Composite Co-ordinated Collection: CCC

A scheme for the co-ordinated submission and assessment of Type IB and Type II variations and Regulation 267 of the Human Medicines Regulations applications Guidance and procedural requirements

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This document should be read together with the EU Guidelines on grouping variations: European Commission (1) procedural guideline and the CMDh Best Practice Guide on variations (grouping (2).).
Also refer to additional guidance and examples of grouping published on the CMDh and MHRA websites (3, 4)

(1) European Commission Procedural Guideline:
http://ec.europa.eu/health/files/eudralex/vol-2/2013_05_16_c2804_en.pdf

(2) CMDh Guideline, Grouping:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_296_2013_Rev20_2014_07_-_clean.pdf

(3) CMDh examples of grouping:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_173_2010_Rev10_2013_07_clean.pdf

(4) MHRA examples of grouping:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Variationstolicences/QualityAuditReportofNewTIANotifications/index.htm

Contents

1 Background

Commission Regulation 1234/2008, Article 7.2(b) (as amended) and paragraph 5(2)(c) of Schedule 10A of the Human Medicines Regulations include the principles of grouping changes of 'higher types' that are related to one another. These changes can be submitted as a single "grouped variation" that is processed as one application in one procedure. This is feasible for groups comprising mixtures of Type IA, Type IB and Type II variations; the procedure that will be followed will be that of the highest type. When identical variations (either individual or grouped variations) are required to different products belonging to the same Marketing Authorisation Holder (MAH), these can be processed together and are known in the UK as "bulk applications", for which reduced fees apply

However, if the changes are totally unrelated and/or rely on separate independent data packages, they are not eligible for grouping and separate applications should be submitted. In this situation the MAH could have multiple pending applications that are submitted in parallel and processed separately by the MHRA, possibly by different business areas depending on the scope of the proposed changes. Where multiple variations impact on the Patient Information Leaflet (PIL) and/or labelling, prior to grant, mock-ups are required for each application, which are updated to reflect only the changes applied for within each procedure. Additionally, companies may submit parallel Regulation 267 of the Human Medicines Regulations (1) applications that concern changes to the PIL/labelling that are not connected with a change to the Summary of Product Characteristics (SmPC). These are separate procedures that cannot be grouped with a variation. The staggered submission and assessment of different procedures and the requirement for interim versions of the PIL/labelling introduces complexity in processing applications and additional costs for companies.

The MHRA has introduced a scheme for co-ordinating the submission and processing of parallel variations and Regulation 267 applications to amend PIL and/or labelling (Patient Information Quality Unit (PIQU) applications).

(5) Regulation 267 was previously referred to in MHRA guidance as Article 61(3) in Council Directive 2001/83/EC.

This initiative, called “Co-ordinated Composite Collection” (CCC), stems from discussions with industry trade associations through the MHRA’s Medicines Industry Liaison Variations Sub-Group (5).
(6)
http://www.mhra.gov.uk/Committees/MedicinesIndustryLiaisonGroup/index.htm

The scope of the CCC scheme includes:

- Type IB and Type II variations (either single or grouped changes) and
- Regulation 267 full applications, type P1, P2, P3 and P4.

The CCC scheme excludes:

- Purely Type IA notifications
- Notifications of changes to labels and PIL under the self-certification scheme
- Urgent or significant variations that impact on product safety information for which implementation should not be delayed
- Changes that do not impact on the product information (SmPC, PIL, label).

The benefits of the CCC scheme for multiple parallel procedures are that:

- The normal rules of grouping and bulking variations apply
- Only one consolidated mock-up is required at submission
- Overall timelines may be reduced as the assessments are not processed serially
- Processing and assessment of applications is co-ordinated and more streamlined
- Variations fee structure is unchanged.

Following the successful completion of a pilot trial of CCCs with a number of participating companies; the CCC scheme is now widely available to companies. In order to make a successful CCC application to the MHRA it is essential to follow precisely the guidance that has been set out for the content of a CCC application and its submission.

General enquiries concerning this guidance on CCCs should be submitted to the MHRA's Regulatory Information Service (RIS) at variationqueries@mhra.gov.uk ensuring that the term "CCC" is quoted in the email header and all other correspondence.

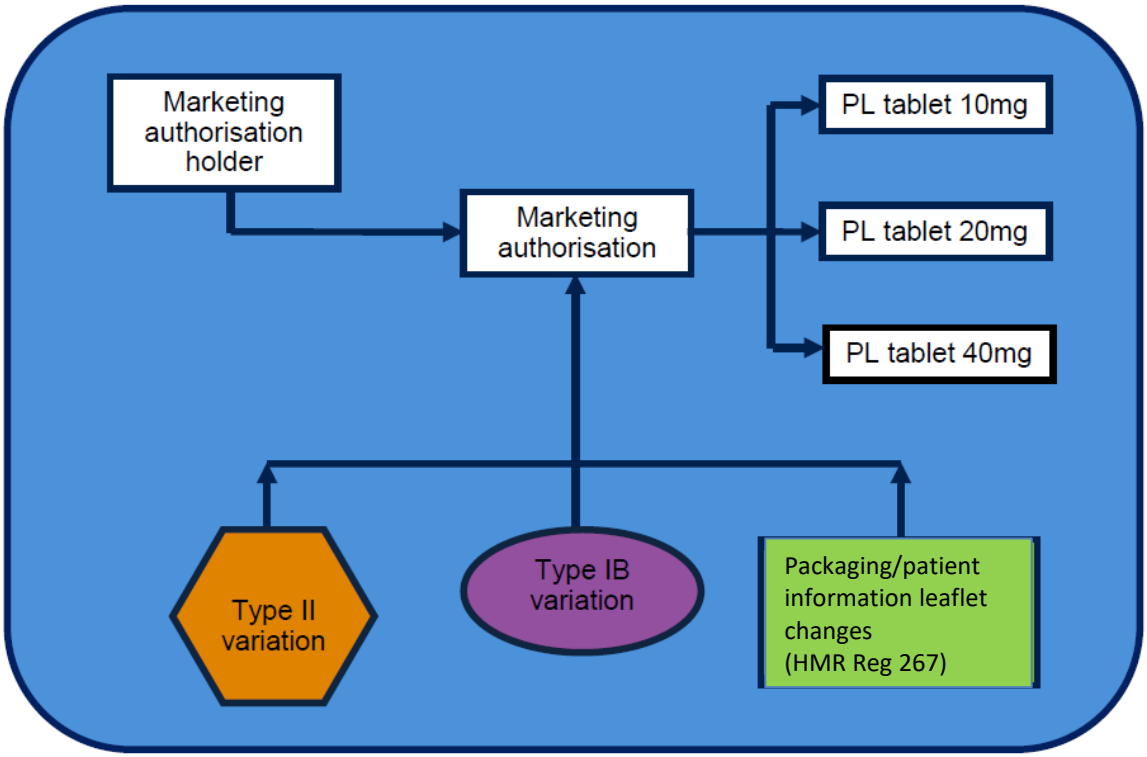
2 Description of a Composite Co-ordinated Collection (CCC)

A CCC comprises 2 or more parallel applications for changes to marketing authorisations (MAs) belonging to the same MAH, as illustrated in Figure 1.

