Integrating RxNorm with medicinal products in SNOMED CT

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1. Introduction

- RxNorm is a standardized nomenclature for medicinal products

- SNOMED CT, internationally used to record medical data, applied IDMP requirements for medicinal products

- Integration of RxNorm with SNOMED CT:
  - Compliance of RxNorm with international requirements
  - Quality assurance of RxNorm and medical products in SNOMED CT
3. Background: SNOMED CT model for medicinal products 1/4

- Model for generic drugs compliant with IDMP requirements: Closed world view for the description of clinical drugs
- Entities (6):
  - **Medicinal Product (2)**: in open and closed world view
  - **Medicinal product form (2)**: in open and closed world view
  - **Medicinal product precisely (1)**: in closed world view (optional)
  - **Clinical drug (1)**: in closed world view
- Definitional roles and types of values
  - Active ingredient: **Substances**
  - Active moiety: **Substances**
  - Basis of strength: **Substances**
  - Strength units: **Units of measure**
  - Strength values: **Numbers**
  - Unit of presentation: **Units of presentation**
  - Dose forms: **Pharmaceutical dose form**
3. Background: RxNorm model 2/4

- Model for generic, branded drugs and packs
- Restrictions for integration with SNOMED CT
  - Branded drugs and packs are out of scope
  - Only dose forms grouper can be provided by RxNorm
- Four (4) main generic entities:
  - Ingredient (IN, PIN), SCDC, SCDF and SCD
- Definitional features
  - Mandatory: ingredient, DF, strength
  - Optional: Quantity Factor, Qualitative Distinction
3. Background: Comparison of models

- **SNOMED CT definitional features**
  - Substances
  - Pharmaceutical Dose Forms
  - Units of presentation
  - Units of measure
  - Numbers

- **RxNorm definitional features**
  - IN/PIN (Substance)
  - Dose Form (DF)
  - Unit

- **RxNorm entities**
  - Ingredient(IN)/Precise ingredient (PIN)
  - Strength
  - Number

- **SNOMED CT entities**
  - Medicinal product
  - Medicinal product Only
  - Medicinal product form
  - Medicinal product form only
  - Clinical drug
According to IDMP requirements, universal restrictions must be used to describe clinical drugs with a closed world view.

Closure axiom “Only” must be used in conventional way.

SNOMED CT DL is based on $\mathcal{EL}++$: universal restrictions not supported.

A workaround consists in adding a “count of ingredient” axiom to emulate universal restrictions.
3. Materials:

- SNOMED CT
  - OWL format
  - Version: 05/30/2018 (preview)

- RxNorm
  - Rest API
  - Version: 09/04/2018
  - Mappings to SNOMED CT (US edition, March 2018)

- Tooling
  - OWLAPI 3.5.0
  - ELK reasoner 0.4.0
4. Methods: Overview

- Mapping of definitional features
  - Types of definitional features
  - Values

- Translation of entities
  - Template definition (based on definitional features)
  - Instantiation

- Evaluation
  - Classification of instantiated templates (to create inferred RxNorm-SNOMED CT mappings)
  - Comparison with mappings asserted by RxNorm
### 4. Methods: Mapping strategy

<table>
<thead>
<tr>
<th>RxNorm</th>
<th>Target in SNOMED CT</th>
<th>Mapping Strategy</th>
<th>Mapping expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitional features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DF</td>
<td>Units of presentation</td>
<td>Manual mapping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmaceutical Dose Forms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN/PIN</td>
<td>Substances</td>
<td>Look-up of RxNorm mapping + type constraint (substance)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Numbers</td>
<td>Numbers</td>
<td>Creation of number hierarchy in RxNorm with label</td>
<td></td>
</tr>
<tr>
<td>Units</td>
<td>Units of measure</td>
<td>Manual mapping</td>
<td></td>
</tr>
<tr>
<td><strong>Entities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN/PIN</td>
<td>MP/ MPO</td>
<td>(Gold standard mapping)</td>
<td>Mapping relation*</td>
</tr>
<tr>
<td>SCDF</td>
<td>MPF/MPFO</td>
<td>Look-up of RxNorm mapping + type constraint (product)</td>
<td></td>
</tr>
<tr>
<td>SCD</td>
<td>CD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Methods: Translation

