White Paper Recommendations for Pooled Submissions with WHODrug B3 Format Data

Final Version 1.0

A White Paper by the PhUSE Optimizing the Use of Data Standards Working Group, Pooling WHODrug B3 Format Project Team

Table of Contents

Disclaimer

The opinions expressed in this document are those of the authors and do not necessarily represent the opinions of PhUSE, members' respective companies or organizations, or regulatory authorities. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities. Application of any recommendations provided in this document should be discussed with the relevant health authority(ies).

Notice of Current Edition

This edition of the *White Paper Recommendations for Pooled Submissions with WHODrug B3 Format Data* is the current edition, which supersedes and rescinds all previous editions of the *White Paper Recommendations for Pooled Submissions with WHODrug B3 Format Data*.

Additions and/or Revisions

Date	Author	Version	Changes
20180620	Pooling WHODrug B3 Format Project Team	v1.0	Final Version
		v1.1	
		v1.2	
		v1.3	
		v1.4	
		v1.5	
		v1.6	
		v1.7	
		v1.8	
		v1.9	
		v2.0	

Overview: Purpose

Integrated summary submission documents often include data from multiple studies collected over many years. With the new FDA requirement to use the current WHODrug Global B3 Format Annual version for coding of studies starting after March 15, 2019, it is likely that future pooled summaries will include data from studies coded in WHODrug Global B3 Format, and data from earlier studies coded in previous versions, formats, or proprietary medication coding dictionaries (e.g. WHODrug B2 Format).

This document is intended to provide best practice recommendations for creating an integrated database with medication data coded using different coding dictionary formats (WHODrug Global B3 Format and whatever format or dictionary was used previously for coding classification).

Scope

This document provides best practice recommendations for creating an integrated database with medication data coded using different coding dictionary formats (WHODrug Global B3 Format and whatever format or dictionary was used previously for coding classification). Criteria to consider when determining the appropriate pooling strategy for WHODrug data within integrated submission documents is also discussed.

Interpretation of current regulatory guidance documentation, recommendations for standard Analyses and Displays associated with Medications, SDTM data variables and models, and ADaM data variables and models are outside the scope of this document.

Definitions

Term	Definition
ATC	Anatomical Therapeutic Chemical classification
B2 Format	An older format of WHODrug, slated for cessation of UMC support in March 2019. Does not display active generic components for combination products or non-unique drug names.
B3 Format	A new format of WHODrug. Displays active generic components for combination products and non-unique drug names.
CAT	Change Analysis Tool developed by the Uppsala Monitoring Centre
Coding	Clinical classification of verbatim reported terms to a defined terminology structure (e.g. MedDRA, WHODrug) in order to support medically meaningful groupings of reported terms for accurate evaluation and analysis of clinical and safety data.

Coding Dictionary	A set of terms and relations defined to support coding and analysis of adverse events, medications and diseases, etc. E.g. MedDRA, WHODrug
CSR	Clinical Study Report
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
ICSR	Individual Case Safety Report
ISS	Integrated Summary of Safety
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
PhUSE	Pharmaceuticals User Software Exchange
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
SCS	Summary of Clinical Safety
SDTM	Study Data Tabulation Model
UMC	Uppsala Monitoring Centre
Verbatim Term	Raw verbatim term as entered by the reporter or investigational site
WHO	World Health Organization
WHODrug Global	Medicinal Product Dictionary maintained by the Uppsala Monitoring Centre. In addition to conventional medicinal products, WHODrug Global includes herbal remedies and traditional Chinese medicines.

Problem Statement

Pooling of data that has been coded using different coding dictionaries within a single integrated summary table display can be challenging. Coding dictionaries may use different terminology standards for preferred grouping categories, and integrating this information could result in similar verbatim term concepts being grouped inconsistently or across multiple categories. The risk of inconsistency may or may not be acceptable, depending on the type of analysis being conducted and whether the included data variables are deemed critical for safety or efficacy analysis.

