Uppsala Monitoring Centre

– Building a global safety culture

2018

WHODrug B3- and C3-formats

Implementation Guide
April 2018

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1. Introduction

The Uppsala Monitoring Centre (UMC) has been providing the de facto standard drug dictionary for analysis of concomitant drug data for over 30 years. We are constantly evolving our products to meet the needs of users and to ensure regulatory compliance. In 2002 we released the C-format in order to comply with upcoming ICH IDMP (International Council for Harmonisation IDentification of Medicinal Products) standards. In recent years the CDISC standards for electronic submission of study data have evolved and regulatory authorities are starting to require or strongly recommend use of the CDISC standards in NDA submissions.

The SDTM (Study Data Tabulation Model) standard of CDISC specifies how concomitant medications should be structured and presented. Based on those standard and regulatory recommendations, it has become evident that some changes need to be made to existing products in order to ensure all WHODrug users are fully compliant and to reduce the need for workarounds to reach compliance.

UMC has, together with the active involvement of user representatives, decided to create new dictionary formats: the B3- and C3-formats. Along with this, again with valuable input from the user community, UMC has taken action to facilitate the transition. The details of the new formats as well as available UMC support are explained in this guidance document.

2. Background

The aim for the new formats is to ensure full compliance without workarounds. There are two particular fields in the CDISC Concomitant Medications (CM) domain model of SDTM causing the need of workarounds in the structure of the existing formats. The SDTM fields of interest are CMDECOD and CMCLAS:

- CMCLAS should be populated with the ATC text for the drug, but due to field-length constraints in the existing formats, the full text is not always displayed and requires a workaround to get the full text.
- CMDECOD should be populated with the generic name of the drug and due to field length limitations and structure for multi-ingredient drugs in the existing formats, a workaround is required to get the correct data.

We are implementing a long-wanted change in the structure: in the new formats, all salt versions of drugs in combinations will be connected to an unsalted, generic combination on the preferred base level. To do this properly, the field length of the drug name needs to be extended substantially.

At the same time there is another long-wanted change, the display of non-unique names in the B2-format: the active ingredients will show attached to the trade name instead of the Drug Code. This will facilitate manual review of the data.

The details of the changes are run-through in this document.

3. Implementation timeline

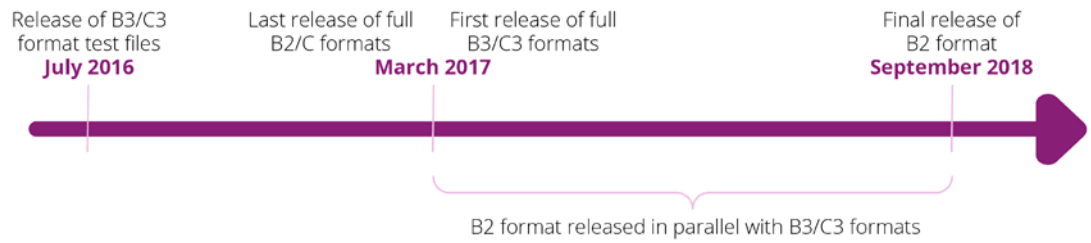

Figure 1. Timeline for the introduction of the B3/C3 formats.

During 2016, test files for the B3/C3 formats have been released, containing all types of changes that will occur in the new formats.

In March 2017, the first full B3/C3 format files are available for download along with the B2-format files, with no additional fee. The B2-format will exist in parallel with the B3/C3 formats until September 2018, but please note that from June 2017 only updated information is added to the B2-format (i.e. new ATC codes and drug names) and no modifications on existing records.

The C-format is available on request from June 2017 until September 2018. If you wish to get the C-format it needs to be requested in time since the production time will be three months.

Cross Reference Tool Japan and Standardised Drug Groupings are only available in the B3-format from June 2017 and onwards.

	2017 Mar	2017 Jun → 2018 Sep		2019 Mar
WHODrug Dictionaries	B2/B3 C/C3	B2*/B3 C*/C3	B2*/B3 C*/C3	B3 C3
Cross Reference ATC5	B2/B3	B2*/B3	B2*/B3	B3
Cross Reference Tool Japan	B2/B3	B3	B3	B3
SDG	B2/B3	B3	B3	B3

Figure 2. Timeline illustrating in which formats the WHODrug products will be released during 2017-2019.
**=updated with new inserts only.*

Please note that Change Request responses from UMC contain B3-format Drug Codes.