- Template definition: **6 templates** for the **6 entities** in MP/MPF/CD model and a
  additional template for the **grouper category** of medicinal product based on Dose Form:

- Instantiation: Logical definitions created using OWLAPI
4. Methods: Evaluation

• Classification of instantiated templates (to create inferred RxNorm-SNOMED CT mappings)
• Comparison with mappings asserted by RxNorm
• Analysis of inconsistencies
## 5. Results: Mappings for definitional features  1/9

<table>
<thead>
<tr>
<th></th>
<th>RxNorm</th>
<th>Mapped</th>
<th>SNOMED CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IN/PIN)-Substances</td>
<td>4,038</td>
<td>2,710</td>
<td>26,728</td>
</tr>
<tr>
<td>Numbers-Numbers</td>
<td>1,924</td>
<td>535</td>
<td>725</td>
</tr>
<tr>
<td>Units-Units of measure</td>
<td>18</td>
<td>10</td>
<td>1236</td>
</tr>
<tr>
<td>Dose Forms-Pharmaceutical dose forms</td>
<td>113</td>
<td>83</td>
<td>307</td>
</tr>
<tr>
<td>Dose Forms- Units of presentation</td>
<td>113</td>
<td>43*</td>
<td>50</td>
</tr>
</tbody>
</table>
### 5. Results: Mappings for entities

<table>
<thead>
<tr>
<th>Corresponding classes in MP/MPF/CD model</th>
<th>SCD</th>
<th>IN/PIN</th>
<th>SCDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP Some</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPF only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-0</td>
<td>15,417</td>
<td>3,378</td>
<td>5,784</td>
</tr>
<tr>
<td>1-1</td>
<td>3,481</td>
<td>2,394</td>
<td>0</td>
</tr>
<tr>
<td>1-N</td>
<td>56</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>18,954</td>
<td>5,784</td>
<td>5,784</td>
</tr>
</tbody>
</table>

Filtering SNOMED CT concepts with multiple mappings:
1-1 mappings for 3479 semantic clinical drugs
5. Results: Instantiation

Rx308135 Amlodipine 10MG Oral Tablet

Equivalent to

Medical Product

Role group

Has_Precise_active_ingredient

Has_Basis_Of_Strength

Has_presentation_strength numerator value: 10

Has_presentation_strength numerator unit: MG

Has_presentation_strength denominator value: 1

Has_presentation_strength denominator unit: 732936001- Tablet

Has manufactured dose form

Rx317541 Oral tablet

Instantiated template for RxNorm SCD

Has unit of presentation

Count of base active ingredient

Has_Basis_Of_Strength

Rx104416 Amlodipine besylate

Rx17767 Amlodipine

732936001- Tablet

Rx317541 Oral tablet

1

732936001- Tablet
5. Results: Instantiation

'Amlopidine 10 MG Oral Tablet' — http://www.nlm.nih.gov/ontology/OntoRxNorm/OntoOnlyRx308135

Annotations: 'Amlopidine 10 MG Oral Tablet'

Annotations

rdfs:label [type: xsd:string]
Amlodipine 10 MG Oral Tablet

Description: 'Amlopidine 10 MG Oral Tablet'

Equivalent To

'Medicinal product (product)'
and ('Has manufactured dose form (attribute) some 'Oral Tablet (Dose Form)')
and ('Role group (attribute) some
  ('Has basis of strength substance (attribute) some 'Amlodipine (substance)')
  and ('Has presentation strength numerator value (attribute) some '10 (qualifier value)')
  and ('Has presentation strength numerator unit (attribute) some 'MG (qualifier value)')
  and ('Has presentation strength denominator value (attribute) some '1 (qualifier value)')
  and ('Has presentation strength denominator unit (attribute) some 'Tablet (unit of presentation)')
  and ('Has precise active ingredient (attribute) some 'Amlodipine Besylate (substance)')
  and ('Has unit of presentation (attribute) some 'Tablet (unit of presentation)')
  and ('Count of base of active ingredient (attribute) some '1 (qualifier value)')
)

