Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 8 November 2023

Case Number: T 1889/20 - 3.3.10

Application Number: 14796762.4

Publication Number: 3068747

IPC: C07B59/00

Language of the proceedings: EN

Title of invention:
DUAL RUN CASSETTE FOR THE SYNTHESIS OF 18F-LABELLED COMPOUNDS

Applicant:
GE Healthcare Limited

Headword:

Relevant legal provisions:
EPC Art. 123(2), 84, 56

Keyword:
Claims - clarity (yes)
Amendments - allowable (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1889/20 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 8 November 2023

Appellant: (Applicant)	GE Healthcare Limited Pollards Wood Nightingales Lane Chalfont St. Giles, Buckinghamshire HP8 4SP (GB)
Representative:	Coles, Andrea Birgit Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 14 May 2020 refusing European patent application No. 14796762.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	P. Gryczka
Members:	A. Zellner
	T. Bokor

Summary of Facts and Submissions

I. The appeal is against the decision of the examining division to refuse the European patent application No. 14 796 762.4 on the basis of Article 97(2) EPC.

II. In the contested decision, the examining division found that neither the main nor the auxiliary request met the requirements of Article 56 EPC.

III. The main request contains two independent claims which read as follows:

"1. A cassette (1) for the synthesis of a plurality of batches of an [^{18}F]-labelled positron-emission tomography (PET) tracer wherein said cassette comprises:

(i) *an anion exchange column (3, 4) for each of said plurality of batches;*
(ii) *a reaction vessel (5);*
(iii) *a vial (2) containing an aliquot of eluent for each of said plurality of batches;*
(iv) *a vial (6) containing an aliquot of a precursor compound for each of said plurality of batches;*
(v) *reagent vials (7, 8, 9) wherein each reagent vial contains an aliquot of reagent for each of said plurality of batches;*
(vi) *optionally, a solid-phase extraction (SPE) column for deprotection (10) and/or one or more SPE columns for purification (11, 12); and,*
(vii) *means for cleaning said reaction vessel and said SPE columns;*

wherein the components (i)-(vii) of the cassette are selectively fluidly connected along a linear fluid pathway made from a rigid pharmaceutical grade polymeric material that is resistant to radiation."

"8. A method for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer wherein said method comprises:

(a) *trapping a first aliquot of [^{18}F]fluoride onto a first anion exchange column(3);*
(b) *providing a first aliquot of a precursor compound in a reaction vessel (5);*
(c) *passing a first aliquot of eluent through said first anion exchange column (3) to elute said first aliquot of [^{18}F]fluoride into said reaction vessel (5);*
(d) *heating the reaction vessel (5) for a predetermined time to obtain crude [^{18}F]-labelled PET tracer;*
(e) *optionally deprotecting said crude [^{18}F]-labelled PET tracer on a SPE column (10);*
(f) *optionally purifying said crude [^{18}F]-labelled PET tracer on one or more SPE columns (11, 12);*
(g) *cleaning said reaction vessel (5) and said SPE columns (10, 11, 12);*
(h) *repeating steps (a)-(g) one or more times, each time using a subsequent aliquot of [^{18}F]fluoride, a subsequent anion exchange column (4) and a subsequent aliquot of a precursor compound;*

wherein said method is carried out on a single cassette (1)."

IV. The following documents are referred to:

D1: EP 0 800 497 B1
D2: WO 2013/053940 A1
D3: WO 2013/053941 A1
D4: US 2013/0144052 A1

V. In the impugned decision, the examining division concluded that the provision of a cassette according to claim 1 of the main request was not based on an inventive step. The disclosure of documents D1 was considered to be closest prior art.

The examining division in particular referred to Figures 1 and 4 of D1. Several differing features between the claimed cassette and the system/array disclosed in these figures were identified. A first difference was seen in that only certain elements of the array were multiplied, *i.e.* the anion exchange columns, instead of the entire array. Another difference was seen in that means for cleaning the reaction vessel and the SPE columns were provided. The examining division furthermore noted that the connection between the components of the cassette according to claim 1 of the main request were fluidly connected along a linear fluid pathway, and were made from a rigid pharmaceutical grade polymeric material which was resistant to radiation.