Standard medication analyses and displays included in integrated submissions are typically provided so that reviewers can get a general understanding of the types of medications being taken by the population under study and to identify if there are any imbalances across subjects. Concomitant medication data is rarely categorized as a critical variable for safety or efficacy analysis. For this type of general medication analysis, overall summary display based on the original coding dictionary(ies)

may be sufficient and re-coding to the most current WHODrug Global B3 Format Annual Version may not be warranted. However, when a special topic medication analysis is required to better elucidate a drug-drug or drug-event interaction, or medication category of interest, the risk of inconsistent classification across pooled data coded using different medication coding dictionaries may be less acceptable.

In the absence of clear regulatory guidance, sponsors will need to collaborate with the health authority reviewer to determine the most appropriate medication pooling strategy for the integrated submission. Factors such as the types of analyses being conducted, whether the included data variables are deemed critical for safety or efficacy analysis, and whether the significant effort required to recode the medication data to the current WHODrug Global B3 Format annual version better supports or improves the analysis should all be considered.

Background

The WHODrug dictionary was originally developed to support global pharmacovigilance by the WHO Programme for International Drug Monitoring in 1968, following the Thalidomide disaster. The medication terminology is currently maintained by the Uppsala Monitoring Centre (UMC) as a commercial service. The UMC releases new versions of WHODrug Global B3 Format bi-annually (March and September). WHODrug contains information about medicinal products and active substances intended for human and medicinal use. More information is available on the UMC website.

The FDA published updates to three documents in October 2017, providing additional information regarding their requirement to use the most current WHODrug Global B3 Format Annual Version for coding of concomitant medications in submissions for studies that start after March 15, 2019.

- Federal Register
- FDA Data Standards Catalog
- Study Data Technical Conformance Guide

The FDA Federal Register states that, “Generally, the studies included in a submission are conducted over many years and may have used different WHODG versions to code concomitant medications. The expectation is that sponsors and applicants will use the most current B3-format annual version of WHODG at the time of study start. However, there is no requirement to recode earlier studies.” Section 6.4.2.1 of the Study Data Technical Conformance Guide provides a “nonbinding recommendation” that, “Concomitant medications in the ISS should be coded in the same version of WHODrug Global.” Sponsors should collaborate with the health authority(ies) to determine the best strategy for WHODrug data pooling to support the submission.

The PMDA has also published information regarding a requirement to use WHODrug in electronic clinical trial submissions. WHODrug is not currently required by the EMA, MHRA, or for pharmacovigilance ICSR reporting.

Considerations

Sponsors may consider several options for pooling WHODrug Global B3 Format data within integrated summary documents.

Option 1:

Medication data for studies coded in WHODrug B2 Format (or other proprietary dictionary) and studies coded in WHODrug Global B3 Format are summarized separately. This approach may be acceptable when no specific medication analysis is required, and the standard concomitant medication table is simply appended to the submission. This approach is consistent with the FDA Federal Register recommendation, but would require discussion with the health authority reviewer.

Option 2:

Aggregate medication table contains mixed data summarized by generic term (generic terms would be a mix of WHODrug B2 Format, or other proprietary dictionary, and WHODrug Global B3 Format). This approach may be acceptable when no specific medication analysis is done for the study, and the standard concomitant medication table is simply appended to the submission. With this approach, a single pooled table can be created. However, a generic for the same product may be listed twice in the output table (e.g. Preferred Name generic and/or ingredients differ between WHODrug B2 and B3 formats for combination products). This approach would require discussion with the health authority reviewer.