4. Description of the B3/C3 formats

The B3/C3 formats provide a new way of presenting and structuring WHODrug information with the intention to facilitate compliance with CDISC standards. Please note that the data and coding decisions made are not changed in any way, it only affects the Drug Codes.

All developments described in this section are valid for both B3- and C3-formats, except section 4.3 Non-unique names and the increased field length in the INA file mentioned in section 4.5. These changes will only be applicable for the B3-format.

4.1. Multi-ingredient Preferred Names

A majority of the multi-ingredient records in the B2/C formats have the first entered trade name of their respective ingredient combinations as the Preferred Name. For single ingredient records, the active substance i.e. the Generic Name, is the Preferred Name.

In the B3/C3 formats, the Preferred Names are generic for both single and multi-ingredient records, i.e. they represent the substance or substance combination. Please note that the single ingredient records remains the same in both B2/C and B3/C3, and that only multi-ingredient Preferred Names are changed in the B3/C3 formats.

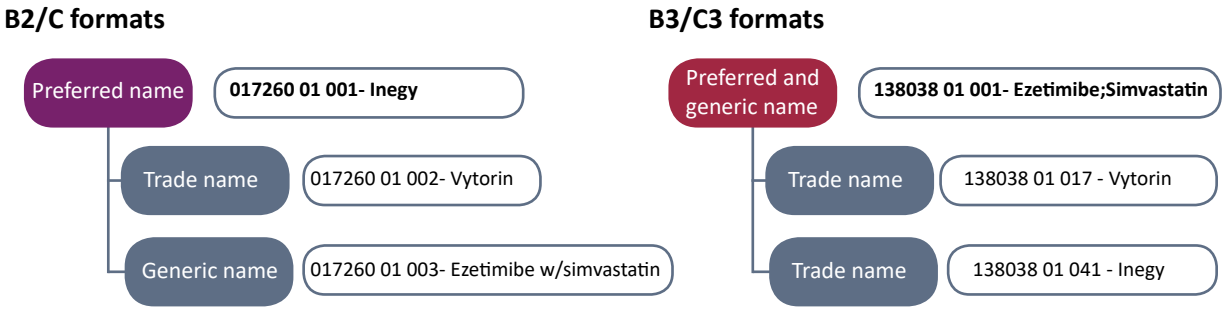

Figure 3. Example of Preferred Names for multi-ingredient records in the B2/C and B3/C3 formats. The Preferred Name is a trade name in the B2/C formats and a generic name in the B3/C3 formats.

4.2. Multi-ingredient salt/base relationship and classifications

4.2.1. Multi-ingredient salt/base relationship

For single ingredient records in the B2/C formats, all salt variations of a substance are connected to the Preferred Base Name. This is not the case for multi-ingredient records. Instead, different salt variations of a substance combination are located on separate Drug Record Numbers.

In the B3/C3 formats, the relationship between salted and unsalted substances is applied for multi-ingredient records, thereby harmonising the Drug Code logic of WHODrug.

