National Drug File – Reference Terminology (NDF-RT™) Documentation

U.S. Department of Veterans Affairs, Veterans Health Administration

May 2010 Version

Contents

Background

In 2003, the Department of Veterans Affairs Veterans Health Administration (VHA) began construction of an Enterprise Reference Terminology (ERT)[1]. ERT includes a federated set of vocabulary content; a hybrid commercial off-the-shelf (COTS) and custom-developed software and technology infrastructure; and supporting business processes and documentation. Since its inception, VHA ERT assembled one of the largest terminology repositories in the country.

Controlled medical terminology provides many benefits, and chief among them is support for the creation and use of comparable patient descriptions. Such data comparability can help:

- Reduce ambiguity while describing medical situations
- Improve human productivity
- Improve the performance of decision support applications
- Improve compliance with existing or emerging VHA and other federal mandates and standards
- Enable the exchange of healthcare information
    - between departments in the same VHA medical center or care facility
    - between VHA and extra-VHA facilities
    - between applications
- Manage and leverage information in electronic medical records
- Improve the display of patient information
- Make CPOE (Computer-based Provider Order Entry) more productive
- Enable decision support to reduce errors and improve quality
- Support evidence-based medicine

Use of controlled terminology in electronic medical records greatly enhances the ability of both healthcare professionals and computer applications to collect and leverage available healthcare data productively. The VHA ERT is designed to provide terminology and terminology services that support these objectives at national scale. In this context, the notion of a *reference* terminology is a resource focused on scalable, longitudinal terminology reuse by computers, applications, and their human users.

As part of the ERT, the VHA National Drug File – Reference Terminology (NDF-RT™)[1,2] is the reference terminology for medications, an enhancement of the VHA National Drug File (NDF) in a formal description logic ontological representation. Since its beginnings under the auspices of the Government Computer-Based Patient Record (GCPR) project in 2001, NDF-RT™ has evolved into a nationally important drug terminology resource. Its unique description logic-based reference model, accessible intellectual property

[1] Lincoln MJ, Brown SH, et al. U.S. Department of Veterans Affairs Enterprise Reference Terminology Strategic Overview. *Stud Health Technol Inform*. 2004;107(Pt 1):391-5.

[2] Brown SH, Elkin PL, et al. VA National Drug File Reference Terminology: A Cross-institutional Content Coverage Study. *Stud Health Technol Inform*. 2004;107(Pt 1):477-81.

status, and championing by informatics experts both within and outside VHA have resulted in NDF-RT's adoption by a number of government and academic projects, including adoption of the mechanisms of action (MoA), physiologic effects (PE), and chemical ingredient by structure (CI) hierarchy subsets as a Consolidated Health Informatics (CHI) standard used to describe medication pharmacologic class. NDF-RT™ is part of the Federal Medication Terminologies (FMT) initiative and has been cited or studied within numerous academic and industry publications.

The NDF-RT™ Interagency Expert Panel (NDF-RT™ IEP), an on-going collaboration among the Department of Veterans Affairs (VA), Food and Drug Administration (FDA), National Library of Medicine (NLM), National Cancer Institute (NCI), Centers for Medicare and Medicaid Services (CMS), and other federal agencies, advises the VHA on maintenance and improvement of NDF-RT™ content, as needed, for use in the FDA's Structured Product Labeling (SPL) initiative and other FMT-related efforts.

The FDA SPL initiative aims to reduce the future costs of drug terminology maintenance and improve patient care and safety. Concepts from the NDF-RT™ MoA, PE, and CI hierarchies have been selected by FDA to index established pharmacologic classes within the SPL. The NDF-RT™ IEP oversees maintenance and enhancement of these concept hierarchies as well as other content issues, leveraging the expertise of a VHA Subject Matter Expert (VHA SME) team that reviews agency requests and recommends specific NDF-RT™ changes.

NDF-RT™ Content Model

Overview

NDF-RT™ is a concept-oriented *terminology*, a collection of *concepts,* each of which represents a single, unique meaning. Every concept has one fully-specified name and an arbitrary number of other names, all of which are intended to mean the same thing and are therefore synonymous terms. Synonymous terms from external vocabulary sources may have associated unique identifiers. Additionally, NDF-RT™ assigns an alphanumeric unique identifier (NUI) to every concept, maintained across releases to label and track that meaning.

Concepts in NDF-RT™ are organized into *taxonomies,* that is, hierarchies of concepts based on generalization. The meaning of each concept within a taxonomy is both more general than the meanings of its descendants (if any) and more specific than the meanings of its ancestors (if any).