SubClass Of

'RXNorm’s semantic clinical drug'
5. Results: Instantiation

IN : Rx177767 - amlodipine

MP

MPO
5. Results: Instantiation

SCDF : Rx370573 – amlodipine oral tablet

DF : Rx317541 oral tablet

Description: ‘Amlodipine Oral Tablet (medicinal product some)’

Equivalent To:

(‘Medicinal product (product)’
and (‘Role group (attribute)’ some (‘Has active ingredient (attribute)’ some ‘Amlodipine (substance)’)))
and (‘Has manufactured dose form (attribute)’ some ‘Oral Tablet (Dose Form)’)

SubClass Of:

‘RXNorm’s semantic clinical dose form as medicinal product in an open world view’

Description: ‘Amlodipine Oral Tablet (medicinal product only)’

Equivalent To:

(‘Medicinal product (product)’
and (‘Role group (attribute)’ some (‘Has active ingredient (attribute)’ some ‘Amlodipine (substance)’)))
and (‘Count of base of active ingredient (attribute)’ some ‘1 (qualifier value)’))
and (‘Has manufactured dose form (attribute)’ some ‘Oral Tablet (Dose Form)’)

SubClass Of:

‘RXNorm’s semantic clinical dose form as medicinal product in a closed world view’

Description: ‘Oral Tablet (medicinal product some)’

Equivalent To:

‘Medicinal product (product)’
and (‘Has manufactured dose form (attribute)’ some ‘Oral Tablet (Dose Form)’)

Grouper

MPF

MPFO
SCD : Rx1795250
1000 ML Glucose 50 MG/ML / SODIUM 4.5 MG/ML injection
5. Results: Evaluation (OSDF only)

- All Ingredients, Precise Ingredients and SCDFs are instantiated
- 1877/18438 SCDs are not instantiated:

<table>
<thead>
<tr>
<th>Clinical drugs</th>
<th>Asserted mappings through RxNorm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inferred mapping (equivalence after classification)</td>
<td>1,889</td>
<td>90</td>
</tr>
<tr>
<td>-</td>
<td>944</td>
<td>15,515</td>
</tr>
<tr>
<td>Total</td>
<td>2833</td>
<td>15,605</td>
</tr>
</tbody>
</table>

* This equivalence correspond to 1876 concepts SNOMED CT. 11 SNOMED CT concepts are mapped to multiple SCD
5. Results: Inconsistencies

- Mappings not found after classification:
  - Difference in units of measure
    - 326309006-Product containing precisely desogestrel 150 microgram and ethinylestradiol 20 microgram/1 each conventional release oral tablet (clinical drug) → 249357-Desogestrel 0.15 MG / Ethinyl Estradiol 0.02 MG Oral Tablet

  - Difference in BoSS or Active ingredient
    - 425766008- Product containing precisely phentermine resin 30 milligram/1 each conventional release oral capsule (clinical drug) → 826910- Phentermine resin 30 MG Oral capsule

  - Errors of mapping in the Gold standard
    - 420402006- Product containing precisely monobasic sodium phosphate 1.5 gram/1 each conventional release oral tablet (clinical drug) → 603011- sodium phosphate 1500 MG Oral Tablet
6. Discussion: Error analysis

- 1,328/4,038 (34%) of RxNorm ingredients, and 11,938/15,417 (77%) of RxNorm clinical drugs have no asserted mappings to SNOMED CT to be added to SNOMED CT
- 30 specific Dose Forms in RxNorm not mapped, and 53 DF are not linked to unit of presentation DF mapping needs to be curated by experts
- Mapping of multiple RxNorm SCDs to the same SNOMED CT CD
  - Due to Qualitative Distinctions in RxNorm
- Inconsistencies in BoSS or Active ingredient between RxNorm and SNOMED CT
- RxNorm-SNOMED CT asserted mapping contains errors
- Difference in Units of measure (microgram vs milligram)
Acknowledgements

• My supervisor: Dr. Bodenreider Olivier

• Dr. Clem McDonald and Dr. Paul Fontelo for the opportunity offered to me

• SNOMED CT Drug Model Working Group: for guidelines and SNOMED CT drug preview

• All the NLM staff