The examining division identified two partial technical problems. A first technical problem was seen in the provision of a way to render a system/array according to Figures 1 or 4 of D1 re-usable after a first run. A second technical problem was seen in the provision of a way to render the apparatus/cassette according to D1 more resistant to the radiation it was exposed to.

The examining division held that none of the solutions

to these partial problems were based on an inventive step.

Firstly, it was seen as self-evident that the skilled person would replace only those units of the array which could not be brought back to a pre-use state, and clean all other units. Finding out which parts of the cassette needed to be replaced, and thus had to be made available more than once, and which parts could be cleaned, was the result of routine testing.

Secondly, the provision of a polymeric material which was resistant to radiation was a self-evident contribution and just the result of routine operation in order to address an existing problem and to obtain a foreseeable result.

The examining division applied the same reasoning to the method according to claim 8 of the main request, as well as to the auxiliary request.

Finally, the examining division held that the auxiliary request contravened Article 123(2) EPC.

2. The appellant argued essentially as follows:

Document D1 represented the closest prior art. The cassette according to claim 1 of the main request differed therefrom by the features as identified by the examining division. In particular, only certain elements of the device disclosed in D1 had to be duplicated in a single cassette, and additional cleaning means were provided. The objective technical problem was seen in how to permit providing several batches of radiolabelled compound on a single set of equipment. According to the appellant, this problem had

not previously been recognised, and was successfully solved by the provision of a cassette according to claim 1, as well as a method according to claim 8, of the main request. In particular, none of documents D1 to D4 suggested re-use of the synthesis equipment, but rather the opposite. The appellant also contested the examining division's conclusion that document D1 disclosed a cassette. They also argued that the use of a radiation-resistant rigid pharmaceutical grade polymeric material required special considerations. Special efforts beyond routine experimentation were required to ensure successful preparation of a plurality of batches on a single cassette.

VI. The appellant requests that the decision under appeal be set aside, and that a patent be granted on the basis of the main request filed before the examining division on 17 January 2020, or on the basis of the auxiliary request filed on the same date.

Reasons for the Decision

Main request

Amendments (Article 123(2) EPC

1. The main request fulfills the requirements of Article 123(2) EPC. The reasons are as follows:

2. Claim 1 differs from claim 1 of the application as filed by the following additional feature:

"... wherein the components (i)-(vii) of the cassette are selectively fluidly connected along a linear fluid pathway made from a rigid pharmaceutical grade polymeric material that is resistant to radiation".

A basis for this amendment can be found in lines 20 to 26 of page 6 of the application as filed.

3. Independent claim 8 of the main request corresponds to claim 21 of the application as filed, wherein the term *"[^{18}F]FDG" in the* expression *"[^{18}F]FDG precursor"* of feature (h) has been deleted.

According to step (h) of the method of claim 21 as filed, steps (a)-(g) are repeated one or more times, each time using a subsequent aliquot of a [^{18}F] fluoride, a subsequent anion exchange column (4) and a subsequent aliquot of an [^{18}F]FDG precursor compound. Although step (h) thus refers to a [^{18}F]FDG precursor compound, the claim requires using a precursor compound according to step (b) of the claimed method. This step (b), however, requires to provide a first aliquot of *"a precursor compound"* in general, rather than the more specific *"[^{18}F]FDG precursor compound"* as mentioned in step (h). If this step (b) has to be repeated, a subsequent aliquot of *"a precursor compound"* has to be provided.

This is also in line with the wording at the beginning of claim 21 as filed. The claim is directed to a method for the preparation of a plurality of batches of an [^{18}F]-labelled PET tracer. It is not directed to the preparation of the more specific tracer compound [^{18}F]fluorodeoxyglucose ([^{18}F]FDG). This compound is only one of the specific PET tracers listed in claim 22 as filed, and only this compound requires the more specific [^{18}F]FDG precursor.

Amending the *"[^{18}F]FDG precursor compound"* to a *"precursor compound"* is thus supported by claim 21 as

filed, in particular when taking into consideration claim 22 as filed.

