INTERNATIONAL RXNORM EXTENSION

to support the expansion of the OHDSI research network beyond the US

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCE AND INFORMATICS

1 Background

The OHDSI network research started as a scientific collaborative out of Columbia University in New York, USA. However, international participation would greatly benefit this network for a number of reasons: First, it is our belief that clinical research is inherently global, as the similarities between populations in different parts of the world by far outweigh the differences. Secondly, the solution of many clinical research problems requires well sized samples in order to develop statistics of effects that might be weak, biased or happen in the shadow of a strong background. And finally, a network that spans different social and healthcare systems allows avoiding bias and understanding the effects introduced by those healthcare systems and distinguishing them from the biological effects on the outcomes of treatment interventions.

Such an expansion to international participants creates the needs to get the data into the OMOP Common Data Model. Part of it is the ability to define the semantic content of the data through the OMOP Standardized Vocabularies, which is commonly but somewhat imprecisely referred to as "Mapping". This Mapping consists of:

1. Mapping of local coding scheme to a set of Standard Concepts, or
2. Creating new Standard Concepts and incorporating them into the existing hierarchy.

Nicotine Chewing Gum [Nicorette]	RxNorm	France, Germany, UK
Nicotine Oral Lozenge [Nicorette]	RxNorm	France, Germany, UK
Nicotine Cartrige Gum [Nicorette]		Germany
Nicotine Dry Powder Inhaler [Nicorette]		France
Nicotine Inhalant Solution [Nicorette]		UK
Nicotine Metered Dose Inhaler [Nicorette]		Germany
Nicotine Nasal Spray [Nicorette]		Germany, UK
Nicotine Oral Solution [Nicorette]		Germany
Nicotine Oral Spray [Nicorette]		France, Germany
Nicotine Sublingual Tablet [Nicorette]		France, Germany, UK
Nicotine Topical Solution [Nicorette]		Germany
Nicotine Transdermal System [Nicorette]		France, Germany, UK

Figure 1. "Nicorette" Dose Form variety over different drug markets

The amount and nature of the effort required for such an effort is very different for the different Domains. Conditions are inherently "international", as people generally have the same diseases, and there is are international initiatives to define them: ICD10 and their modifications (ICD10CM for US, ICD10GM for Germany) and SNOMED-CT. However, the Drug Domain captures Concepts describing the exposure of patients to drug products available on local markets, the knowledge of the content of these products, and their participation in classification systems. These local markets are governed by the authorities of the countries (even though there is some harmonization efforts going on), and as a result there are common products all over the world, but drugs distinct to a subset or a single market.

In the US, there are several organizations providing a comprehensive system of drugs sold in the country. Some of them are commercial vendors to EMR systems, such as First Databank, GPI or Multum. However, a very well curated system is also available for free by the National Library of Medicine, called RxNorm. It consists of:

1. Unique Concepts for each drug, with a Concept identifier (RxCui), defining it unambiguously through a set of attributes:
   a. Its Ingredients
   b. The strengths of the ingredients
   c. The Dose Form
   d. The Brand Name (if there is one)
   e. The total volume or quantity.

Each of these components is also represented as a Concept, and so are combinations of attributes that don't represent full products, but semantic notions of exposure to patients, such as Clinical Drug Components (Ingredients and strength, but without a specified Dose Form or Brand Name). The latter proved very useful when dealing with partial clinical data.

2. A standardized naming convention for all Concepts.
3. A set of relationships between these Concepts. This set creates a graph, which connects Concepts of higher specificity to those of lower specificity, making hierarchical querying of data very elegant and reliable.

Such a system is not available internationally, preventing researchers with clinical data containing drugs to participate in the OHDSI research network. We therefore created RxNorm Extension, which contains drugs available on international markets in the RxNorm System: With Concepts constructed by the same principles and attributes, connected through the graph.

2 Solution: Make RxNorm for the World

We created a system that can add any international systematic drug terminology to the existing RxNorm implementation in the Standardized Vocabularies. Note that this implementation differs in its format from the original provided by the NLM, but leaving its content or logic almost entirely intact.

- ✓ Active Ingredients not approved for marketing in the US are added
- ✓ Dose Forms not used in the US are added, which is not common
- ✓ Brand Names not used in the US are added.
- ✓ Additional attributes are added that are necessary to project foreign drug markets:
  - Box Size: Prescription drugs are mostly pre-packed to standardized products, similar to the situation in the US
  - Over-the-Counter market. Therefore, it is necessary to capture this attribute in the RxNorm Extension, as prescription o orders generally don't contain a variable of drug amount.
- ✓ Supplier: RxNorm does not normalize Suppliers, even though that the NDC system does. In international markets, this attribute is also essential since coding systems explicitly state the supplier.
- ✓ All relationships between Concepts, which cross between RxNorm and RxNorm extension depending on whether or not attributes exist in RxNorm or not.
- ✓ Relationship to classification systems such as ATC.