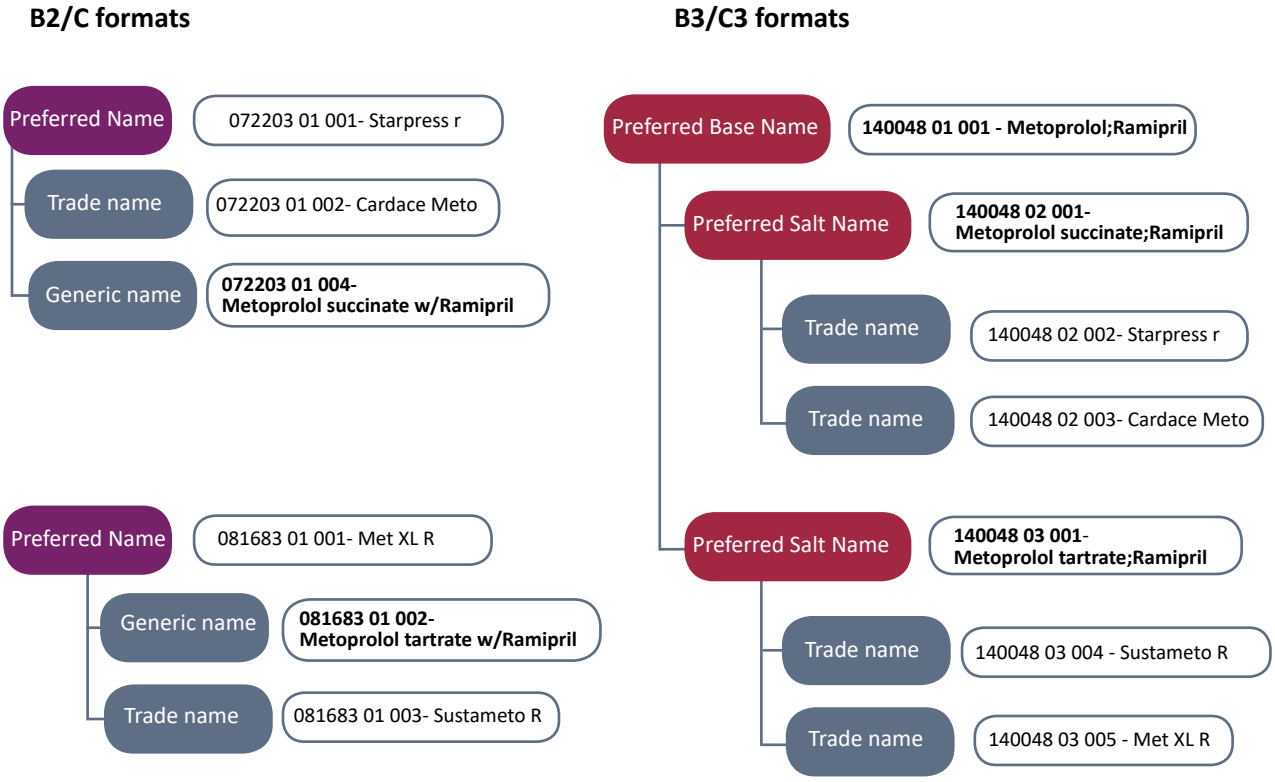

Figure 4. Ramipril and salt variations of metoprolol exist under separate Drug Record Numbers, and are consequently connected to separate Preferred Names in the B2/C formats. In the B3/C3 formats, combinations of ramipril and salt variations of metoprolol are connected to the same Preferred Base Name, consisting of the unsalted substance combination.

4.2.2. ATC assignments for multi-ingredient records

In the B2/C formats, different salt variations for a specified combination of substances do not necessarily have the same ATC codes assigned, as there is no connection between the different combinations.

As various salt combinations of multi-ingredient records are connected in the B3/C3 formats, ATC assignments of these records are impacted. In the B3/C3 formats, all salt variations of the same combination of substances, have the same ATC codes assigned. Note that the differences in ATC assignments in the B3/C3 formats compared to the B2/C formats only are due to additions - no ATC assignments have been removed in the new formats. Moreover, no ATC assignments for single ingredient WHODrug records are affected by the introduction of the B3/C3 formats.

4.3. Non-unique names

Non-unique names are made unique in the B2-format by the addition of /DRECNOSEQ1/ after the trade name. To facilitate review, this is replaced by [INGREDIENT(S)] in the B3-format. If more than one ingredient they will be written in alphabetical order, separated by semicolons.

Table 1. Non-unique names in the B2-format.

Drug Code	Drug name	Ingredients
00668101261	ZYFLOX /00668101/	Norfloxacin
00697202724	ZYFLOX /00697202/	Ciprofloxacin hydrochloride

Table 2. Non-unique names in the B3-format.

Drug Code	Drug name	Ingredients
00668101261	ZYFLOX [Norfloxacin]	Norfloxacin
00697202724	ZYFLOX [Ciprofloxacin hydrochloride]	Ciprofloxacin hydrochloride

4.4. Multi-ingredient Generic Names

Generic Names consist of semicolon separated substance names in alphabetical order in the B3/C3 formats, whereas they are represented by w/ in the B2/C formats.

Table 3. Comparison of Generic Names in the B2/C and B3/C3 formats.

Format	Generic Name
B2/C	Glimepiride w/Metformin hydrochloride
B3/C3	Glimepiride;Metformin hydrochloride

4.5. Technical developments

In the B3/C3 formats the number of characters is increased to 1500 in the Drug Name fields in the files DD.txt and MP.txt. The rationale for increasing the field length is to make sure the full Generic Names are displayed to the data reviewer. There are currently records in WHODrug with as many as 1200 characters but only 3% actually exceed 200 characters.

The ATC code text field in the INA file of the B3-format is increased to 110 characters in order to display the full ATC text.

Table 4. INA file in the B2-format. The ATC text field allows 50 characters.

ATC code	Text
A10AC	Insulins and analogues for injection, intermediate
A10AD	Insulins and analogues for injection, intermediate

Table 5. INA file in the B3-format. The ATC text field allows 110 characters.

ATC code	Text
A10AC	Insulins and analogues for injection, intermediate-acting
A10AD	Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting

5. Impact

5.1. General considerations

When upversioning to the B3-format, users who have large amounts of multi-ingredient records in their synonym lists may experience an increase in the number of modifications and deletes.

It is also important to ensure all systems and databases using WHODrug data, both upstream and downstream, are compatible with the field-length changes.

5.2. File size

Due to the field length extensions in the B3/C3 formats, some of the B3/C3 format files are considerable larger compared to the corresponding B2/C format files. This particularly applies to the MP.txt file in the C/C3 formats, which in the C3-format is around five times larger in size

compared to the corresponding file in the C-format.

6. UMC Resources

6.1. WHODrug Change Analysis Tool

6.1.1. The B3-format

From March 2017, the B3-format is included in WHODrug Change Analysis Tool (CAT). This enables a complete change analysis of any two versions of WHODrug, including a comparison of the B2-format with the same or a later B3-format release. CAT generates an output file in Excel format in which all modifications and deletes between the selected versions are displayed (see example in Appendix 1).

In addition, CAT generates a text file containing the corresponding B2 and B3 Drug Codes for WHODrug versions from 2015 and onwards.

B2 Drugcode	B3 Drugcode
08994001002	12712102002
01676501003	01676501003
00110501209	00110501209
06278401004	06278401004
08068001002	11358602001
09002701001	12716002001
06383901003	11564202001
09150101002	12767302002
00923101017	12186603009
03445701008	12340303008
07832101002	11590602004
00329601002	13603901001
00707801002	12193802001
07662101002	07662101002
06371201002	13779901001
06926001001	13779001001
00211401002	13294101001
01247701002	13290101001
01247601002	10578902001
00099901002	10817602001
00085501002	00085501002
01101401002	11512502001
06900501002	13225101001
06293601002	13476001001
07742401002	07742401002
00343601111	13453001020
06282701011	13453002007
06282701016	13453002006
06282701020	13453002004
06282701019	13453002005
00700401001	13387601002

Figure 5. Example of the text file containing the corresponding B2 and B3 Drug Codes.

Please contact us at **WHODrug@who-umc.org** if:

- You would like to request a test version of the B2- to B3-format change analysis excel file (see example in Appendix 1)
- You are interested in using the CAT B2- to B3-format change analysis excel or text file for WHODrug versions before 2015

As an alternative to the above described functionality, you can choose to upload your own study list or study data, and the outcome will be a B2- to B3-format change analysis file on your own data.

6.1.2. The C3-format

For upversioning to the C3-format, both the B2 to B3 change analysis excel file and the text file containing the corresponding B2 and B3 Drug Codes can be used to compare a C and C3 version. Please contact WHODrug@who-umc.org if you need further assistance.

6.2. Time plan for upversioning to the B3/C3 formats

The B2-format will exist until the end of 2018 which allows organisations to upversion to either the B2- or the B3-format during a period of two years. We however strongly recommend to upversion to the B3-format rather than B2 during this time period since it will significantly facilitate the implementation of B3 and ensure that the most recent and updated data is used.

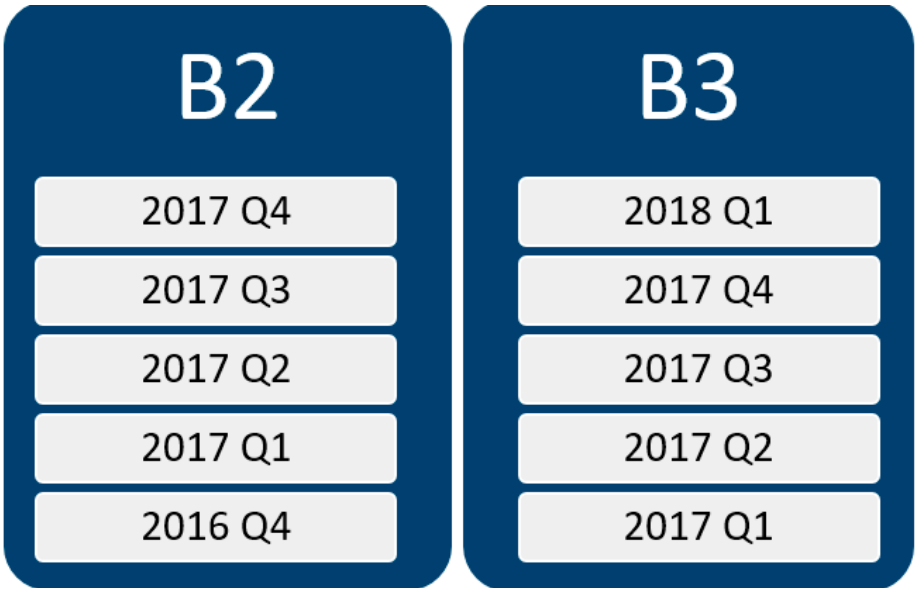

Figure 5. Examples of various upversioning alternatives.

6.3. B3/C3 format test files

A test dataset with a limited number of drug names is available for both the B3 and C3 formats. Previously, there was also an extensive test dataset available, to test-load dictionary files with a realistic B3/C3 format file size. However, since the first release of the WHODrug B3/C3 formats in March, 2017, UMC recommends test loading systems by using any released version (March, 2017 or later) of the B3/C3 format data, for accurate and realistic test results.

Note that you may request access to the March, 2017 release of the B3/C3 format files for testing purposes, even though this release is not necessarily included within your regular subscription. Please contact **WHODrug@who-umc.org** for access.

6.4. Viewing B3/C3 in WHODrug Insight

Both B2/C and B3/C3 formats are displayed in WHODrug Insight from March 2017. By choosing your preferred version and format you can easily browse the different formats and compare records.

6.5. UMC consultancy

UMC offers to update company specific synonym lists to be compliant with the automated Drug Code changes in the B3/C3 formats. Ordinary changes related to ATC alterations and similar will not be handled by UMC unless separately agreed to. The UMC assistance gives best effect if done prior to B3 or C3 upversion. If the synonym list is updated before the B3/C3-format is implemented, the number of manual changes are substantially reduced. Please contact **WHODrug@who-umc.org** for more information.

7. Regulatory expectations and UMC recommendations

In October 2017, the U.S. Food and Drug Administration (FDA) published a notice in the Federal Register, in which they state that the use of the B3-format of WHODrug Global is supported and will be required in submissions for studies starting after March 15, 2019. Furthermore, the U.S. FDA Data Standards Catalog has also been updated with this information.

C3-format users can also comply with the above mentioned FDA requirement, as the WHODrug data required for study data submissions can be retrieved from the C3-format, just as from the B3-format. For details, please see table 7 below and our document 'How to use WHODrug for compliance with CM domain in the CDISC SDTM standard'.

Table 7. A generic example of how the same information can be retrieved from the B3/C3 formats, for study data submissions, thus making it possible for both B3- and C3-users to be compliant with regulatory expectations.

SDTM variable	Populate with	Applicable for	
		B3-format	C3-format
CMDECOD (and possible connected variables in the supplemental dataset)	Corresponding Preferred Name (Seq2=001)	√	√
CMCLAS and CMCLASCD (and possible connected variables in the supplemental dataset)	Option 1: ATC texts and codes of the corresponding Preferred Name *alternatively* Option 2: ATC texts and codes of the coded drug name itself	√	√*

** To comply with nonbinding recommendations from the U.S. FDA related to ATC code/text submissions (read more in the latest version of the Study Data Technical Conformance Guide), UMC recommends retrieving ATC code/text information from the Preferred Name (Option 1), if using the C3-format.*

As a general recommendation from UMC, companies planning to submit study data (to the U.S. FDA or other regulatory agencies) are recommended to make use the B3/C3 formats as soon as possible, to meet regulatory SDTM expectations and benefit from the improvements of the new formats.

Companies using systems not compatible with a field length of 1500 characters are recommended to truncate the text files and display the truncated names in their systems. When generating the SDTM dataset, the truncated names should be replaced with the complete, non-truncated Preferred Names in the original text files. Please note that truncation may result in non-unique names and users of a system displaying truncated drug names need to be aware of this.

When using the WHODrug data in software, databases and tables and listings, make sure to use a trimming function or similar to avoid the usage of unnecessary white space.

8. Definition of terms

Table 8. Definition of WHODrug terms and concepts.

Term	Description
Dictionary format	WHODrug is distributed to all users in two core formats – the B-format and the C-format and the user decides which format to use. The differences between the formats are described below and are applicable for both B2 and C, as well as B3 and C3. The B-formats contains information about trade names, ingredients and ATC classification(s). The unique key is the alphanumeric Drug Code. The C-formats contains all the B-format information (including the Drug Code) but has in addition information regarding the countries in which the product is marketed, Marketing Authorisation Holders, pharmaceutical forms and strengths. The unique key is the alphanumeric Medicinal Product ID.
Preferred Name	A record with a Drug Code that ends with 001. It can either be a Preferred Base Name (Drug Code ends with 01 001), or a Preferred Salt Name (Drug Code ends with 0# 001 where # represents a number higher than 1).
Generic Name	A record with a name representing one or more active substances.

9. Contact details

For questions and concerns please contact: WHODrug@who-umc.org
The UMC team will do everything we can to help when organisations upgrade to the B3/C3 formats.

10. Summary

Table 9. A summary of the differences between the B2- and B3-formats.

	B2-format	B3-format
Field length 'drug name'	45	1500
Field length 'ATC text'	50	110
Non-unique trade names	Separated by adding /Drug Code/	Separated by adding [ingredient(s)]
Preferred multi-ingredient names	Most often a trade name	Always a Generic Name

Table 10. A summary of the differences between the C- and C3-formats.

	C-format	C3-format
Field length 'drug name'	80	1500
Preferred multi-ingredient names	Most often a trade name	Always a Generic Name

Appendix 1

Trade name B2	Trade name B3	Drug code B2	Drug code B3	ATC code(s) B2
2,6-DIBROMOPHENOL-4-SULFONATE SODIUM W/BROMCH	2,6-DIBROMOPHENOL-4-SULFONATE SODIUM;BROMCHLOROPHENE;PROPANOL	01112001002	11940602001	D08AE, PHENOL AND DERIVATIVES
20/20 ACONDICIONADOR	20/20 ACONDICIONADOR	06841401001	10915902002	S01AX, OTHER ANTIINFECTIVES
20/20 ARTFICL TEAR	20/20 ARTFICL TEAR	02338001001	11717302002	S01XA, OTHER OPHTHALMOLOGICALS
20/20 REWETTING	20/20 REWETTING	02338001002	11717302003	S01XA, OTHER OPHTHALMOLOGICALS
222 /00200501/	222 [ACETYLSALICYLIC ACID;CAFFEINE CITRATE;CODEINE PHOSPHATE]	00200501007	12818603003	N02AA, NATURAL OPIUM ALKALOIDS N02BA, SALICYLIC ACID AND DERIVATIVES
222 /00223601/	222 [ACETYLSALICYLIC ACID;CAFFEINE;CODEINE PHOSPHATE]	00223601016	12818602006	N02AA, NATURAL OPIUM ALKALOIDS N02BA, SALICYLIC ACID AND DERIVATIVES
246	246	00212501459	00212501459	A01AB, ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREA D01AC, IMIDAZOLE AND TRIAZOLE DERIVATIVES G01AF, IMIDAZOLE DERIVATIVES P01AB, NITROIMIDAZOLE DERIVATIVES S01AX, OTHER ANTIINFECTIVES S02AA, ANTIINFECTIVES
25 BILLION GOOD BACTERIA	25 BILLION GOOD BACTERIA	07319701004	13068201005	A07FA, ANTIDIARRHEAL MICROORGANISMS
282	282	00223601011	12818602007	N02AA, NATURAL OPIUM ALKALOIDS N02BA, SALICYLIC ACID AND DERIVATIVES
282 MEP	282 MEP	00448201001	11904902002	N02AA, NATURAL OPIUM ALKALOIDS N02BA, SALICYLIC ACID AND DERIVATIVES

An example of B2- to B3-format change analysis excel file generated in WHODrug CAT. Preferred Name, Preferred base, Ingredient(s) and Old form changes B2 to B3 are displayed in the generated file in addition to the columns seen above.

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Uppsala Monitoring Centre advances the science of pharmacovigilance and inspires patient safety initiatives all over the world. As an independent, non-profit foundation, we engage stakeholders who share our vision and collaborate to build a global patient safety culture. As a leader in the research and development of new scientific methods, we explore the benefits and risks of medicines to help minimise harm to patients, and offer products and services used by health authorities and life-science companies worldwide. Our unique expertise makes us an organisation with the capacity to transform patient safety from an ambition into a reality. For almost 40 years, we have provided scientific leadership and operational support to the WHO Programme for International Drug Monitoring, expanding the global pharmacovigilance network to reach more than 95% of the world's population (www.who-umc.org).

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