Pattern: Representing Reference Substances, Reference Strength, and the Basis of Strength, including in Different Jurisdictions - APPROVED

Introduction

Medicinal products consist of substances, where each substance has an objective, whether to stimulate pharmacological activity, enhance bioavailability and drug activity or protect and stabilize the medicinal product. An ingredient is a substance as qualified by its role and quantity in the product composition. See Pattern: Representing Ingredients - APPROVED for the top-level ingredient pattern. As can be deduced from the ingredient roles, not all components of a product are responsible for the pharmacological activity. It is the active ingredient of a product that results in the designated pharmacological activity and would thus indicate drug potency. The basis of strength substance(s) (BOSS) refers to the active ingredient(s) in a drug product that is measured to provide the product strength. The strength refers to the quantity or range of quantities of the substance/specified substance present per unitary volume (presentation-based, activity-based, or mass-based). It should be noted that the strength here refers to a nominal value instead of an actual measurement.

For some complex substances (such as a salt), the measurement of strength is additionally based on a substance (referred to as the reference substance) that is not present in the product until transformation. Around 50% of drug products exist as a free acid or base and do not need to be in a salt form to be active in the body. However, other drug products frequently require salt formulations to enhance dissolution or absorption in the body for optimal therapeutic effects. For drug products in their salt form, the basis of strength is measured against a reference substance. The relationships between a pharmaceutical product, the substances or ingredients it is made out of, and their roles and strengths within the pharmaceutical product are shown as a generic model in Diagram 1, on the Patem: Representing Ingredients - APPROVED page.

Some examples of the various products with ingredients and a reference substance/strength, depending on the product, are given below in Table 1. These include:

1. A simple definition of strength of the main ingredient for the Amlodipine and Nexavar
2. Including a reference substance/strength as the basis of strength, depending on the role of the active ingredient
3. Including two reference substances with reference strengths as in the case of the Infanrix Hexa vaccine

Table 1. Examples of Drug Products, their Active Ingredient(s), and Reference Strength/Substance(s) as Applicable

<table>
<thead>
<tr>
<th>Product name</th>
<th>Active ingredient</th>
<th>Ingredient role (ISO 20443 classCode)</th>
<th>Strength</th>
<th>Reference substance</th>
<th>Ingredient role (ISO 20443 classCode)</th>
<th>Reference strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine EMC</td>
<td>Amlodipine mesylate monohydrate</td>
<td>ACTIR</td>
<td>6.41 mg</td>
<td>Amlodipine</td>
<td>ACTIM</td>
<td>5 mg</td>
</tr>
<tr>
<td>Nexavar</td>
<td>Sorafenib Tosylate</td>
<td>ACTIR</td>
<td>275 mg</td>
<td>Sorafenib</td>
<td>ACTIM</td>
<td>200 mg</td>
</tr>
<tr>
<td>Infanrix hexa partial</td>
<td>&quot;Powder Hib&quot; Lactose anhydrous</td>
<td>IACT</td>
<td>20 mg (dummy value)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>component: &quot;Powder Hib&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b polysaccharide, adsorbed on aluminum phosphate, conjugated to tetanus toxoid as carrier protein</td>
<td>ACTI</td>
<td>Not applicable</td>
<td>Haemophilus influenzae type b polysaccharide Tetanus toxoid (carrier protein)</td>
<td>ACTIM</td>
<td>10 µg/0.5 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 µg/0.5 ml</td>
</tr>
</tbody>
</table>

Each of these examples and variations is shown in depth on the pages that describe Specifying Example Datasets and will not be repeated below. On this page, we will highlight the relevant modeling patterns and then point to the pages that cover the examples. We will also show how to incorporate the jurisdictional context – as in the Teripressin example discussed towards the bottom of this page, where the same pharmaceutical product is tied to several medicinal products with different descriptions of the basis of strength depending on the jurisdiction of the relevant marketing authorization.

Related Competency Questions

- What is the basis of strength for <substance x> in <product y>? Here product can be a pharmaceutical product or a manufactured item.

Relation to ISO-IDMP Standards

In Figure 12 from ISO 11238, the relationship between a product and the strength of an ingredient, including a reference strength, is implied. As described in Pattern: Representing Ingredients - APPROVED, there is a connection in the ontology that is more direct with respect to an ingredient and its strength. Whether or not a reference substance/strength is required depends on the jurisdiction, and for the same pharmaceutical product, the representation may vary.
Modeling Patterns

Representing Strength of an Ingredient in a Pharmaceutical Product

Table 1 on Pattern: Representing Ingredients - APPROVED lists the variations in options for active ingredient roles, each of which requires a distinct approach to representing the strength of one or more active ingredients and any reference substance/reference strength depending on the case. The typical pattern for representing the strength of any ingredient, such as an inactive ingredient as in the case of Lactose anhydrous as an ingredient of Infanrix Hexa shown in Table 1, would follow the pattern given in Figure 3 in Pattern: Representing Ingredients - APPROVED. Combining the diagrams in Figures 2 and 3 on Pattern: Representing Ingredients - APPROVED and focusing solely on the pharmaceutical product ingredient strength part of the model yields the pattern shown in Figure 1, below.