As far as purely national products are concerned a Marketing Authorisation (MA) corresponds to a single Product Licence (PL, PLNI or PLGB).

Each CCC may comprise single changes or grouped changes to a MA. Urgent or significant variations that impact on product safety should be excluded from CCC applications in order to avoid delays in their implementation. A Regulation 267 application can be included in the CCC.

Figure 1 Schematic of a Composite Co-ordinated Collection (CCC)



2.1 Examples of acceptable CCCs

In order to assist companies, details are given of scenarios that have been identified during the initial CCC pilot. These are illustrated below with practical examples of the types of applications received and are expected to cover the majority of CCC types encountered. To ensure eligibility to the scheme, written agreement for the CCC must be obtained prior to submitting the CCC application (see Section 4) and this should be appended to the cover letter (even for those scenarios listed in this section).

2.1.1 CCC Scenario 1

The example in Table 1 illustrates a typical CCC, where the MAH simultaneously submits three separate applications, each proposing the same changes to the licences of three product strengths:

- v1: Type IB variation, change code A.2.b; to change to the product name.
- v2: Type II grouped variation, change code C.I.z; to update sections 4.3 – 4.9 of the SmPC in line with the Company Core Data Sheet (CCDS).
- A1: Regulation 267 grouped applications, change code P2/3 to introduce new redesigned artwork for the products and to update mock-ups of label and PIL to include all the changes arising from variations v1 and v2.

Table 1: Scenario 1: CCC comprising three separate applications, each proposing the same changes to the licences of three product strengths

Product name and PL No.	**Proposed change**		
	Type IB change code A.2.b Change to the product name	**Type II grouped change code C.I.z Update in line with CCDS (section 4.3-4.9)**	**HMR Reg 267 application change code P2/3 Update label, PL and artwork redesign**
Tablets 25 mg PL xxxxx/0001	v1	v2	A1
Tablets 50 mg PL xxxxx/0002	v1	v2	A1
Tablets 100 mg PL xxxxx/0003	v1	v2	A1

In this scenario it can be seen that:

- v1 and v2 are bulk variations (as highlighted by colour coding) applied to all three product strengths. For applications to qualify for bulking and

associated fee reduction, the changes must be identical for each product (see Section 5.2).

- A1 are bulk Regulation 267 applications to introduce new artwork, as the same change(s) applies to all the products within the bulk.
  NOTE: If the redesign of the artwork is unique to each individual product to allow for specific product differentiation, as often applies to OTC products, individual Regulation 267 applications should be submitted within the CCC**.**

Other more complex scenarios are feasible as shown in the following examples.

2.1.2 CCC Scenario 2

Changes may be applied across more than one MA for purely national procedures (Table 2). In the example shown, changes are applied to six product licences.

The MAs may either belong to the same MAH or to different MAHs if for example two MAHs have entered into an agreement to market identical MAs of three product strengths under branded livery for company “xxxxx” and generic livery for company “yyyyy”. The companies are affiliated..

Table 2: Scenario 2, CCC comprising four separate applications covering changes to two MAs each of which comprise three product strengths; the different MAHs are affiliated

Product name and PL No.	**Proposed change**		
	v1: Type IB, change code A.2.b New product name	**v2: Type II grouped change code C.I.z Update in line with CCDS (section 4.3-4.9)**	**HMR Reg 267 application change code P2/3 Update label, PL and inclusion of changes to the artwork**
Brand Tablets 25 mg PL xxxxx/0001	v1	v2	A1
Brand Tablets 50 mg PL xxxxx/0002	v1	v2	A1
Brand Tablets 100 mg PL xxxxx/0003	v1	v2	A1
Generic Tablets 25 mg PL yyyyy/0001	-	v2	A2
Generic Tablets 50 mg PL yyyyy/0002	-	v2	A2
Generic Tablets 100 mg PL yyyyy/0003	-	v2	A2

Branded products owned by company “xxxxx”

Generic products owned by affiliated company “yyyyy”

In the example shown, the CCC comprises four applications:

- v1: Type IB variation, change code A.2.b; to change to the product name.
- v2: Type II grouped variation, change code C.I.z; to update sections 4.3 – 4.9 of the SmPC in line with the Company Core Data Sheet (CCDS).
- A1: Regulation 267 application, change code P2/3 to introduce minor changes to the artwork for the product range and to update mock-ups of label and PIL to include all the changes arising from variations v1 and v2.
- A2: Regulation 267 application, change code P2/3 to introduce minor changes to the artwork for the product range and to update mock-ups of label and PIL to include all the changes arising from variation v2.

In this scenario bulking is applied as follows:

- v1 is a bulk variation, applied to the three branded products
- v2 is a bulk variation, applied to both branded and generic products
- A1: is a bulked Regulation 267 application as identical changes to the three branded products are applied
- A2: is a bulked Regulation 267 application as identical changes to the three generic products are applied.

  NOTE: The changes for the generics are different to those proposed for the branded products therefore requiring separate bulked applications.

2.1.3 CCC Scenario 3

The MAH may propose different changes to a number of product licences within the CCC (Table 3); this should be supported by a robust justification, based on a clear regulatory strategy (ie. products being part of the same “brand” or duplicate licences or part of the same GMA). In this situation, the MAH is required to clearly indicate which changes are applied to the respective products using a tabulated colour-coded grid.

Table 3: Scenario 3, CCC comprising seven separate applications covering different changes to five product licences

Product name and PL No.	**Proposed change**				
	v1 Type IB change code A.2.b New product name	**v2 Type IB code B.II.e.5 Change in pack size**	**v 3 Type II grouped change code C.I.z Update in line with CCDS (section 4.3-4.9)**	**v 4:Type IB change code C.I.3a Update to section 4.8 of SmPC**	**HMR Reg 267 application change code P2/3 to update label, PL and artwork**
Capsule 25 mg PL xxxxx/0001	v1	v2			A1
Tablets 50 mg PL xxxxx/0002				v4	A2
Tablets 100 mg PL xxxxx/0003				v4	A2
Oral solution 25 mg/ml PL xxxxx/0004			v3		A3
Oral solution 50 mg/ml PL xxxxx/0005			v3		A3

In the example shown, the CCC comprises four separate variations and three separate Regulation 267 applications as follows:

- v1: Type IB variation, change code A.2.b; to change to the product name
- v2: Type IB variation, change code B.II.e.5; to add new pack size
- v3: Type II grouped variation, change code C.I.z; to update sections 4.3 – 4.9 of the SmPC in line with the Company Core Data Sheet (CCDS)
- v4: Type IB change code C.I.3a to update section 4.8 of SmPC, to add information in relation to the Yellow Card scheme

  NOTE: The MAH is implementing agreed wording as published on the MHRA's website. Ordinarily, this change may be implemented within a suitable regulatory intervention (e.g. unrelated variation to the SmPC) or by a Type IA notification procedure. Following the implementation of the change, the company has the option to submit a Type IA notification. However, in this scenario, the company elected to submit this change as a Type IB variation in order to benefit from the CCC scheme. This is because CCCs can include only applications that

need assessment i.e. a Type IA notification cannot be considered as it is an administrative submission with no scope for assessment input and runs to a different procedure.