As a reference terminology and ontology, NDF-RT™ provides a formal content model that describes and defines medications, both computationally and to humans, by naming relevant concepts via preferred and synonymous terms, and describing them via named relations to other terminology concepts, either within NDF-RT™ or in external terminologies. By content model, we mean the specific concepts and kinds,

role and associational relationships, and conceptual properties in a reference terminology and ontology. Assuming a basic knowledge of content modeling and representational elements, the next sections flesh out the specific content model of NDF-RT™.

In NDF-RT™, generic ingredients or combinations thereof are described in terms of their active ingredients, mechanisms of action, physiologic effects, and therapeutics (indications and contraindications). Orderable (clinical) drug products inherit the descriptions of their generic ingredients, and are further described by local (VHA) drug classification, strength, units, and dose forms. All of the descriptive concepts can themselves be explained via their position in hierarchical classifications or taxonomies of related concepts. A simplified diagram of the NDF-RT™ content model is shown in Figure 1. This description-logic representation of knowledge is formally-computable, enables classification inferences, closely resembles natural scientific descriptions, and is quite easy for people to read and understand.

In support of the FDA Structured Product Labeling (SPL) initiative, a non-hierarchical collection of External Pharmacologic Class concepts has also been added to NDF-RT™ in parallel and analogous with the VA Drug Classification hierarchy depicted in Figure 1. These concepts are distinguished by an “[EPC]” tag suffixed to their preferred names. Role relationships originating from these EPC concepts target concepts from the NDF-RT™ MoA, PE, and CI hierarchies that were selected by the FDA to index their Established Pharmacologic Classes for SPL purposes. At this time, EPC classes are not fully integrated into the NDF-RT™ content model; hence, clinical drugs are not now classified into EPC classes. More content relationships may be created in the future to integrate them fully.

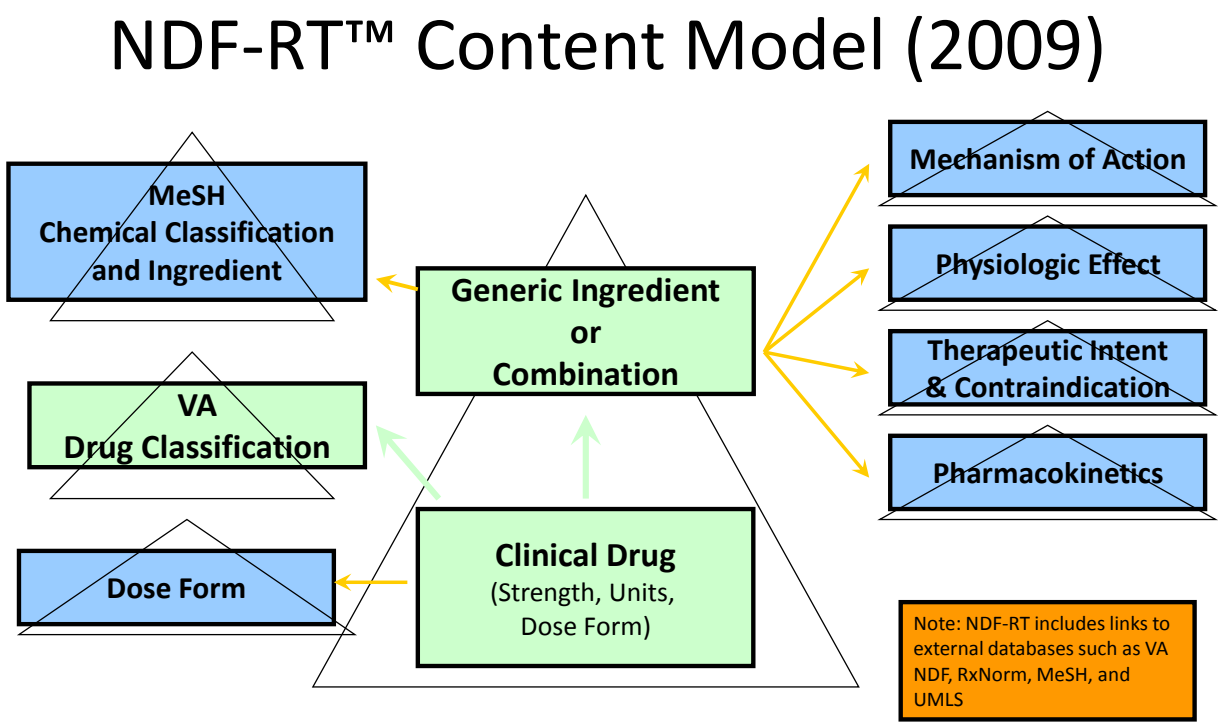

Figure 1 – Content Model for NDF-RT™

Triangles denote hierarchies of related concepts, categorized in the rectangles within the triangles. Taxonomic or ISA relationships (upward-pointing green arrows) unify NDF-RT™ clinical drug concepts into a polyhierarchy, classified both by their VA drug class and their generic ingredient(s). Various named role relationships (sideways-pointing amber arrows) define the central drug concepts (green) from which they originate in terms of the reference hierarchy concepts (blue) pointed to.