Examples of this pattern are included in the Example: Terlipressin - REVIEW and the Qlaira ontology in GitHub.

Augmenting the Representation to include a Reference Substance/Reference Strength

Given a pharmaceutical product with a single active ingredient without differentiation by jurisdiction, we can augment the pattern for all three cases: (1) active moiety as the basis of strength, (2) entire substance as the basis of strength, and (3) reference substance/reference strength as the basis of strength.

Active Moiety as Basis of Strength

The first of these options, active moiety as the basis of strength is relatively straightforward. But, in order to answer competency questions properly, including others from UC-1, the knowledge graph needs to reflect the fact that a given substance (or moiety) is the active moiety for a substance that is the active ingredient in some pharmaceutical product. The pattern for this follows the generic conceptualized roles pattern given in Pattern: Contextualized Roles - APPROVED. Secondly, the knowledge graph also needs to reflect that the ingredient role for the substance in the product composition is the more specific active moiety as the basis of the strength role, rather than the more general version shown in Figure 1. Finally, connections representing the strength of the substance (moiety) that is the active moiety in this case needs to be represented. The resulting pattern is shown in Figure 2, below.
In Figure 1, the class that actually has the relationship via a restriction to strength is the top-level ingredient (role) class. The class that has the relationship, via a restriction, to the reference strength is on the active ingredient class. These restrictions are inherited by the various more specific ingredient roles, and in some cases are optional. In the case shown in Figure 2 above, for an active moiety as the basis of strength, the strength is required, and reference strength is optional. This allows for variations depending on the jurisdiction. Note that although the class used to specify strength is a single class in the figure (which would be implemented as an individual whose type is that of one or more subclasses of strength, such as presentation and mass-based strength), individuals of type strength will be distinct — one for the strength of the ingredient and one for the strength of the active moiety that is the reference strength.

Entire Substance as the Basis of Strength

The second option, the entire substance as the basis of strength is also straightforward and similar to the active moiety case, with less indirection. The pattern for this case is given in Figure 3.

Reference Substance as the Basis of Strength

Note that although the class used to specify strength is a single class (as in the active moiety case), the individuals of type strength may be distinct — one for the strength of the ingredient and one for the reference strength. Note too that in this case there is only a single reference strength.
The pattern for this case looks very much like the case for an entire substance as the basis of strength BUT in this case, the target of the restriction on substance is NOT the same as the target for the reference substance, as shown in Figure 4, below.

Examples of this pattern are included in the Example: Amlodipine - REVIEW.

Figure 4 covers the most basic case, but does not link it to the role that the reference substance (or moiety) is playing, e.g., as an active moiety or entire substance providing the basis of strength, as given for Amlodipine in the example in Table 1. To represent that explicitly, one would need to augment the model as shown in Figure 5, below.

Using this approach would require the application of the pattern for the appropriate role from Pattern: Representing Ingredients - APPROVED, Figure 2 as the target of has reference ingredient role. Note that this goes beyond what is shown in Figure 12, above, but may be useful to provide additional support within a pharma company environment. For example, if it is important to have both the ACTIR and ACTIM roles as given in Table 1, the substance role (which would be active ingredient active moiety basis of strength in the case of Amlodipine EMC and Nexavar) would be signified by the proper code, in this case, ACTIM.

Multiple Reference Substances for the Same Substance

In Table 1, above, Infanrix Hexa is defined as having multiple reference substances in addition to including other substances playing other roles (which is possible with any of the patterns described above).
One could also expand the substance to role parts of the diagram, above to leverage a more complete set of relationships with respect to the substance role, such as in Figure 2, for the active moiety case, above, and, for example, replacing the substance role with the more specific active moiety role including all of the relationships required to support that representation. If the more general role is used and a relationship to the role identifier, such as ACTIM is added to the higher level role, a reasoner would infer that the role is actually an individual of the more specific ACTIM role, however. The use of a reasoning engine to do this dynamically is not recommended over a large data set, however.

Extending Representation of Reference Substances for Multiple Jurisdictional Contexts

The primary challenges with respect to supporting jurisdictional differences in the documentation for a given medicinal product are related to shortcuts taken in the IDMP specifications. The most definitive source for jurisdiction is the authorization for a given product. That product may be a generally authorized medicinal product in some jurisdiction, or it may be authorized for some investigational purpose in a jurisdiction. This makes querying more complicated, but the end result will include the proper provenance and enable proper labeling. The example we have used to test the model is the Terlipressin example, which is documented in Example: Terlipressin - REVIEW. The pattern provided in the ontology to tie all of this together is provided in Figure 7, below.
There are a number of ways to query the graph to get to the reference strength that applies in a jurisdiction, but specifying the details so that the queries work properly is very important. Using this diagram and the Terlipressin example given at Example: Terlipressin - REVIEW, together with the example queries should enable users to create the proper mappings for their target systems of record.

Examples

The reference substance/reference strength/basis of strength patterns described above are used in several examples. These include:

1. Example: Amlodipine - REVIEW
2. Example: Terlipressin - REVIEW
3. Example: Infanrix Hexa - DRAFT
4. Example: Nexavar - DRAFT
5. Example: Ciprofloxacin - DRAFT

See also the presentation provided below (which may be dated).