All together, a new vocabulary "RxNorm Extension" is created containing all the additions as specified above. **The RxNorm and RxNorm Extension vocabularies together form a comprehensive Drug Domain able to codify the local drug market of any country and therefore the patient data containing the drug exposure in these markets.**

3 RxNorm Extension development and building

1. **First, we consider any drug concept as a set of Attributes, for example:**

30 ML Risperidone 1 MG/ML Oral Solution [Risperdal] Box of 1 by Janssen

Attribute	Ingredient	Drug strength	Dose form	Brand name	Quantity factor	Box size	Supplier
Concept_class_id							
Ingredient	Risperidone						
Clinical Drug Component	Risperidone	1 MG/ML					
Clinical Drug	Risperidone	1 MG/ML	Oral Solution				
Branded Drug	Risperidone	1 MG/ML	Oral Solution	Risperdal			
Quantified Branded Drug	Risperidone	1 MG/ML	Oral Solution	Risperdal	30 ML		
Quant Pack Branded Box	Risperidone	1 MG/ML	Oral Solution	Risperdal	30 ML	Box of 1	
Marketed Product	Risperidone	1 MG/ML	Oral Solution	Risperdal	30 ML	Box of 1	Janssen

Figure 2. Attributes and Drug Concept Classes corresponding to Attributes combinations

2. **Map attributes** to corresponding ones in RxNorm. If more than one may correspond, use precedence which represents the degree of similarity to RxNorm one.

Source attributes		Target attributes	precedence
Risperidone	→	Risperidone	1
1 mg/ml	→	1 MG/ML	
solution buvable	→	Oral Solution	1
	→	Oral Suspension	2
RISPERDAL	→	Risperdal	1
30 ML	→	30 ML	
1 vial	→	Box of 1	
Janssen-Cilag	→	Janssen	1

Figure 3. Attributes mappings

3. **Match:** Compare drugs to existing vocabulary set (RxNorm and RxNorm Extension) by matching attributes:
   Ingredients by precedence
   Dose Form by precedence (in a current example „Solution buvable" might be "Oral Solution"(1) or "Oral Suspension"(2)
   Dosage by 90% corridor
   Brand Name by precedence
   Suppliers by precedence
4. **Build:** For all those without mapping: Create RxNorm Extension
5. **Assemble:** Build combined RxNorm-RxNorm Extension hierarchy with creation of all hierarchical logical entities, such as Clinical Drug Form, Clinical Drug Comp, Branded Drug Form, etc.

In a current case we build a new RxNorm Extension concept (30 ML Risperidone 1 MG/ML Oral Solution [Risperdal] Box of 1 by Janssen), while the hierarchicaly-closest RxNorm concept is Branded Drug Risperidone 1 MG/ML Oral Solution [Risperdal]"

4 Hierarchy and structure

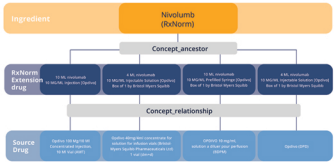

Figure 4. Simplified Drug domain hierarchy

For example, to find all patients using products containing Nivolumab, the hierarchy (concept_ancestor) table cabe be utilized to retrieve all the RxNorm or RxNorm Extension drugs containing Nivolumab (fig 4). If the original country-specific source codes are needed for quality checks, they can be found using the 'Maps to' / 'Mapped from' relationships in the concept_relationship table. This approach performs at a much more reliable retrieval rate than the conventional keyword search for Brand Names or (non-standardized) Ingredient names in the description fields of the source code reference tables (Defalco FJ, Ryan PB, Soledad Cepeda M. Health Serv Outcomes Res Methodol. 2013 Mar;13(1):58-67)

5 Results

Source Vocabulary	Country	Number of Drugs
AMT: Australian Medicines Terminology (NEHTA)	Australia	76 512
BDPM: Public Database of Medications (Social-Sante)	France	20 181
Dm+d: Dictionary of Medicines and Devices (NHS)	UK	291 589
DPD: Drug Product Database (Health Canada)	Canada	36 693
GRR: Global Reference Repository	Germany	347 736

Figure 5. Counts of drugs in national drug markets

Figure 6. Non-US markets attribute expansion

Current RxNorm Extension Source Vocabularies Summary

RxNorm Extension already consists from drug markets of Canada (DPD), UK (dm+d), France (BDPM), Germany (AMIS and GRR), Australia (AMT). Drug markets will be covered in the nearest future: Belgium (BCFI), Japan (JDBC).

RxNorm Extension extends at different degree into the four attributes:

1. Ingredients: There are 1506 new ingredients, but most of them are herbal medicines or homeopathic preparations . In rare cases, non-FDA approved compounds are added, such as: Anecortave Acetate, Cefacetrile, Buformin, etc.