Example: Unique Verbatim Term can be linked to more than one generic entry

Dictionary	*Verbatim Term (CMTRT)*	*Preferred Name (CMDECOD)*	*Ingredient(s) (CMDECOD if using Ingredients_LongText table translation)*
WHODrug B2 Format	ALEXIA D	ALLEGRA-D /01367401/	FEXOFENADINE HYDROCHLORIDE;PSEUDOEPHEDRINE HYDROCHLORIDE
WHODrug B3 Format	ALEXIA D	FEXOFENADINE HYDROCHLORIDE;PSEUDOEPHEDRINE SULFATE	FEXOFENADINE HYDROCHLORIDE;PSEUDOEPHEDRINE SULFATE

Option 3:

Studies coded in WHODrug B2 Format (or other proprietary dictionary) are recoded in WHODrug Global B3 Format by creating a terminology bridge between the older terminology and WHODrug Global B3 Format. Depending on the structure of the older terminology, the bridge could be created from the synonym, trade, or preferred generic level in the older terminology to one of the levels of WHODrug Global B3 Format. Direct matches between the older terminology and WHODrug Global B3 Format could be identified programmatically, however, non-matches would require manual classification in order to create the terminology bridge. For example, terms from the generic level in the older terminology could be coded to the appropriate preferred name generic in WHODrug Global B3 Format. The Generic-to-Generic bridge could be used to support creation of a single pooled table in WHODrug Global B3 Format. This approach requires sponsor clinical coding resources to create the appropriate classifications across the terminology bridge and would be reserved for submissions where specific medication analyses are included or where WHODrug Global B3 Format is required by the health authority reviewer.

Example: Unique Verbatim Term manually linked to one generic entry based on coding bridge		
Verbatim Term (CMTRT)	*Old Proprietary Dictionary Generic (CMDECOD)*	*New WHODrug B3 Format Generic (CMDECOD)*
CALCIUM/VITAMIN D	CALCIUM NOS/VITAMIN D NOS	CALCIUM;VITAMIN D
ASPIRIN E.C.	ASPIRIN	ACETYLSALICYLIC ACID

Option 4:

For studies coded in WHODrug B2 Format, B2 drug codes are submitted to the UMC CAT (Change Analysis Tool). UMC CAT suggestions are used to up-version the WHODrug B2 Format data to WHODrug Global B3 Format. UMC suggestions for deleted terms may require review and modification. This approach would be reserved for submissions where specific medication analyses are included or where WHODrug Global B3 Format is required by the health authority reviewer.

Example: Unique Verbatim Term linked to one generic entry based on CAT replacement suggestion			
Verbatim Term (CMTRT)	*Old WHODrug B2 Format Preferred Name (CMDECOD)*	*Old WHODrug B2 Format Ingredient(s) (CMDECOD if using Ingredients_LongText table translation)*	*New WHODrug B3 Format Preferred Name Generic (CMDECOD)*
GYNOPAC	FASIGYN VT	TINIDAZOLE;TIOCONAZOLE	SECNIDAZOLE;TINIDAZOLE;TIOCONAZOLE
DOANS	DOANS /00897201/	ALTEPLASE;CAFFEINE;MAGNESIUM SALICYLATE	CAFFEINE;MAGNESIUM SALICYLATE
MEMOPLUS	CAFFEINE W/CYANOCOBALAMIN/GINKGO BILOBA/MAGNE	CAFFEINE;CYANOCOBALAMIN;GINKGO BILOBA;MAGNESIUM;PHOSPHATIDYL CHOLINE	CAFFEINE;GINKGO BILOBA;MAGNESIUM;PHOSPHATIDYL CHOLINE;PYRIDOXINE HYDROCHLORIDE

Option 5:

Studies coded in WHODrug B2 Format (or other proprietary dictionary) are recoded in WHODrug Global B3 Format, starting from the original verbatim medication term. This approach may require significant sponsor clinical coding resources and would be reserved for submissions where specific medication analyses are included or where WHODrug Global B3 Format is required by the health authority reviewer.

Additional Considerations:

In addition to the various options for pooling WHODrug Global B3 Format data with older medication terminology data, there are other considerations that could influence the sponsor pooling strategy.