- A1, A2 and A3: Three individual Regulation 267 applications, change code P2/3 to introduce changes to the artwork for the product range and to update mock-ups of label and PIL to include all the changes arising from variations v1 v2, v3 and v4, as described in Table 3 .

In this scenario it can be seen that:

- v1 is applied to PL xxxxx/0001 only
- v2 is applied to PL xxxxx/0001 only
- v3 is a bulk variation, applied to PL xxxxx/0004 and PL xxxxx/0005.
- v4 is a bulk variation, applied to PL xxxxx/0002 and PL xxxxx/0003
- A1: is an individual Regulation 267 application for PL xxxxx/0001 only
- A2: is a bulked Regulation 267 application for PL xxxxx/0002 and PL xxxxx/0003
- A3: is a bulked Regulation 267 application for PL xxxxx/0004 and PL xxxxx/0005

2.1.4 CCC Scenario 4 comprising only variations

In this scenario the CCC excludes Regulation 267 applications and comprises only variation applications that impact on the product information (SmPC, PIL, and label). There are two possibilities, which are described in the following Sections:

2.1.4.1 Scenario 4a consequential updates to the PIL/label

The CCC comprises variations to update the SmPC that result in multiple consequential changes affecting the PIL and/or labelling.

In this scenario companies may benefit from the CCC procedure in situations where a Regulation 267 application is not needed, in that only one mock-up encompassing all the changes arising from the separate variations is required. This is shown in the example in Table 4.

Table 4: CCC comprising two separate applications covering changes to the licences of two product strengths with consequential changes to the PIL.

Product name and PL No.	**Proposed change**	
	v1: Type IB change code C.I.3.a: Update to sections 4.3 to 4.6	**v2: Type II grouped change code C.I.4: To update section 4.8 of the SmPC**
Tablets 25 mg PL xxxxx/0001	v1	v2
Tablets 50 mg PL xxxxx/0002	v1	v2
	Format of updated common PIL (see Section 5.3.2.2 for further detail)	
	Word document in tracked and clean versions (or annotated currently approved mock-up) reflecting only changes submitted for v1	Word document in tracked and clean versions (or annotated currently approved mock-up) reflecting only changes submitted for v2
		Full colour mock-up encompassing all changes arising from the CCC variations v1 and v2

In the example shown, the CCC consists of two separate variations applied to the licences of two product strengths. There is a common PIL covering both product strengths:

- v1: Type IB change code C.I.3.a, to update sections 4.3 to 4.6 of the SmPC, in line with the final assessment report and Core Safety Profile (CSP) for a PSUR work-sharing procedure with consequential changes to the PIL.
- v2: Type II grouped change code C.I.4 to update section 4.8 of the SmPC to add new side-effects supported by new data and to update the frequency of side-effects, with consequential changes to the PIL.

In this scenario it can be seen that:

- v1 and v2 are both bulk variations applied to the two product strengths.
- for v1 and v2 the updated PIL is submitted as Word documents in tracked and clean versions reflecting only the respective changes
- A consolidated full mock-up PIL, encompassing all the changes arising from variations v1 and v2 is submitted with v2 only.

NOTE: Further detail regarding the submission of updated SmPC fragments and labels and leaflets is provided in Section 5.3.

2.1.4.2 Scenario 4b no change to the PIL/label

The CCC comprises only variations to update the SmPC that do not have any consequential changes affecting the PIL and/or labelling. In this scenario the MAH may benefit from a co-ordinated assessment of the variations, for example when multiple changes are implemented to the same or different fragments of the SmPC. As the PIL/label are not affected by the variations these are not required to be submitted (this should be explained in the cover letter and/or the variation application form).

3 Essential considerations for planning a proposed CCC

It is essential that CCCs are planned as part of the MAH's regulatory strategy for life cycle management of their product portfolio. To maximise the potential benefits of a CCC particular consideration should be given to the following prior to submission.

3.1 Pending variations

The MAH should avoid submitting a CCC if there are ongoing pending variations or Regulation 267 applications under review with the MHRA that impact on the same area(s) of the dossier as proposed by the CCC, e.g. same SmPC fragment and/or PIL/label. It is advisable to wait for the approval of pending applications. Otherwise, if a CCC submission is made whilst there are pending overlapping variations, the SmPC fragments/mock-ups submitted with the CCC application must exclude any pending changes – it cannot be assumed that these will be approved. A potential drawback of submitting a CCC in this way is that it negates the benefits of the scheme.

3.2 Grouped variations

The principle of the CCC scheme is to co-ordinate the submission and processing of multiple applications (variations and PIQU applications). It is emphasised that CCC is not a means of combining the different submissions into one single

application, as this is contrary to Schedule 10(A) of the Human Medicines Regulations. Similarly, groupings that contain unrelated changes will be rejected.

3.2.1 Advice on acceptable groupings

In line with current requirements for grouped variations, the MAH is responsible for submitting appropriate (acceptable) grouped changes within a variation application. Justification for the particular grouping should be provided in the cover letter and/or the background or scope section of the variation application form. This may refer to acceptable groupings as published on the CMDh (6) or MHRA websites (7) or to previously agreed similar groupings.

If approval for grouping is needed, this must be obtained prior to submitting the request for a CCC. This should only be necessary in exceptional cases (for example if the grouping is considered complex or is an un-published example). The request for prior approval of a grouping is submitted to the MHRA's Regulatory Information Service (RIS) by email: variationqueries@mhra.a.gsi.gov.uk.

Where the MAH has obtained advice from the MHRA on a particular grouping, this must be appended to the request for a CCC (see Section 4) and included in the cover letter at the time of submission (see Section 5.1).

(7) CMDh:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_173_2010_Rev10_2013_07_clean.pdf

4 Submitting a request for a CCC

The MAH should obtain prior agreement for a CCC before it is submitted. An email requesting approval for a proposed CCC should be send to the RIS at variationqueries@mhra.gov.uk, inclusive of the following required information:

(i) Email subject header: the email header (and all other correspondence) must include:

- The term "request for CCC"
- PL number
- Product name as applicable.
- Unique CCC reference number which is the responsibility of the MAH to provide. **This is needed for tracking purposes**.
  The following format is suggested:
  "CCC" then "MAH name or initials" then "Company five digit number" (i.e. the first five digits of the Product Licence (PL) number) then "unique three digit number"
  For example, company "Pharmalabs Consumer Healthcare Products" has licences PL 01234/xxxx and allocates the following reference number for its first CCC application: CCC-PCHP-01234-001.
  Sequential numbers are then allocated by the MAH for subsequent CCC applications e.g. CCC-PCHP-01234-002 and so forth. The MAH retains a record of all their CCC numbers.