Kinds

NDF-RT™ concepts are partitioned into a small number of very general, distinct, non-overlapping categories or *kinds*, such that each concept is assigned to exactly one kind. Valid concept kinds currently include:

- **DRUG_KIND** – the primary, central hierarchy in NDF-RT**.** It includes VA classifications of medications, generic ingredient preparations used in medications, and orderable (clinical) VA drug products. A set of External Pharmacologic Classes are also represented in this kind. Concepts at different levels of the hierarchy were extracted from different NDF legacy files. Packaged (NDC-coded) drug products, disposable supplies, and durable medical equipment have been deprecated from NDF-RT. All **DRUG_KIND**

concepts are organized into the main hierarchy beneath the "Pharmaceutical Preparations" concept.

- **DISEASE_KIND** – pathophysiologic as well as certain non-disease physiologic states that are treated, prevented, or diagnosed by an ingredient or drug product. May also be used to describe contraindications. These concepts are organized into a classification hierarchy from NLM's MeSH (Medical Subject Headings), beneath the "Diseases, Manifestations or Physiologic States" concept.
- **INGREDIENT_KIND** – chemicals or other drug ingredients, organized into a chemical structure classification hierarchy, generally from NLM's MeSH, beneath the "Chemical Ingredients" concept.
- **MECHANISM_OF_ACTION_KIND** – molecular, subcellular, or cellular effects of drug generic ingredients, organized into a chemical function classification hierarchy, beneath the "Cellular or Molecular Interactions" concept.
- **PHARMACOKINETICS_KIND** – collections of concepts describing the absorption, distribution, and elimination of drug active ingredients, beneath the "Clinical Kinetics" concept.
- **PHYSIOLOGIC_EFFECT_KIND** – tissue, organ, or organ system effects of drug generic ingredients, organized into an organ system classification hierarchy, beneath the "Physiological Effects" concept.
- **THERAPEUTIC_CATEGORY_KIND** – a small, experimental collection of general therapeutic intents of drug generic ingredients, organized into an organ system-oriented classification hierarchy, beneath the "Therapeutic Categories" concept. These concepts are experimental, and are used exclusively to model external pharmacologic class concepts with diverse, poorly defined, or undefined mechanisms of action and/or physiologic effects.
- **DOSE_FORM_KIND** – NDF-RT™-specific hierarchy of administered medication dose forms from RxNorm, beneath the "Dose Forms" concept.
- **DRUG_INTERACTION_KIND** – pair-wise drug ingredient interactions from NDF, beneath the "VA Drug Interactions" concept.

Concepts

As of this writing, the conceptual coverage of NDF-RT™ is derived through a periodic algorithmic "refresh" from the latest National Drug File (NDF) files, including all orderable drug products together with their pharmaceutically-active generic ingredients or combinations thereof. NDF-RT™ is organized around its **DRUG_KIND** consisting of medications. NDF-RT™ also includes reference concepts used in the "knowledge base" aspect of reference terminology modeling to describe the structural and functional chemical classification, physiologic effects, kinetics, and therapeutics of generic active ingredients and, via inheritance, the orderable medications containing them. The maintenance of the reference concepts and terminology modeling is described in more detail later (Periodic Maintenance).

Medication concept instances within the **DRUG_KIND** are organized into a so-called "Pharmaceutical Preparations" polyhierarchy having two primary paths, each consisting of two increasingly specific levels *[associated with stated legacy NDF files]*:

Drugs by chemical, functional, and/or therapeutic classification (as classified using the legacy VA Drug Class concept hierarchy):

1. VA Drug Classes
2. Orderable (Clinical) Drugs

Drugs by generic ingredient or combination:

1. Generic Ingredients
2. Orderable (Clinical) Drugs

Orderable or clinical drug names, those used by clinicians in patient care, consist of the active generic ingredient(s) at specified strength(s), unit(s), and dose form, adhering to the definition proposed by the HL7 Medication Terminology technical committee. The set of clinical drug concepts at the lowest level has alternative superconcepts at the next higher hierarchical level, namely: generic ingredients and combinations thereof (aka "preparations"), as well as VA-specific drug classes for orderable drug products. For example, the ETANERCEPT 50MG/ML INJ SYRINGE concept (Figure 3) has two parent superconcepts, namely: [MS190] ANTIRHEUMATICS,OTHER and ETANERCEPT.