4. Dependent claims 2 to 7 and 9 to 14 of the main request have not been amended, they are identical to claims 2, 5, 6, 18 to 20 and 22, 25, 26 and 38 to 40 of the application as field, respectively.

Clarity (Article 84 EPC)

5. In its communication of 29 August 2018 the examining division objected to the clarity of the wording *"... an anion exchange column (3, 4) for each of said plurality of batches ..."*, which was used in item (i) of claim 1 of the then pending main request. The division argued that the wording can either mean that a separate anion exchange column is used for each batch of tracer to be synthesised, or that a single anion exchange column is used for the entirety of the batches. A similar wording was used and objected to in items (iii) and (iv) of the claim. Claim 1 of the present main request also contains the same wording.

6. The Board comes to the conclusion that claim 1 of the main request meets the requirements of Article 84 EPC for the following reasons:

6.1 The claim is directed to a cassette (1) for the synthesis of a plurality of batches of a [^{18}F]-labelled PET tracer. The cassette comprises *"an anion exchange column (3, 4) for each of said plurality of batches"* (see item (i)). The cassette further comprises *"a vial (2) containing an aliquot of eluent for each of said plurality of batches"* (see item (iii)), *"a vial (6) containing an aliquot of a precursor compound for each of said plurality of batches"* (see item (iv)) and

"reagent vials (7, 8, 9) wherein each reagent vial contains an aliquot of reagent for each of said plurality of batches" (see item (v)).

6.2 The claimed cassette has to be suitable for the synthesis of a plurality of batches. In order to synthesise a plurality of batches, an aliquot of eluent, of precursor compound and of reagent is required for each batch. The cassette comprises several **reagent vials (7, 8, 9)**. Each of these vials contains an aliquot of reagent for each batch (item (v) of claim 1). The cassette further comprises **a vial (2)** for eluent and **a vial (6)** for the precursor compound (items (iii) and (iv) of claim 1). These vials (2) and (6) need to contain an aliquot of eluent and of precursor compound, respectively, for each of the batches to be synthesised. Consequently, they must contain a plurality of aliquots, *i.e.* one for each of the batches. The wording used in items (iii) and (iv) is thus clear.

6.3 The skilled person will also understand that the claimed cassette comprises more than one anion exchange column. Item (i) of claim 1 is worded the same way as items (iii) and (iv). Whereas items (iii) and (iv) imply several aliquots per vial (necessary for each of said plurality of batches), item (i) consequently implies the cassette to comprise several anion exchange columns, *i.e.* one per batch of PET tracer to be synthesised.

6.4 This understanding is supported by the use of two reference numerals (*3* and *4*) in item (i) of claim 1. It is also supported by Fig. 3 (see numerals 3 and 4) and page 14, lines 23 to 25 of the description as filed.

6.5 The understanding is furthermore supported by page 14, lines 14 to 17 of the description, and step (h) of claim 21, as filed. The description discloses the use of a second QMA (anion exchange SPE column, see page 12, lines 5 to 13) for the synthesis of a second batch of [^{18}F]FDG. Claim 21 also discloses in item (h) the use of a subsequent anion exchange column when repeating steps (a) to (g).

7. A further lack of clarity objection has been raised in the Written Opinion of the International Searching Authority (WO-ISA) with respect to claim 2 of the PCT-application on which the the application in suit is based. Claim 2 of the main request is identical to claim 2 of the original PCT-application.

Claim 2 was considered to lack clarity because it defined the product to be synthesised, rather than the cassette according to claim 1, on which it was dependent. The claim was thus not considered to further limit the cassette of claim 1.

8. This objection is not conclusive for the following reasons:

Claim 2 is dependent on claim 1, which is directed to a cassette for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer. The claimed cassette must be suitable for the synthesis of the labelled PET tracer. It contains *i.a.* a vial (6) containing a precursor compound for the labelled PET tracer, *i.e.* a non-radioactive derivative of the radiolabelled target compound (see page 8, lines 22 to 32 of the description as filed). This precursor, contained in the vial (6) of the cassette, may be different for each of the PET tracers which may be synthesised. The more specific

definition of the labelled target PET tracer according to claim 2 thus further limits the cassette as claimed in claim 1. Claim 2 of the main request thus fulfills the requirements of Article 84 EPC.