Sponsors need to determine which variables from the medication dictionary to include within the medication table display. The SDTM standard for the concomitant medication (CM) domain includes the CMDECOD field for the generic ingredient(s) specified within the WHODrug preferred name variable and the CMCLAS and CMCLASCD fields for WHODrug ATC Class information. However, there are other variables that may be relevant for special topic medication analyses, including WHODrug Trade Name, alternate ATC Class hierarchy levels, Standardized Drug Groupings (SDGs), and sponsor-defined custom drug grouping categories. The variables required to support the specific medication analysis may need to be considered when determining the WHODrug pooling strategy.

Recommendations for standard medication table display are outside the scope of this white paper.

Sponsors should refer the guidance provided by the PhUSE Computational Science Standard Analyses and Code Sharing Working Group white paper on *Analyses and Displays Associated with Demographics, Disposition, and Medications in Phase 2-4 Clinical Trials and Integrated Summary Documents*. The preferred medication table display in the 2018 revision does not include the ATC Class variable.

Within WHODrug Global B3 Format, each preferred generic entry may have one or more associated ATC Classes. If the sponsor includes drug class information within the pooled medication display, they may need to consider the drug class selection strategy across included sub-studies. WHODrug B2 Format and proprietary dictionary drug class categories may differ from those in WHODrug Global B3 Format (e.g. a multi-ingredient trade name in B3 format may have more associated ATC Classes than the same trade name in B2 format) and if ATC Class is required for the analysis, this may need to be considered when determining the WHODrug pooling strategy. The FDA Study Data Technical Conformance Guide recommends that the CMCLAS be populated with the primary ATC Class per intended use. However, selection of primary class may be of minimal value to support special topic medication analyses. All ATC Classes associated with a generic are potentially relevant for top-down analysis and it is unlikely that records under a given ATC Class would be excluded from a special topic analysis based on the intended use selection. Variables that capture intended use information such as medication indication or route may not be collected within a study or available for primary ATC selection and the quality of the data collected in these fields may also be insufficient for primary ATC assessment. Given the significant clinical resource effort required to support primary ATC Class selection and impact on subsequent up-versioning, careful consideration should be given to determine whether ATC Class information is truly required to support the planned analysis and if additional selection of a primary class adds any value to this analysis.

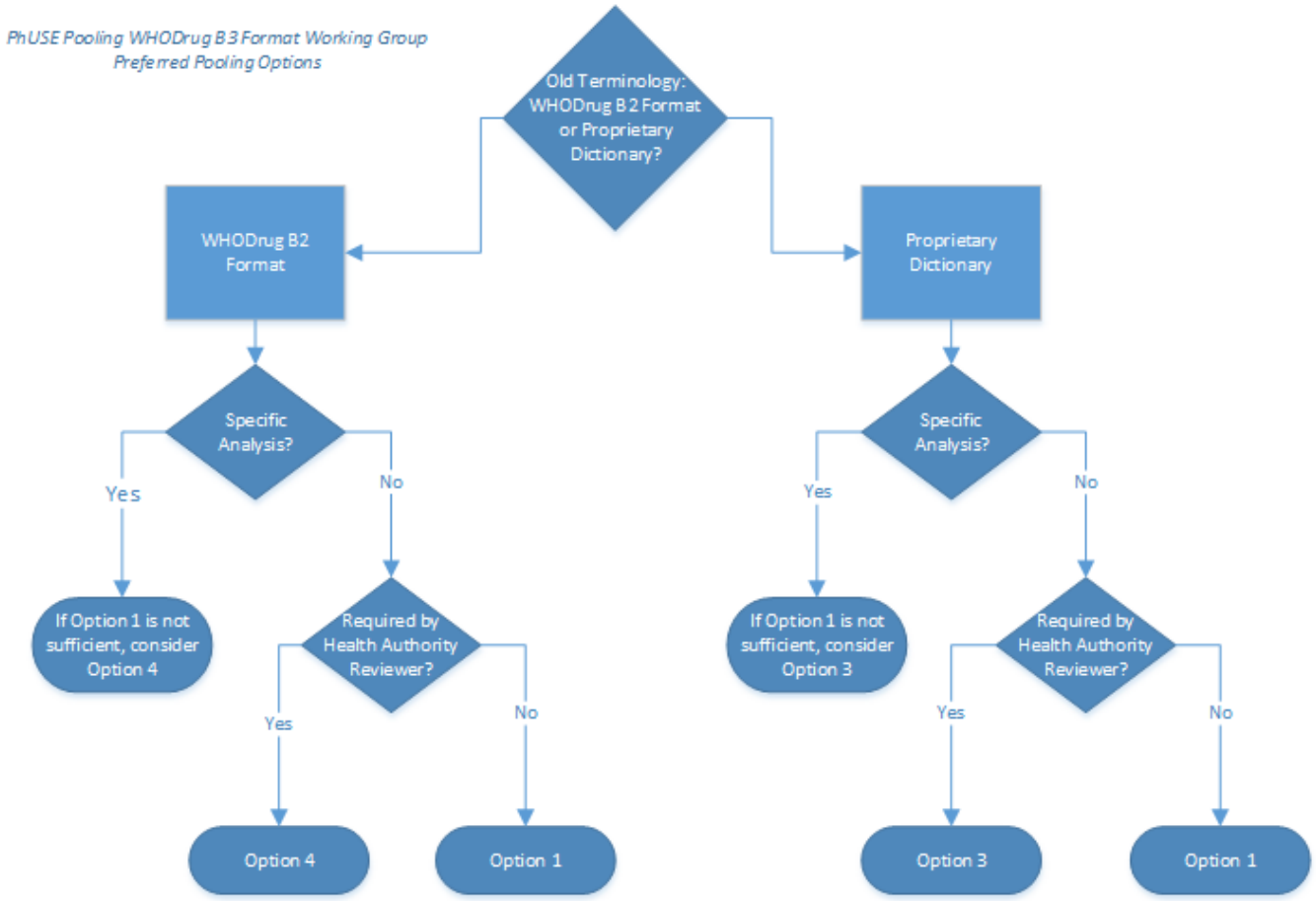
The UMC releases WHODrug Global B3 Format versions bi-annually in March and September. Even if all studies included in an integrated submission were coded using WHODrug Global B3 Format, it is possible that they were coded using different dictionary versions. Integrating this information within a single table could result in similar verbatim term concepts being grouped inconsistently. Again, these version-related inconsistencies may or may not be acceptable, depending on the type of analysis being conducted and whether the included data variables are deemed critical for safety or efficacy analysis. Dictionary versions may need to be considered when determining the WHODrug pooling strategy.

Recommendation

The strategy for Pooling WHODrug Global B3 Format should be determined by the sponsor in collaboration with the health authority reviewer. The preferred pooling approach may be different depending on whether WHODrug B2/C Format was used for earlier studies, or whether a proprietary

medication dictionary was used. The approach may also differ depending on whether specific medication analyses are being conducted within the submission, and depending on which variables are included in the summary table.

The decision chart below outlines the PhUSE Pooling WHODrug B3 Format project team preferred options for WHODrug summary in integrated submissions.



While the PhUSE Pooling WHODrug B3 Format preferred options may be sufficient for general medication data summary, sponsors should work with the health authority reviewer to determine the strategy that best supports the specific analysis plan for the submission.

Project Contact Information

Marlo Searcy, RPh
Genentech (a member of the Roche group)
South San Francisco, CA 94080
650-452-9088
searcy.marlo@gene.com

Joyce Leflar
Janssen Pharmaceutical Companies of Johnson & Johnson
Malvern, PA 19355
610-651-7262
JLeflar@its.jnj.com