The hierarchical level of each NDF-derived concept in the **DRUG_KIND** is recorded in its **Level** property, the value of which can be one of the following: **VA Class, Ingredient,** or **VA Product**. Generic Ingredient concepts in the **DRUG_KIND** at the **Ingredient** level are linked to their chemical constituents in the **INGREDIENT_KIND** by a **has_Ingredient** role to each constituent, single ingredient chemical concept. Currently, only the "Generic Ingredient" concepts are fully modeled. Other roles, enumerated in the Roles section immediately below, have also been modeled. If necessary when adding a new orderable drug, the modeler works backwards through higher levels as far as needed, adding any defining superconcepts required. While doing so, relevant additions to concepts in one or more of the reference kinds may also be in order.

Role Relationships

Role relationships help to describe and define concepts according to their relationships with other concepts. Each role has a *domain* – the *kind* of concept whose definition may use the role, as well as a *range* – the *kind* of concept that the role can refer to. As definitional relationships, roles support tool-based automated classification and are inherited into descendant concepts in the resulting inferred taxonomy.

In NDF-RT™, concepts in the **DRUG_KIND** have role relationships, which are inherited down the drug hierarchy from generics into orderable drug products. Role names may be prefixed with "*has_*" and suffixed with the name of the role's range kind or an acronym thereof, although exceptions are made for several different roles that refer to the same kinds. Roles are specified only with the *some* restriction. Figures 2 and 3

illustrate how several important role relationships in the NDF-RT™ content model can be used to semantically model, that is, to describe and define, an antirheumatic agent generic ingredient and an orderable, clinical drug containing that ingredient.

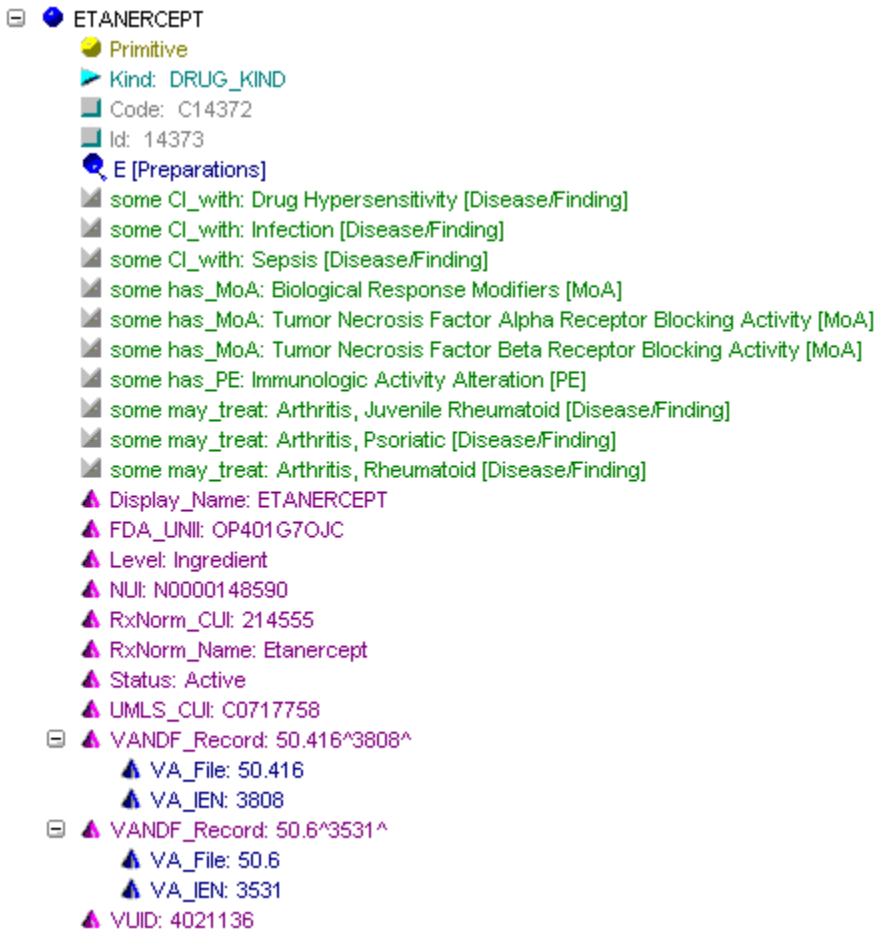

Figure 2 – Generic Ingredient Content Modeling with Role Relationships (green)

Figure 3 – Orderable Drug Content Modeling with Incremental Role Relationship (green)

Only one additional role (has_DoseForm) has been modeled at this orderable drug level of the drug hierarchy. Generic ingredient level modeling (Figure 2) will be inherited down the drug hierarchy to all descendant concepts (such as this one) automatically by inference.