Inventive step (Article 56 EPC)

9. The application relates to devices and methods for the automated synthesis of [^{18}F]-labelled compounds for use as *in vivo* imaging agents for positron emission tomography (PET). It relates in particular to the synthesis of more than one batch of [^{18}F]-labelled compound in a single disposable cassette (see page 1, lines 3 to 7). The independent claims of the application are directed to a cassette for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer, and to a method for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer, which is carried out on a single cassette.

Closest prior art

10. The Board concurs with the examining division and the appellant that document D1 is the closest prior art. D1 relates to a system, apparatus and method for synthesising radiopharmaceuticals, *e.g.* [^{18}F]-labelled PET imaging agents, such as [^{18}F]FDG (see paragraphs [0002] and [0003]). It mentions the preparation of multiple batches of radiopharmaceutical compounds, and suggests means for that purpose (see paragraph [0130] and Fig. 7). The document is concerned with the provision of a simpler platform for the synthesis of radiolabelled compounds (see paragraph [0131]).

Differing features

11. D1 discloses in Figures 1 and 4 as well as 5 and 6 systems and apparatuses for the synthesis of [^{18}F]-labelled PET tracer compounds (see paragraphs [0042] to [0050]). The document furthermore discloses in Figure 7 a synthesis platform (*"a stand 704 such as a cube or rectangular box"*) with four or more sets of synthesis equipment (see paragraphs [0051] and [0130]). D1 does not disclose that the four sets of synthesis equipment of the synthesis platform according to Figure 7 are different. They may thus be used for the synthesis of a plurality of batches of a single compound.

12. The appellant agrees with the examining division's assessment that the cassette according to claim 1 of the main request differs from the disclosure of D1, in particular Figure 7, in that it comprises only selected parts more than once (anion exchange columns; multiple aliquots of eluent in a vial, and multiple aliquots of precursor component in a different vial; several vials with aliquots of reagent), whereas other parts are present only once (reaction vessel; means for cleaning the reaction vessel and the SPE columns for purification). It also agreed in that the components of the claimed cassette are selectively fluidly connected along a linear fluid pathway made from a rigid pharmaceutical grade polymeric material and resistant to radiation, in contrast to those according to D1.

The appellant disagrees with the division's assessment concerning the disclosure of a cassette in D1. The appellant argues that D1 doe not disclose a cassette.

13. The Board observes that claim 1 of the main request does not exclude the presence of additional parts. The absence of parts which are present in a system as disclosed in D1 is thus not a differentiating feature.

The question whether the *"stand 704 such as a cube or rectangular box"* disclosed in Figure 7 of document D1 (see paragraphs [0129] and [0130]) is a cassette in the meaning of claim 1 of the main request is not decisive for the outcome of the present decision. It may thus be assumed that this is the case.

The cassette according to claim 1 of the main request therefore differs from the synthesis platform disclosed in Figure 7 of document D1 at least in that it comprises cleaning means, in that it comprises a vial (2) containing eluent for more than one of the plurality of batches to be synthesised, and in that it comprises a vial (6) containing an aliquot of precursor compound for more than one of the plurality of batches to be synthesised. Since each of the multiple sets of the synthesis equipment arranged in or adjacent to each face of the cube or box in Figure 7 is intended to be used for one run, it is evident that each vial of each of the individual units contains only the amount of eluent and precursor compound which is necessary for a single batch. The claimed cassette furthermore differs in that it comprises means for cleaning the reaction vessel and the SPE columns, and in that the components of the claimed cassette are selectively fluidly connected along a linear fluid pathway made from a rigid pharmaceutical grade polymeric material that is resistant to radiation.