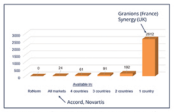

Figure 7. Suppliers in RxNorm Extension, and distribution over country-specific markets

2. Suppliers. Most of Suppliers are country specific, with the large multi-national pharmaceuticals comprising a small portion only.
Also these international companies have marketing agreements with local companies allowing them to sell drugs under the same Brand Name. For example, Brintellix initially was developed by Lundbeck and then distributed in other markets by variety of other pharmaceutical companies, such as Gerke, 2care4, Aca Mueller, Orifarm Leverkus, Eurim-Pharm, Abacus Medicine, Axicorp, Medicopharm.

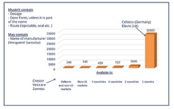

Figure 8. Brand Names in RxNorm and RxNorm extension, and distribution over country-specific markets.

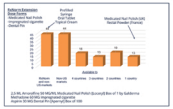

Figure 9. Dose Forms in RxNorm and RxNorm extension, and distribution over country-specific markets.

Figure 10. Single-ingredient and combined drugs distribution over US and non-US markets

3. Brand Names: Most of the 42 thousand new Brand Names are country specific, withi a few worldwide household names like "Crestor", "Vesicare", "Zometa", etc.

4. Drug Forms: RxNorm covers most of the conventional Dose Forms, except some exotic ones such as medicated nail polishes or those that those that are usually categorized as devices, such as intrauterine drug delivery systems.

Ingredients used in different countries are similar, with the above mentioned exception for traditional drugs. But they are sold in a different variations and combinations worldwide.

Non-US, fixed ingredient combinations are much more popular than in the US, where they constitute about half of the drug market.
However, the larger amount of fixed ingredient combination ex-US are used with a smaller variety of attributes (Brand Names, Dosages and Dose Forms)

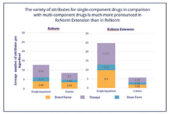

Figure 11. Attributes distribution over Single-ingredient and combined drugs along US and non-US markets.

The examples of the antipsychotic Thioridazine and the corticosteroid Desonide illustrate Brand Name variety while Fruribiprofen case illustrates Dosage and form variety over US and non-US markets:Dose Forms:

Thioridazine		Desonide	
US-market Drugs	Non-US market Drugs	US-market Drugs	Non-US market Drugs
Ridoril	Mellaril	Verdeso	Desocort
Melleril	Sonapax	Tridesilon	LOCATOP
Mellaril-S	Ridoril	Desowen	Stersa
	Pms-Thioridazine	Desonate	Topifug
	Thioridazin-Neuraxpharm	Delonide	Tridesilon Crm
	Melleril	Desoral	TRIDESONT
	Novo-Ridazine	Lokara	LOCAPRED
	Mellerettes		
	Thioridazin Neurax		
	Aldazine		
	Prefilled Applicator		

Figure 12. Single-ingredient and combined drugs distribution over US and non-US markets

Form	US-market Drugs	Non-US market Drugs
Oral Lotion	Fluribiprofen 100 MG Oral Tablet	Flurbiprofen 8.75 MG Oral Tablet
Extended release Oral Tablet /Caplet	Flurbiprofen 50 MG Oral Tablet	
	Flurbiprofen 200 MG Extended Release Oral Capsule	Flurbiprofen 100 MG Delayed Release Oral Tablet
		Flurbiprofen 50 MG Delayed Release Oral Tablet
Ophthalmic Solution	Flurbiprofen sodium 0.3 MG/ML Ophthalmic Solution	Flurbiprofen 0.75 MG/ML Ophthalmic Solution
	Flurbiprofen sodium 1 MG/ML Ophthalmic Solution	Flurbiprofen 0.0003 MG/ML Ophthalmic Solution
	Flurbiprofen sodium 3 MG/ML Ophthalmic Solution	
Rectal Suppository	Flurbiprofen 100 MG Rectal Suppository	
Oral Lozenge	Flurbiprofen 8.75 MG Oral Lozenge	
Topical Solution		Flurbiprofen 16.2 MG/ML Topical Solution
		Flurbiprofen 1 MG/ML Topical Solution
Prefilled Applicator		Flurbiprofen 0.06 MG/ML Prefilled Applicator

Figure 13. Dosage and form variety on an example of Flurbiprofen

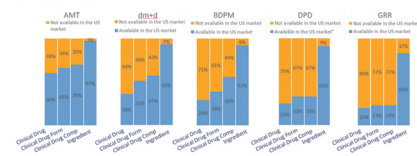

Figure 14. Overlap of Clinical Drug (products), Drug Forms, Drug Components and Ingredients between US and ex-US markets. The vast amount of ingredients are shared between markets, but products can differ substantially

6 Conclusion

- ✓ **RxNorm Extension has 5 drug markets covered: Germany, France, Canada, Australia and UK.**
- ✓ **Significant variety in drug distribution in the world that makes RxNorm Extension vocabulary extremely needed for a worldwide drug markets and corresponding patient data analysis.**

Authors

Dmitry Dymshyts MD,
Anna Ostropolets MD,
Odysseus Dataservices Inc, Cambridge MA USA;
Christian Reich MD PhD,
QuintilesIMS, Cambridge MA USA