The following enumeration of different sections within the **DRUG_KIND** shows the default levels where role relationships are introduced, along with the kind of concepts referenced by the role and what each role describes or defines:

- **Drug/Pharmacologic Class (VA or External)**
  - **has_Chemical_Structure → INGREDIENT_KIND**
    - chemical structure classification of a pharmacologic class
  - **has_MoA → MECHANISM_OF_ACTION_KIND**
    - molecular, subcellular, or cellular level functional activity of a pharmacologic class
  - **has_PE → PHYSIOLOGIC_EFFECT_KIND**
    - tissue, organ, or organ system level functional activity of a pharmacologic class
  - **has_TC → THERAPEUTIC_CATEGORY_KIND**
    - therapeutic intent categorization of a pharmacologic class

- **Generic Ingredients or Combinations**
  - **has_Ingredient → INGREDIENT_KIND**
    – chemical ingredient of a generic ingredient preparation or drug
  - **CI_ChemClass → INGREDIENT_KIND**
    – contraindicated structural chemical class of another generic if co-administered with the generic ingredient preparation or drug
  - **has_active_metabolites → INGREDIENT_KIND**
    – chemically-active metabolic product of a generic ingredient preparation or drug
  - **metabolized_by→ INGREDIENT_KIND**
    – chemical or enzyme which metabolizes a generic ingredient preparation or drug
  - **has_MoA → MECHANISM_OF_ACTION_KIND**
    – molecular, subcellular, or cellular level functional activity of a generic ingredient preparation or drug
  - **CI_MoA → MECHANISM_OF_ACTION_KIND**
    – contraindicated mechanism of action of another generic if co-administered with the generic ingredient preparation or drug
  - **has_PE → PHYSIOLOGIC_EFFECT_KIND**
    – tissue, organ, or organ system level functional activity of a generic ingredient preparation or drug
  - **CI_PE → PHYSIOLOGIC_EFFECT_KIND**
    – contraindicated physiological effect of another generic if co-administered with the generic ingredient preparation or drug
  - **has_PK → PHARMACOKINETICS_KIND**
    – absorption, distribution, and elimination of a generic ingredient preparation or drug
  - **site_of_metabolism → PHARMACOKINETICS_KIND**
    – metabolic anatomic site of a generic ingredient preparation or drug
  - **may_treat → DISEASE_KIND**
    – therapeutic use or indication of a generic ingredient preparation or drug
  - **may_prevent → DISEASE_KIND**
    – preventative use or indication of a generic ingredient preparation or drug
  - **may_diagnose → DISEASE_KIND**
    – diagnostic use or indication of a generic ingredient preparation or drug
  - **induces → DISEASE_KIND**
    – therapeutic effect or state caused by a generic ingredient preparation or drug (e.g., abortifacient induces therapeutic abortion)
  - **CI_with → DISEASE_KIND**
    – therapeutic or co-morbid contraindication of a generic ingredient preparation or drug
  - **effect_may_be_inhibited_by → DRUG_KIND**
    – preparation or drug which interferes with therapeutic effect of a generic ingredient preparation or drug

- **Orderable (Clinical) Drug**
  - **has_DoseForm → DOSE_FORM_KIND**
    - RxNorm standard name for physical form of a drug (e.g., oral tablet, topical cream)

Although roles are shown at the level where they should be modeled by default, most could be stated at lower levels when the particular drug concepts are best modeled in that way. Selection of role values is based on reference sources and explicit modeling guidelines, as explained in Appendix I: Appendix I: NDF-RT™ Modeling Guidelines.

Modeling also follows these guidelines:

- The **has_Ingredient** and **has_DoseForm** roles are mandatory, initialized during import, and not changed unless incorrect.
- The **has_MoA**, **has_PE, may_*, induces, and CI *** roles are mandatory and human-modeled.
- Remaining roles are optional and human-modeled.

Figure 4 illustrates content modeling in an External Pharmacologic Class concept in order to capture FDA SPL indexing of an FDA Established Pharmacologic Class.