Technical effect and objective technical problem

14. The synthesis platform disclosed in Figure 7 of document D1 allows for the synthesis of a series of batches of [^{18}F]-labelled PET tracer compounds. The use of a cassette according to claim 1 of the main request

also allows for the synthesis of more than one batch. However, the claimed cassette has the advantage that fewer parts are required for the synthesis of more than one batch. Instead of duplicating the entire synthesis equipment required for a single batch, as in Figure 7 of D1, only selected parts need to be provided more than once, although some additional means - for cleaning the reaction vessel and SPE columns for purification - are required. The claimed cassette thus provides for a simplification of the synthesis platform according to Figure 7 of D1.

As shown below, the provision of a cassette according to claim 1, and a method according to claim 8, is based on an inventive step considering the presence of a vial (2) containing eluent for more than one of the plurality of batches to be synthesised, and a vial (6) containing an aliquot of precursor compound for more than one of the plurality of batches to be synthesised. Whether any further technical effect may be caused by the use of the radiation resistant and rigid pharmaceutical grade polymeric material, or by the presence of cleaning means, need not be decided.

The objective technical problem can thus be seen in the provision of a simpler system/array for the synthesis of multiple batches of [^{18}F]-labelled PET tracers.

Solution to the technical problem

15. According to claim 1 of the main request, a device in the form of a cassette is provided. This cassette comprises in particular a vial (2) containing eluent for more than one of the plurality of batches to be synthesised, and it comprises a vial (6) containing an aliquot of precursor compound for more than one of the

plurality of batches to be synthesised. The Board is convinced that the provision of a cassette as claimed allows for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer. Due to the fact that it contains fewer parts, the cassette is also simpler than the system/array disclosed in D1, Figure 7. According to the description as filed, the use of the claimed cassette leads to good yields and good trapping and elution of the incoming activity (see page 5, lines 1 to 5). The Board sees no reason to doubt this.

16. *Inventiveness of the claimed solution*

Document D1 does not provide any hint towards the claimed solution. The document discloses in paragraph [0129] that there may be multiple *"sets"* of the synthesis equipment as shown in Figures 5 and 6. This allows for multiple runs. This arrangement is shown in Figure 7. D1 dose not suggest to change the set-up of each of the individual sets of synthesis equipment in order to obtain a layout of the cassette according to claim 1. The document does in particular not suggest to eliminate specific parts of the synthesis platform shown in Figure 7. D1 also mentions inconveniences when parts of the synthesis equipment need to be cleaned from run-to-run (see paragraphs [0014] and [0026]). The skilled person will thus not be motivated to re-use parts of equipment, which is essential when using the cassette according to claim 1, or when applying the method according to claim 8 of the main request.

Documents D2 and D3 disclose the use of cassettes which are fitted to an automated radiosynthesis apparatus, as well as an automated method for the synthesis of a single batch of [^{18}F]-labelled biomolecules (D2: see page 4, lines 1 to 3 and page 14, lines 15 to 23, D3:

see page 4, lines 10 to 12 and page 15, lines 15 to 21). The documents do not provide any hint towards using a single cassette for several batches, nor to amend the synthesis platform disclosed in Figure 7 of document D1 according to claim 1 of the main request.

Document D4 discloses that selected parts of the synthesis device are part of a disposable element, which can be inserted into a stationary element and used for the one-time synthesis of a radio-labelled compound (see paragraph [0024]). D4 does not suggest to re-use certain elements of the synthesis device, or to provide a single synthesis device for several batches.

17. Since none of the cited documents suggests how to adapt a device as disclosed in Figure 7 of document D1 in order to provide a re-usable device for the synthesis of a plurality of batches of an [^{18}F]-labelled PET tracer, the provision of a cassette according to claim 1 of the main request is based on an inventive step. The same reasons apply to the method of claim 8.

The invention meets the requirements of Article 56 EPC.

18. Since no other objections were raised by the examination division, the Board concludes that the subject-matter claimed in the main request fulfills the requirements of the EPC, and the European patent can be granted (Article 97(1) EPC), with an appropriately adapted description.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the examining division with the order to grant a patent on the basis of claims 1 to 14 of the main request as filed on 17 January 2020, and a description yet to be adapted thereto.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated