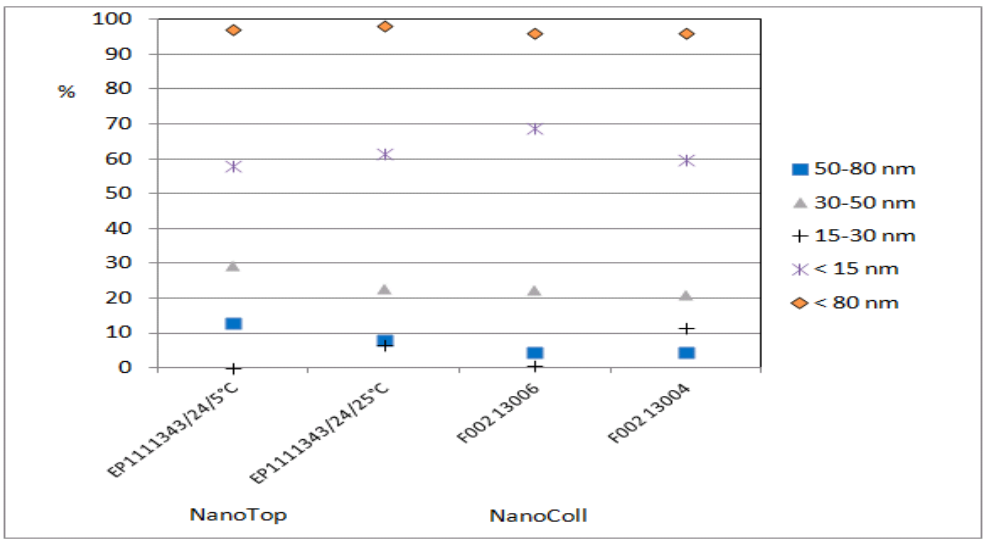


Figure 5: Single data points of Nanotop size groups and Nanocoll analysed on the same day



These data have been provided by the MAH to support the notion that variability may decrease when batches were analyzed over a shorter period of time. This additional supportive data was considered acceptable by the CHMP to demonstrate that the particles size distribution for the studied size ranges as well as the batch variability is in the same range as for Nanocoll, the product referred to in the submitted literature.

- *Particle size range and its implication for clinical practice*

As mentioned previously, the efficacy of a Tc-99m albumin colloid is the ability to identify the first draining SLN. Once the Tc-99m albumin colloid is administered, the passage of the tracer through the lymphatic system is recorded by imaging. If the s.c. injected particles are too small they "run" through the lymphatic system too quickly and disappear before imaging techniques can be applied. On the other hand, if the particles are too large they would mostly remain trapped at the injection site and need too much time for transition to the lymph nodes, which is not practical. Based on this, an optimal particle size range has been established for SLN detection.

The MAH has discussed particle size ranges and its implication for clinical practice in general, with reference to clinical guidelines. The relevant quality attributes including upper particle size limits are defined in the European core summary of product characteristics (SmPC) for Tc-99m Albumin Microcolloid (nm), in the relevant European and national Treatment Guidelines[1,2,3] and in the SmPC of the approved products (e.g. Nanocoll) and have been cited by the MAH. In addition the MAH's clinical expert states that any variability in particle size within the specified range of Nanotop (≤ 80 nm of at least 95% of the particles) is not relevant for the clinical outcome.

The HSA nanocolloid has the prerogative to be made up of particles smaller than other colloidal agents for SLN detection. The particle size range is in this respect the crucial parameter that characterises the particular compound since small-sized colloids allow identification of a greater number of sentinel

[1] Buscombe et al. Sentinel node in breast cancer procedural guidelines. Eur J Nucl Med Mol Imaging (2007) 34:2154.
[2] Chakera et al. EANM-EORTC general recommendations for sentinel node diagnostics in melanoma. Eur J Nucl Med Mol Imaging (2009) 36:1713.
[3] Giammarile et al. The EANM and SNMMI practice guideline for lymphoscintrigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging (2013) Oct 2.

lymph nodes with a high statistical significance[4]. There have been no studies so far investigating the clinical effects of variability occurring within the particle size range of HSA nanocolloid (of 0 to 80 nm).

The MAH therefore argues that particle size range is the pivotal relevant quality attribute when "similarity" related to efficacy between different products is to be established.

Considering the particle size and the particle size ranges range discussed above, the CHMP was of the view that Nanotop is comparable to Nanocoll - the product referred to in the submitted literature, and that therefore an impact on clinical efficacy is not expected.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

To support the CHMP concern regarding the clinical impact of the batch variability shown for the different particle size ranges, the MAH provided additional supportive batch data to demonstrate that the particle size group distribution as well as the batch variability is comparable for the two products – Nanotop and Nanocoll, the product referred to in the submitted literature.

Data from three additional batches of Nanotop and Nanocoll respectively, have been provided. In addition one batch of Nanotop from two stability samples were analyzed and compared to two Nanotop batches analyzed on the same day, as well as six batches of Nanocoll and Nanotop respectively that were analysed on four days.

The focus of this procedure is the comparability, and the additional supportive batch data provided has acceptably demonstrated that the particles size distribution for the studied size ranges as well as the batch variability for Nanotop is in the same range as for Nanocoll. The CHMP therefore considers that the qualitative and quantitative composition of the medicinal product Nanotop is comparable to Nanocoll - the product referred to in the submitted literature, and that an impact on clinical efficacy is not expected.

2.5. Conclusions and benefit risk assessment

Whereas,

- The Committee considered the notification of the referral triggered by the Germany under Article 29(4) of Directive 2001/83/EC;
- The Committee reviewed the bibliographic data submitted by the marketing authorisation holder to address the potential serious risk to public health with regard to the impact of the observed batch variability on the efficacy of Nanotop in comparison with Nanocoll, which is the product referred to in the submitted literature.
- The Committee was of the view that further analysis of the supportive data from additional batches of Nanotop and Nanocoll have demonstrated acceptably that the particles size distribution for the studied size ranges as well as the batch variability for Nanotop is in the same range as for Nanocoll.
- The Committee therefore concluded that the MAH has satisfactorily demonstrated that Nanotop is comparable to Nanocoll, and that therefore an impact on clinical efficacy is not expected.

[4] Leidenius MH, et al. The impact of radiopharmaceutical particle size on the visualization and identification of sentinel nodes in breast cancer. Nucl Med Commun 2004;25(3):233-238.

the CHMP has recommended the granting of the marketing authorisation for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure for Nanotop and associated names.