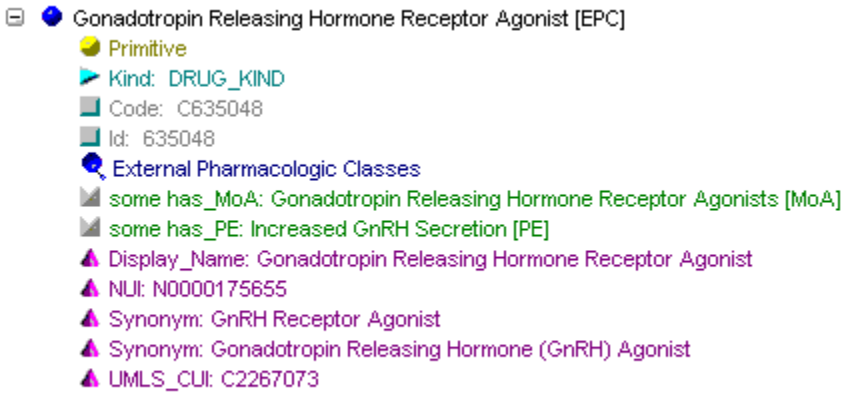

Figure 4 – External Pharmacologic Class Content Modeling with Role Relationships (green)

FDA SPL indexing for this EPC concept is represented by two role relationships. In addition to the untagged display name, note two more synonymous names for this concept.

Association Relationships

Concepts may also have association relationships to other concepts. Associations are treated as non-definitional, unlike role relationships. Consequently, they are ignored by automated classification and are not inherited into descendant concepts in the resulting inferred taxonomy.

NDF-RT™ association names describe the specific inter-concept relationship. The following lists NDF-RT™ associations along with the kind (and level) of concepts referenced by each. Valid *association qualifiers* required by relationship semantics are shown indented beneath the listed association.

- **Product_Component**
  from **DRUG_KIND where Level = VA Product** →
  to **DRUG_KIND where Level = Ingredient**
  - **Strength**
  - **Unit**
  - **VA.IEN**

  – generic ingredient component of orderable drug product, qualified by strength, unit, and VA NDF file IEN (individual entry number)
- **Ingredient_1**
  from **DRUG_INTERACTION_KIND** →
  to **DRUG_KIND where Level = Ingredient**
  – first generic ingredient in a VA NDF ingredient-ingredient paired interaction
- **Ingredient_2**
  from **DRUG_INTERACTION_KIND** →
  to **DRUG_KIND where Level = Ingredient**
  – second generic ingredient in a VA NDF ingredient-ingredient paired interaction

Concept Properties

Concept properties are informational attributes of concepts. A property value is a text string (e.g., external name, UI, data flag) attached to a single concept, without any inheritance to descendant concepts in the inferred taxonomy.

Most NDF-RT™ concept properties were assigned during initialization or periodic updates (see the Periodic Maintenance section). Assignment of default property values was based on the original source content or upon property semantics.

Salient drug and ingredient properties initialized from legacy NDF files during periodic NDF updates have been “adopted” by NDF-RT™ as scientifically valid and meaningful data for a medication reference terminology. In most cases, their property name prefix of “NDF_” or “VA_” has been deprecated. Remaining “VA*_” properties provide pointers to original NDF file records or other VA-specific data.

Properties derived from external terminology sources will have their names prefixed accordingly ("MeSH_", "RxNorm_", "SNOMED_", "FDA_", or "UMLS_"). These properties provide synonymous mappings via source-specific identifiers or display other attributes of that synonymous external source concept. External source property values are also populated automatically during periodic updates.

The remainder of this section indicates where specific properties belong in the NDF-RT™ content model. The following properties are relevant for all NDF-RT™ concepts:

- **NUI** – NDF-RT™ unique identifier (a unique "N#" assigned to *every* concept)
- **Display_Name** – *untagged* concept name for import and export
- **Synonym**
- **UMLS_CUI** – unique concept identifier from the NLM UMLS Metathesaurus

Every NDF-RT™ concept has been assigned a unique identifier (NUI) and may have other synonymous, internal or external names as needed and described.

The following properties, with further indented qualifiers, are relevant for all VA NDF-sourced concepts having legacy NDF content:

- **VUID** – VA Unique IDentifier only for VA NDF concepts
- **Status** – VA NDF concept aggregate status = (Active, Inactive)
- **VANDF_Record** – concatenated triple of the following qualifier values, delimited by "^"
    - **VA_File** – VA NDF file number
    - **VA_IEN** – VA NDF file IEN (individual entry number)
    - **VA_Status** – VA NDF file record status = (Active, Inactive)

For **DRUG_KIND** concepts, the following indented list shows the hierarchical levels at which the specific properties [associated with listed NDF legacy files] are relevant; the **Level** property denotes the hierarchical level value, as indicated:

- **VA Drug Class**
    - **Level** = (VA Class)
    - **Class_Code**
    - **Class_Description**
- **Generic Ingredients or Combinations**
    - **Level** = (Ingredient)
    - **FDA_UNII** – FDA UNII code
    - **RxNorm_Name** – RxNorm semantic ingredient name (IN)
    - **RxNorm_CUI** – RxNorm source CUI (RXCUI) for IN
- **Orderable (Clinical) Drug**
    - **Level** = (VA Product)
    - **Print_Name** – concise clinical drug name for labels, etc.
    - **Strength**
    - **Units**
    - **CS_Federal_Schedule** = Federal Controlled Substance Schedule (0-3)
    - **VA_National_Formulary_Name**
    - **RxNorm_Name** – RxNorm semantic clinical drug name (SCD)

- **RxNorm_CUI** – RxNorm source CUI (RXCUI) for SCD

NDF-RT's **INGREDIENT_KIND** was initialized from the Medical Subject Headings (MeSH) and is periodically resynchronized by computer algorithm. For **INGREDIENT_KIND** concepts, the following specific properties apply:

- **MeSH_Name** – *untagged* MeSH main heading name
- **MeSH_CUI** – M# unique MeSH concept identifier within main heading
- **MeSH_DUI** – D# or C# unique MeSH descriptor identifier for main heading
- **MeSH_Definition** – MeSH definition for MeSH main heading

NDF-RT's **DISEASE_KIND** was initialized from the Medical Subject Headings (MeSH) and is periodically resynchronized by computer algorithm. For concepts in the **DISEASE_KIND** and **MECHANISM_OF_ACTION_KIND**, the following specific properties apply**:**

- **MeSH_Name** – *untagged* MeSH main heading name
- **MeSH_DUI** – D# or C# unique MeSH descriptor identifier for main heading
- **MeSH_Definition** – MeSH definition for MeSH main heading
- **SNOMED_CID** – SNOMED-CT concept ID mapping (only for MeSH disease name)

NDF-RT's **DOSE_FORM_KIND** was initialized from RxNorm and is periodically resynchronized by computer algorithm. For **DOSE_FORM_KIND** concepts, the following specific properties apply:

- **RxNorm_Name** – *untagged* RxNorm dose form name
- **RxNorm_CUI** – RxNorm source CUI (RXCUI)

For **DRUG _INTERACTION_KIND** concepts, periodically resynchronized with current VA NDF data, the following specific property applies:

- **Severity** = (Significant, Critical)

For any remaining kinds not discussed above**,** there are no specific properties other than those listed earlier for all NDF-RT™ concepts.

NOTE: Review_Status, **Last_Reviewed**, **Reviewed_By, Alert,** and **Comment** properties were assigned for administrative and tracking purposes during semantic modeling. They have been excluded from the NDF-RT™ Public Edition release and are not documented here.

NDF-RT™ Maintenance and Publication

Periodic Maintenance

Automated Content Enhancements and Updates

NDF-RT™ contains links to relevant external terminologies such as NDF, RxNorm, and MeSH. These links must be refreshed regularly in order to keep content up-to-date and in synch with these other sources in accordance with their input data flows and release schedules. On a monthly basis, prior to release processing, NDF-RT™ is synchronized with updated NDF and RxNorm content. The NDF monthly refresh process involves the revision of core NDF data within NDF-RT™ identified by comparative programmatic analyses of selected files across the monthly VANDF patch databases. VA Drug Classes, Generics and Ingredients, Products, and Interactions are all updated programmatically from these VANDF patches. Via RxNorm collaborative processes, Dose Forms and Dose Form roles, as well as RxNorm_CUI and RxNorm_Name concept properties, are also updated programmatically as part of the monthly NDF-RT™ refresh.

The NDF-RT™ chemical/ingredient structural concept hierarchy is also refreshed from the NLM MeSH chemical/drug hierarchy twice a year, following revisions of MeSH released in semi-annual editions of the NLM UMLS Metathesaurus. Along with these periodic refreshes from MeSH based on content extracted from the Metathesaurus, UMLS_CUI properties are programmatically updated in NDF-RT™ as well. Data-mining the above content releases extracts the mappings needed to refresh external unique identifiers in a variety of NDF-RT™ concepts.