(ii) Eligibility for the CCC scheme: a brief justification for the CCC explaining the regulatory strategy underpinning the request to co-ordinate the proposed submissions. Reference may be made to one of the scenarios described in Section 2.1.
NOTE: Changes that do not impact product information (SmPC, labelling and PIL) are not eligible for the CCC scheme.

(iii) The proposed changes and product licences affected should be summarised in a tabulated format (or schematic);

- colour coding should be used to highlight the different applications and bulking proposals.

- It should clearly state which variation the mock-ups have been submitted with if relevant PIQU applications are not included in the CCC (i.e. Scenario 4a). See examples in Section 2.1.

(iv) A brief list of all the variations/PIQU applications proposed.
NOTE: A detailed description of the proposed changes or current/proposed comparison tables are not required at this stage and should not be provided.

(v) Brief justification for any proposed grouping of variations.
NOTE: If prior agreement for grouping of variations is required, this should be obtained before submitting the CCC; grouping advice should be requested via variationqueries@mhra.gsi.gov.uk (see Section 3.2.1).

(vi) A list of any pending variations that overlap with the same areas being updated by the CCC (see Section 3.1).

On receipt of the above, the MHRA will confirm the suitability of the proposed CCC. The CCC request and confirmation of acceptance should be appended to the cover letter for each submission made as part of the CCC (see Section 5.1).

5 Documentation requirements for a CCC (how to compile an application)

The actions taken by the MAH to compile a CCC are summarised in the flow chart in Annex 1. The documentation, supporting data requirements and fees payable are essentially unchanged for the component applications of a CCC. Thus, in line with current requirements, each individual application is a standalone procedure, supported by the data and documentation relevant only to the change(s) applied for. It is emphasised that the MAH cannot submit one single data package covering all the applications in a CCC submission. Such applications will be rejected. In particular, it is important to comply with the requirements for the cover letter and updated product information (SmPC, PIL, label).

The CCC application should comprise the following documentation as detailed in the Sections below. This is illustrated in Table 5 using Scenario 1 as an example.

Table 5: Documentation requirements, process timescales and fees for CCC Scenario 1 comprising three separate applications, each proposing the same changes to the licences of three product strengths

Product name and PL No.	**Proposed change**		
	v1: Type IB change code A.2.b: Change to the product name	**v2: Type II grouped change code C.I.z: Update in line with CCDS (section 4.3 – 4.9)**	**HMR Reg 267 application change code P2/3: Update to the PIL and labelling in line with the SmPC including a redesign the artwork for the product range**
Tablets 25 mg PL xxxxx/0001	v1	v2	A1
Tablets 50 mg PL xxxxx/0002	v1	v2	A1
Tablets 100 mg PL xxxxx/0003	v1	v2	A1
	Updated module 1 documentation to be submitted with each application See Section 5.3		
Cover Letter	Include common cover letter attached to each application of the CCC. The letter is as per the template in Annex 2 and includes all information detailed in Section 5.1		
SmPC fragments (clean versions only)	Section 1 and other sections requiring update of the product name ONLY	Sections 4.3 -4.9 as updated by the variation ONLY	Not applicable
Full SmPC	Full SmPC document (tracked and clean versions): either • Consolidated with all the changes arising from v1 and v2 where each change attributed to v1 and v2 is clearly indicated (preferred option), or • Containing changes arising from v1 only	Full SmPC document (tracked and clean versions): either • Consolidated with all the changes arising from v1 and v2 where each change attributed to v1 and v2 is clearly indicated (preferred option), or • Containing changes arising from v2 only	Not applicable
Label/leaflet update	Label and PIL updated only with v1 changes concerning the new product name: either • Word version in tracked changes, or • Annotated current approved mock-up if the proposed changes are not extensive	Label and PIL updated only to reflect the v2 CCDS changes: either • Word version in tracked changes, or • Annotated current approved mock-up if the proposed changes are not extensive	Full colour mock-ups that have been updated with all the changes that arise from v1 and v2 and the HMR Reg 267 changes
	Process timescales (see Sections 6.3 and Section 7)		
Time to procedure start (from receipt of application to validation)	Within 14 days	Within 14 days	Within 14 days
Assessment timescale (RFI or approval letter issued)	By 30 days	By 60 days	Assessment carried out in parallel with variation(s) assessment and wherever possible within the same timeframe. The statutory timeframe of 90 days still applies.

Fees payable See Section 5.2	Type IB fee for the first PL and 2x Type IB bulk fees for the two other PLs	Type II Grouped fee for the first PL and 2x Type II Group bulk fee for the two other PLs	PIQU fees for the first PL and 2x bulk fees for the two other PLs

5.1 Common cover letter and associated information

The common cover letter is a key document that underpins the CCC. This must be attached to each component application (variation(s) and PIQU application(s)) of the CCC. A template for the common cover letter is provided in Annex 2 and ensures that the following essential information is provided:

(i) Unique CCC reference number assigned by the MAH according to the numbering convention described in Section 4 (e.g. CCC-PCHP-01234-001). **This is important for tracking purposes.**

(ii) Brief tabulated summary of the CCC detailing the product licence numbers affected by each application.

NOTE: The table in Annex 2 includes a column for the CESP/Portal ID reference numbers. These will not be available at this stage; therefore the column may be left blank. The numbers are added by the MAH and communicated to the MHRA at a later stage, after the CCC has been submitted and the MAH has obtained the reference numbers (see Section 6.2).

(iii) Attached MHRA's acceptance of the CCC submission as described in Section 4. This should include the MAH's original proposal including justification for any proposed groupings.

(iv) It should clearly state which variation the mock-ups have been submitted with if relevant PIQU applications are not included in the CCC (i.e. Scenario 4a).

(v) Declaration regarding any pending applications at the time of submitting the CCC for the concerned product licences.

NOTE: Pending variations should be listed in the application form in line with current requirements.

(vi) Application forms as currently required for each component variation and PIQU application that form part of the CCC.

5.2 Fees

There are no additional fees for submissions under the CCC scheme. The fees payable for the CCC scheme are the same as if the applications were submitted and processed as individual, un-co-ordinated procedures.

The usual fees for grouping and bulking of variations and Regulation 267 applications apply as illustrated for Scenario 1 in Table 5. It is important to note the following:

- The MAH is responsible for ensuring the correct fees are paid at the time of submission and for providing evidence of this at submission. Failure to do so may result in rejection of the relevant application and cause delays in the start of the CCC procedure. (See Section 6.3.)
- For applications to qualify for bulk fees the changes to the different products must be identical in each case.
- Full variation fees are payable for each product licence where the changes are unique to each product. For Regulation 267 applications full fees are payable for each application when specific differentiation in the product information may be necessary, which will require individual assessment, as often applies to OTC products.

5.3 Supporting data/documentation

In line with current requirements, the supporting data required for assessment of each component variation of the CCC is linked to the relevant application.

NOTE:

- Each individual application is a standalone procedure, supported by the data and documentation relevant only to the change(s) applied for.
- One single data package covering all the applications in a CCC submission cannot be submitted. Such applications will be rejected.
- Updated product information concerning SmPC, PIL, and label should be submitted, as described below and summarised in Table 5.

5.3.1 Updated SmPC documents

5.3.1.1 SmPC fragments

The following clean SmPC fragments are required:

- Each variation (v1 and v2) should include only the fragments being amended by the respective proposed change(s).
- Clean, appropriately formatted, Word documents should be provided as per normal MHRA submission guidelines.

  NOTE: Tracked changed fragments should not be submitted.

The correct format for the SmPC fragments can be found on the MHRA website (8).

(8) http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Licenceapplicationforms/SummaryofProductCharacteristicstemplatesandfragments/

Thus in Scenario 1 (see Table 5), relevant SmPC fragments to be submitted with the variations are as follows:

- v1 (name change): updated section 1 (and other sections as applicable where the product name is stated)
- v2 (grouped CCDS changes): updated sections 4.3, 4.4, 4.5, 4.6, 4.7 4.8 and 4.9.

5.3.1.2 Full SmPC

In addition to the above SmPC fragments, the full SmPC should be submitted with each variation (v1 and v2) according to one of the following options:

- Option 1 consolidated SmPC (preferred): Each variation application (v1 and v2) contains a full consolidated SmPC (tracked and clean) clearly showing all the changes arising from the CCC. However, it is essential that the tracked version clearly indicates which variation each change is attributed to. This may be done by colour coding or annotations in the margins. This option has the advantage of requiring the preparation of only one consolidated document that is shared across all the variations.
- Option 2: Each variation application (v1 and v2) contains a full SmPC (tracked and clean version) clearly showing only the changes that are applicable to that application.

NOTE: The full SmPC should not be provided with the PIQU application of a CCC (this is applicable to both Option 1 and Option 2).

5.3.2 PIL and Label updates

The assessment of the CCC variations and the Regulation 267 (PIQU) applications will be conducted in parallel. The relevant assessment teams will co-ordinate the assessment of the pending variations (see Section 7.) Consequently, the following requirements for PIL and label apply.

5.3.2.1 Requirements for a CCC inclusive of a Regulation 267 application

(i) Updated PIL/label to be submitted with the variation(s)

Each variation (v1 and v2) requires a label/PIL that has been updated only with changes concerning the particular variation; this is a current requirement for variations and it is unchanged by the CCC scheme. However, mock-ups are not required to be submitted with the variations at any stage during the CCC procedure; this is a new concession, introduced for the CCC scheme.

The label/PIL updates may be provided as:

- a Word document in tracked version or
- current approved mock-ups annotated with the proposed changes – for minor updates only.

  NOTE: Annotation will not be appropriate if the proposed changes are extensive and will hinder the assessment process. An example of acceptable annotation is provided in the following link (9):

(9)
http://www.mhra.gov.uk/home/groups/comms-ic/documents/regulatorynews/con241805.pdf

(ii) Updated PIL/label to be submitted with the Regulation 267 application(s)

Full consolidated colour mock ups are **only** required to be submitted with the Regulation 267 application(s).

This mock-up includes all the changes that arise from the CCC variations as well as the Regulation 267 changes. Thus, as illustrated in Scenario 1 (see

Table 5) only one consolidated full colour mock-up is required which must be submitted only with the PIQU applications (this includes changes arising from v1, v2 and A1).

NOTE: See Section 7.2 for updated PIL/label to be submitted following a request for further information during the assessment phase.

5.3.2.2 Requirements for a CCC not inclusive of a Regulation 267 application

It is feasible that a CCC includes only Type IB/II variations, each with consequential changes to the label/PIL, as described in Scenario 4a (Section 2.1.4.1). The requirements for submitting SmPC fragments, the full SmPC and annotated label/PILs for each variation are as described above. However, in this case, only one consolidated full colour mock-up is still required, which should be submitted with a designated variation as follows:

- a Type II variation if one is included, otherwise
- one of the Type IB variations which has the most changes.

NOTE: The MAH should provide the above information when requesting agreement for the CCC prior to submission and the cover letter should state which variation the mock-ups have been linked to.

6 Submission and validation of a CCC

It is essential that CCCs are planned and reviewed for accuracy before submission to ensure their content is complete (see Section 5) and correctly formatted. Within a CCC, those applications that do not comply with these requirements and/or the MHRA submission guidance as set out below will not be processed and will be rejected or invalidated. This will delay the start of the CCC procedure.

A flowchart summarising the process for validating a CCC is provided in Annex 3. There are 3 steps:

- Submission: MAH submits electronically via CESP or Portal
- Notification: MAH send an email to inform MHRA of the submission

- Validation by MHRA

NOTE: The usual MHRA submission requirements apply, unless otherwise stated in this guideline, as outlined on the MHRA website (10).

(10) http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Submittinganapplicationtotheemhra/MHRAsubmissionrequirements/

6.1 Submission routes for a CCC

The general administrative requirements for the submission of variations are applicable to CCCs; however, only electronic applications will be accepted via CESP (the preferred route) or the Portal.
NOTE: Portal submission must be completed on the same day (see Section 6.1.2).

The MAH should take care to ensure that the individual applications of a CCC are technically valid, complying with submission guidelines and that all the required documents as listed in Section 5 are provided.

Any component application of a CCC that is not submitted in line with this guidance will be rejected or invalidated, which will delay the start of the CCC procedure.

6.1.1 Submitting via CESP

The advantages of CESP are that it is has the capability to receive the CCC application:

- In a single submission (on the same day).
- In a single folder; this effectively ring-fences the component parts of the CCC ensuring that they travel together. The folder can be structured into sub-folders containing the individual applications of the CCC.
- With an unlimited file size.

NOTE: Currently there is no two-way electronic communication available with CESP. Any correspondence sent from the MHRA will be sent by post, or via email if

you have registered with eComms. For more information on how to register with eComms please contact e-commsproject@mhra.gov.uk

Further information on CESP is provided on the following link (11).

(11) https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk#ways-to-make-your-submission

6.1.2 Submitting via HM Portal

The functionality of the HM portal is similar to the CESP Portal except there are extra options for Submission types

If not registered for the HM Portal please use the following link to apply https://www.gov.uk/guidance/registering-to-make-submissions-to-the-mhra-from-1-january-2021

The correspondence for applications submitted through HM Portal is the same as CESP submissions with the preference for communications to be sent by eComms where possible.

6.1.3 Portal Applications

The CCC requires careful planning to ensure that the submission of the entire CCC can be achieved sequentially on the same day when using the Portal; this is automatically done by CESP. Submission on different days introduces a high degree of complexity for the MHRA in tracking and linking the individual components of the CCC. Therefore, for logistical reasons **a CCC will be rejected if not submitted on the same day**. MAHs are strongly advised to start their CCC submission in the morning to allow sufficient time for the submission to be completed on the same day.

NOTE: Following submission of the CCC via CESP or the Portal, the MAH makes a note of the CESP/Portal ID reference numbers and enters these into the template cover letter as illustrated in Annex 2. This is important for tracking purposes, see Section 6.2.

6.2 Notification of CCC submission

After submission of the CCC has been completed, the MAH will have obtained the relevant CESP/Portal ID reference numbers. These should be inserted into the common cover letter (Annex 2). The completed letter containing all the submission details must then be sent by email to the MHRA to indicate that the relevant CCC submission has been made – this is important for tracking purposes.

NOTE: Only the cover letter should be sent (i.e. not any additional attachments that may have been included in the submissions). The email (quoting CCC in the subject header and the MAH's unique reference number) is sent to the following mailbox:

Newly approved CCC submissions/re-submitted component: IPUScientificValidation@mhra.gsi.gov.uk

Or RFI responses for CCC: Area3-VARIATIONS-RFI-queries@mhra.gsi.gov.uk

6.3 Validation of the CCC:

6.3.1 Validation process and timescale

The component applications of a CCC are validated according to current procedures as for non-CCC applications. However, in order to co-ordinate the start of a CCC procedure, the validation timescale (from receipt to procedure start) defaults to 14 days as applicable to Type IB/II variations. In this way the procedure start date of all the applications in a CCC is synchronised to enable a parallel assessment of the variations and/or PIQU applications.

6.3.2 Validation issues: failure to meet the CCC and MHRA submission guidelines

Applications which do not comply with the guidelines outlined in this document and on the MHRA website will be rejected or invalidated.

Common reasons for rejection and invalidation include:

- Technical validation failure of the eCTD provided
- Portal form not completed correctly or at all
- Failure to provide proof of the correct payment

- Failure to provide all correct updated documentation

6.3.3 MAH actions to be taken if part of the CCC submission is invalid or rejected

If one component of the CCC application (e.g. a variation) fails to meet submission or validation requirements, then this component will be rejected or invalidated. A 10% administrative fee is chargeable for the component that is invalided, in line with current requirements. The MAH will be informed via email that this submission has been rejected or invalidated and the reasons why. This will cause a delay in validating the CCC.

If the submission has failed to create due to an issue with the form, either technical or due to completion, the MAH should contact the Portal team: manager.portal@mhra.gsi.gov.uk

NOTE: The component(s) of the CCC must be resubmitted **within 48 hours** of receipt of the rejection/invalidation correspondence. Additionally, at the same time the original contact persons (as listed in Section 6.2) must be informed of the resubmission.

Failure to re-submit within this timescale will result in the entire CCC application being considered invalid and rejected. The MAH must then re-submit the entire CCC.

7 Assessment process for a CCC

A key feature of a CCC is that the start date of the assessment of each individual application is synchronised. This ensures the assessment of the variation(s) and/or PIQU application(s) is conducted in parallel with the assessment teams co-ordinating the procedures. However, each application will be assessed independently according to the usual relevant timeline i.e. within 30 days for a Type IB and 60 days for a Type II variation. It is important to note that the assessment of Regulation 267 applications will start at the same time as the variations, and, wherever possible, it will be conducted within the same timeframe of the associated variation(s); alternatively statutory timelines for assessment of Regulation 267

applications will apply (90 days) Regulation 267applications will be the last to be approved since it is a prerequisite that the associated variations must be first approved in order for the composite artwork to be finalised.

A summary flow chart describing the key steps in the assessment phase is shown in Annex 4. The assessment procedure is described below, illustrated using Scenario 1.

7.1 Initial assessment

Each application is assessed in parallel according to the following timelines i.e. within

- 30 days for a Type IB variation (v1)
- 60 days for a Type II variation (v2)
- within the same timeframe of the associated variations, when possible (see section 7).

The outcome of the first assessment phase will be:

- For the variations (v1 and v2): Individual grant letters or RFI letters will be issued, as appropriate.
- For the PIQU applications (A1): Individual RFI letters will be issued listing the label/PIL deficiency points, as appropriate. If there are no deficiency points on the artwork, a RFI letter will be sent to communicate this to the MAH and stop the regulatory clock on the applications, which will remain pending until the variations (v1 and v2) are approved. This will enable the MAH to submit updated mock-ups if changes are required, arising from the assessment of the variations.

7.2 Request for further information (RFI), submission of updated product information (SmPC, PIL, label)

In the event of an RFI being issued, the MAH should provide a response to the individual applications that form the CCC as outlined below.

Variations: where a RFI has been issued for the variation(s), the company should provide the response according to the usual procedural timeframes. Updated SmPC

fragments and updated PIL/label documents should include any amendments required for the respective variations (see Section 5.3). This is illustrated below using Scenario 1 as an example (see also Table 5):

- RFI responses for variations (v1, v2) should be submitted within:
  - 30 days for v1 (type IB variation)
  - 60 days for v2 (type II variation)
- Relevant updated documentation should be provided in the responses:
  - Updated SmPC fragments containing only the changes related to the respective variations (i.e. section1 for v1 and sections 4.3 to 4.9 for v2).
  - Consolidated SmPC including all the changes arising from both v1 and v2.
  - Updated label/PIL as Word document versions (or annotated current approved mock-ups) containing only the changes related to the respective variations (i.e. new product name for v1 and CCDS updates for v2).

PIQU application: Should a RFI from PIQU be issued requesting updated label/PIL mock-ups, these should not be submitted until the outcome of the assessment of the variations included in the CCC is known, i.e. after approval or approval following resolution of amendments requested in a RFI (see Annex 4).

Following the RFI, the company should provide only one updated proposed mock-up that takes into account of all the amendments approved for the variations and any RFI changes that have been requested by PIQU. **Finalised mock-ups should be submitted only after all variations concerned are approved.**

This is further illustrated below using Scenario 1 as an example (see also Table 5):

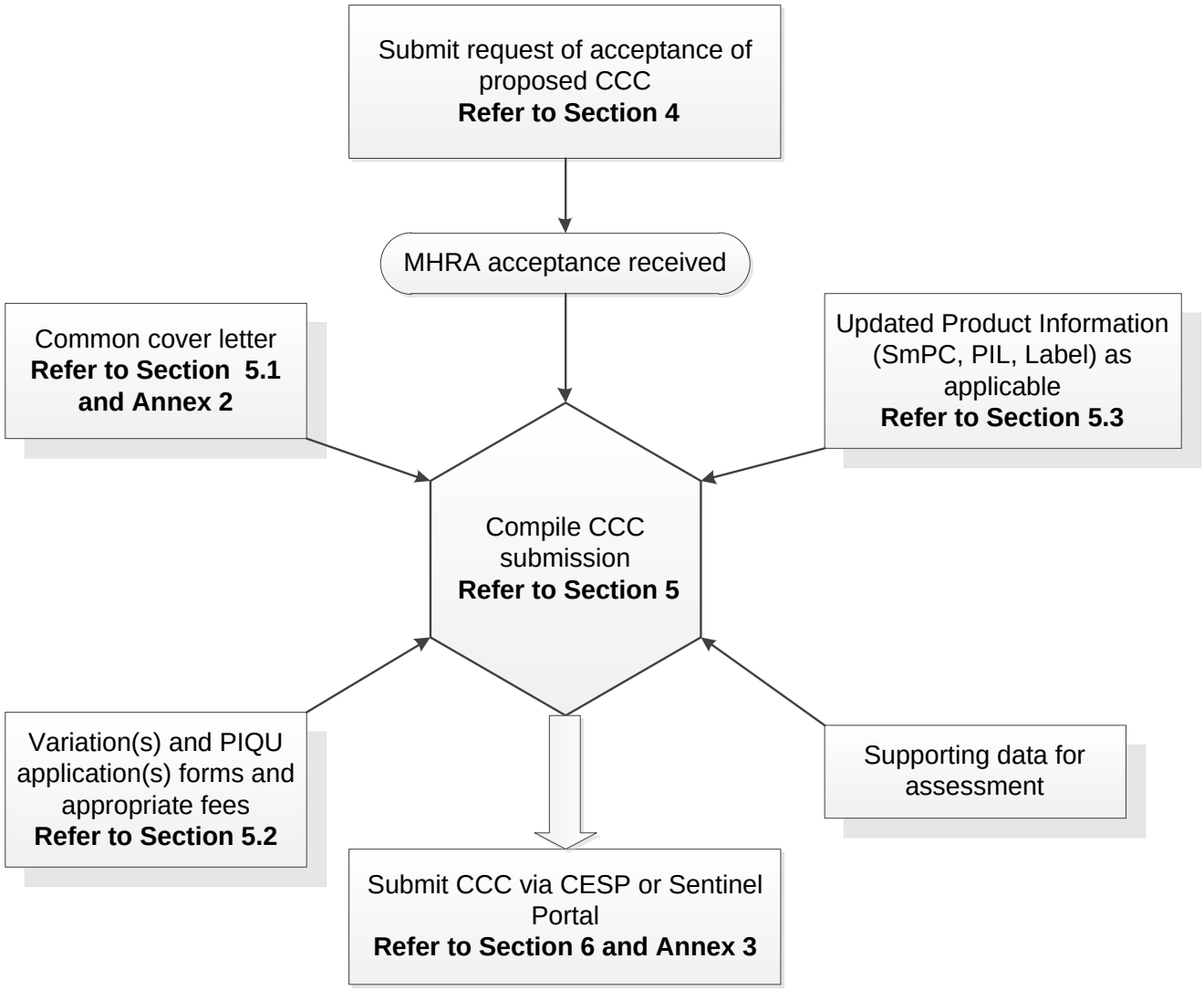
- RFI response for PIQU applications (A1) should be submitted:
  - only after v1 and v2 are approved
- Relevant documentation should be provided in the response:
  - finalised mock- ups, including any change arising from the assessment of the variations (v1 and v2) and PIQU application (A1)

NOTE: Finalised mock-ups are submitted only with the PIQU applications.

7.3 Finalisation of the CCC procedure (approval)

Upon completion of the assessment of the revised mock-ups, the PIQU applications are approved and the CCC procedure is concluded.

ANNEX 1 Flowchart for MAH actions to request and compile a CCC



ANNEX 2 Template cover letter

CCC Unique Ref Number: e.g. "CCC-PCHP-01234-001"	**Date of Submission:** 09/10/2014

Dear MHRA

Please find enclosed the component applications of the CCC as listed below.

Submission Work Schedule	**PL Number(s)** (Provide a list of all PL Numbers in the CCC)	**CESP/HM Portal ID (to be entered when available)**
v1 **Type IB change code A.2.b** **Change to the product name**	PL xxxxx/0001 (lead) PL xxxxx/0002 PL xxxxx/0003	84441
v2 **Type II grouped change code C.I.z** **Update in line with CCDS (section 4.3-4.9)**	PL xxxxx/0001 (lead) PL xxxxx/0002 PL xxxxx/0003	84356
A1 **HMR Reg 267 application change code P2/3** **Update label, PL and artwork redesign**	PL xxxxx/0001 (lead) PL xxxxx/0002 PL xxxxx/0003	84675

Declaration regarding pending variations for the above listed PLs that are currently under review by the MHRA at the time the CCC is submitted:

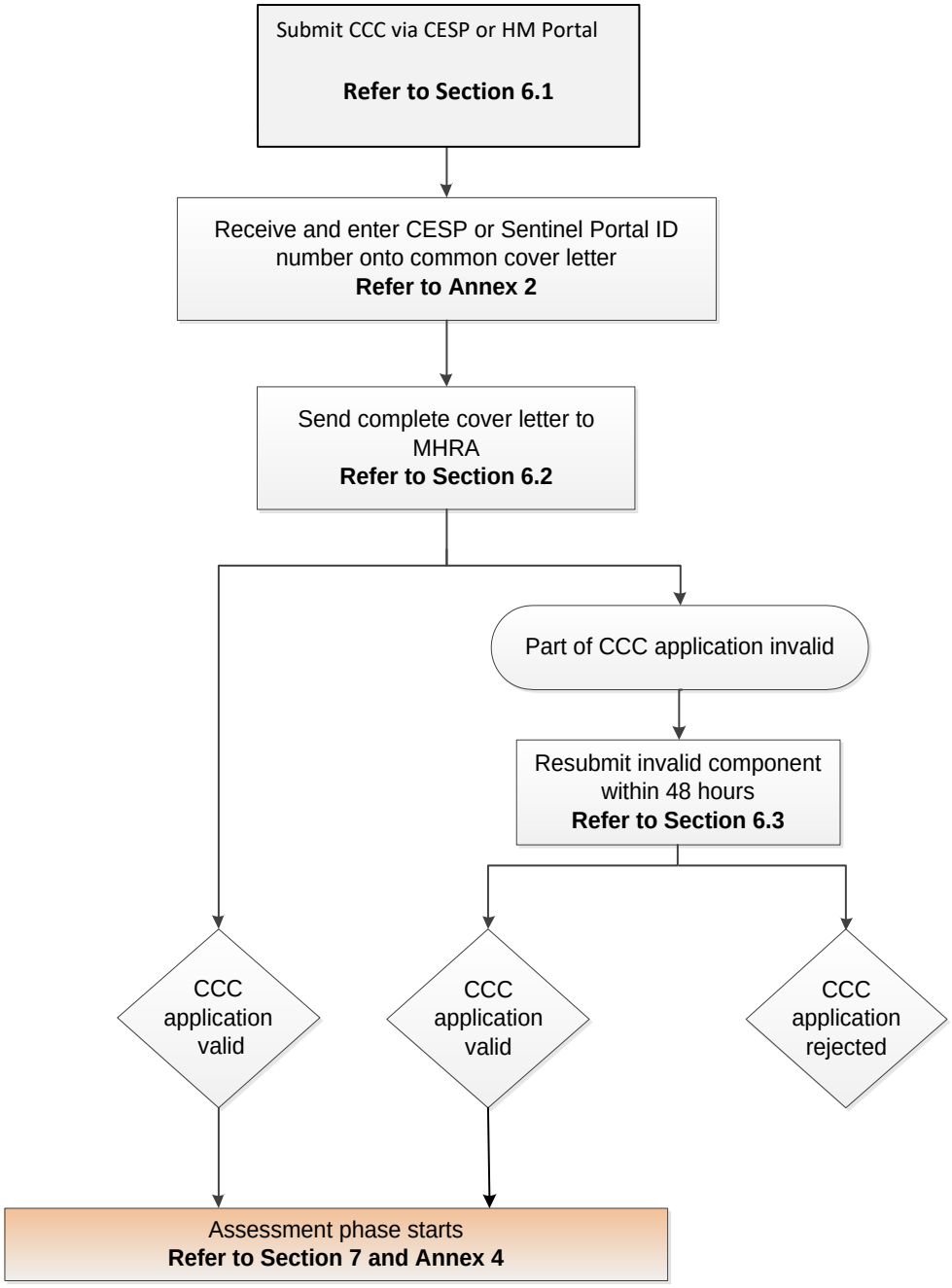
I confirm that the changes proposed by any pending variations are excluded from the SmPC/Label/PIL documentation submitted for this CCC

□ Yes, confirmed □ Not applicable

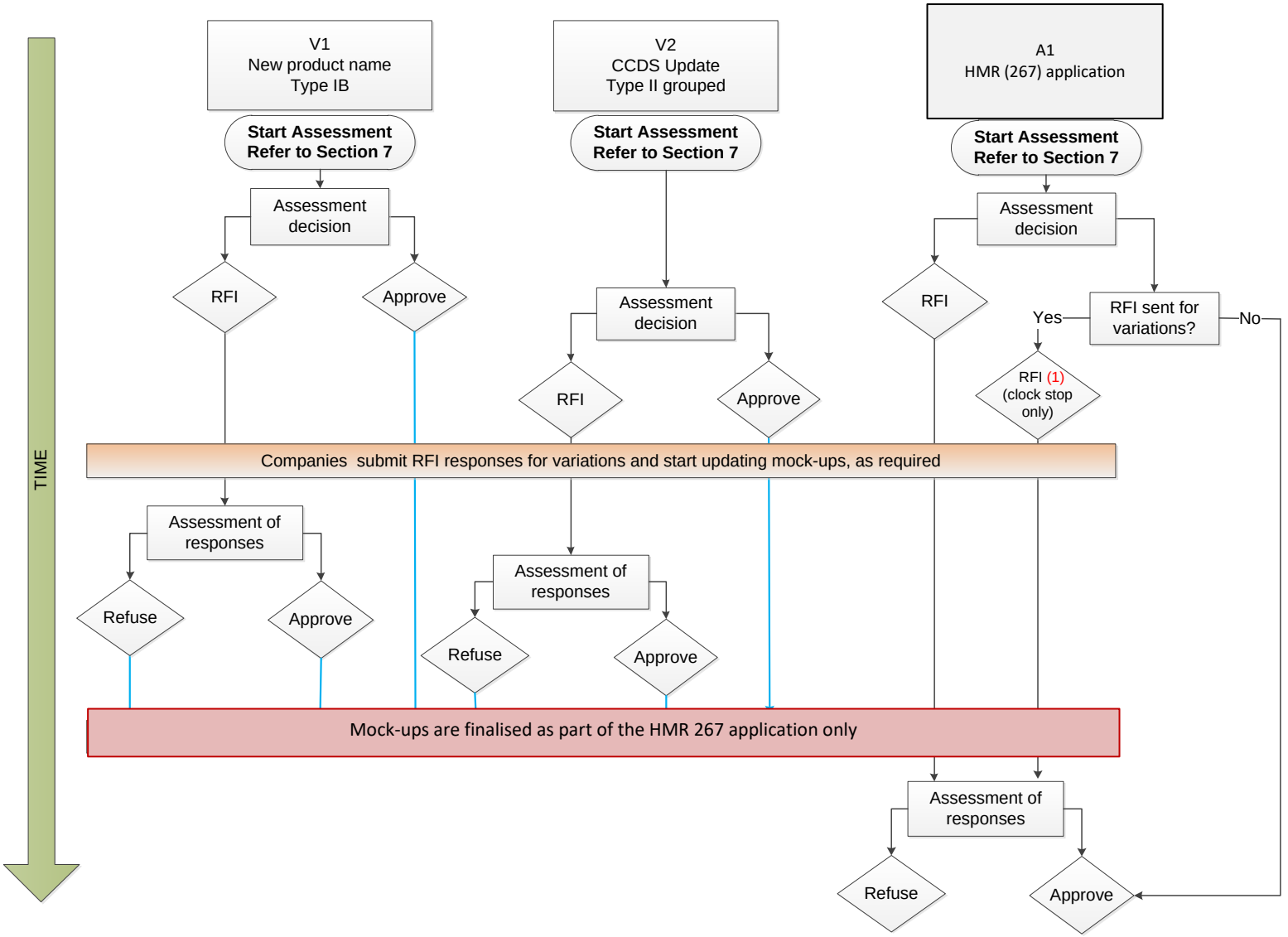
NOTE:

- **This letter should be completed and submitted with each component application of the CCC.**
- **Further information as detailed in Section 5.1 of the CCC guidance should be appended to this letter.**

ANNEX 3 Flowchart for submission, notification and validation (IPU business)



ANNEX 4 Assessment flowchart



NOTE: The regulatory clock will be stopped following the issue of all the RFI letters described in this flowchart. RFI (1) is issued with the sole purpose to stop the clock for application A1 (to be aligned with v1 and v2).

If v1 and /or v2 are refused, the mock-ups should be amended to eliminate the changes introduced by v1 and v2, as appropriate.