Expert Content Modeling

In order to assure continual accuracy of content and to remain current with emerging drug knowledge, the NDF-RT™ Interagency Expert Panel (NDF-RT™ IEP) was convened in 2006 to review and vet recommended changes to NDF-RT™. Initially responsible for maintenance and revision of the MoA, PE, and Chemical/Ingredient hierarchies in response to pharmacologic class requests received from FDA, the IEP is the primary body overseeing modeling taking place in the aforementioned hierarchies. It also works in conjunction with a VHA Subject Matter Expert (VHA SME) team, which meets weekly to evaluate MoA, PE, and Chemical/Ingredient modeling, as well as external agency modeling requests beyond the three reference hierarchies that may be deemed necessary for clinical decision support. Based on input from these meetings, modelers from Apelon make needed changes to NDF-RT™. The IEP, comprised of members from various agency stakeholders with interest in drug terminologies, including VA, FDA, NLM, NCI, and CMS, meets monthly to discuss changes recommended for that month's release.

Publication

Release Schedule and Distribution Sites

NDF-RT™ is published ten times per calendar year, with combined releases occurring for December/January and August/September, following a consistent process that is briefly summarized in this section.

Following review, comment, and approval of changes recommended by the IEP for the current release, processing of the new release begins, beginning with the content refreshes mentioned above. During the programmatic update process, new NDF-RT™ concepts are assigned NUIs, the database is refreshed with new content via XML imports and exports, namespace statistics and change summary files are produced, and the release files discussed below are packaged.

New versions are posted on a password-protected Apelon-hosted download site[3] on the first Monday of the month. Notification of the new NDF-RT™ version is also given to external (government) publication locations, which post the updated files as well. At this time, NDF-RT™ release files are available from the National Cancer Institute Enterprise Vocabulary Services (EVS) on the Federal Medication Terminologies webpage. NDF-RT™ inferred (post-classification) content is also integrated into the National Library of Medicine RxNorm Full Monthly Release, available on the RxNorm webpage, to UMLS licensees on the first Monday of the month.

Release Formats

The monthly NDF-RT™ release includes the following files in .zip format:

- **NDFRT_Public_YYYY.MM.DD_TDE.zip**: Contains the NDF-RT™ Public Edition as a defined view (pre-classification) Apelon TDE XML file, a flat text file listing all NDF-RT™ concepts and their NUIs, change summary files, a .PDF file describing data elements in the NDF-RT™ Public Edition, and release notes.
- **NDFRT_Public_YYYY.MM.DD_TDE_inferred.zip**: Contains the NDF-RT™ Public Edition as an inferred view (post-classification) Apelon TDE XML file, a .PDF file describing data elements in the NDF-RT™ Public Edition, and release notes.
- **NDFRT_Public_YYYY.MM.DD_TDE_ByName.zip**: Contains the NDF-RT™ Public Edition as an inferred view (post-classification) Apelon TDE XML file, exported by concept name, a.PDF file describing data elements in the NDF-RT™ Public Edition, and release notes.
- **NDFRT_YYYY.MM.DD_SPL.zip**: Flat text file extracts of the MoA, PE, and Chemical/Ingredient hierarchies, listing concepts in those hierarchies with their NUIs.
- **NDFRT-Public_YYYY.MM.DD.UUU_DTS_full.zip** and **NDFRT-Public_YYYY.MM.DD.UUU_DTS_diff.zip**: Contain the NDF-RT™ Public

[3] User accounts may be set up upon request by contacting Apelon.

Edition inferred view (post-classification) as Apelon DTS full and diff load files for import into a DTS 3.4+ namespace. [**Note:** The "_UUU" segment of the filenames denotes the three-letter UMLS version from which NDF CUI and STY (semantic type) files were derived.]

The monthly integrated NDF-RT™ and RxNorm release consists of a .zip archive:

- **RxNorm_full_MMDDYYYY.zip**: Contains NDF-RT™ Public Edition inferred (post-classification) content within various RxNorm full release relational files in NLM's Rich Release Format (RRF). An overview and documentation are available on the RxNorm webpage.

Appendix I: NDF-RT™ Modeling Guidelines

This section has explicit modeling guidelines for those domain experts (pharmacists, pharmacologists, clinicians) responsible for content modeling, using the Apelon TDE in order to maintain and extend the NDF-RT™ content model described earlier in this NDF-RT™ documentation, as diagrammed in Figure 1. Historically, it served as the Style Guide during initial NDF-RT™ content modeling. Going forward, it provides continuing guidance for consistent maintenance and extension of such medication modeling. Understanding and maintaining the content model are the most important considerations for NDF-RT™ semantic modelers.

Economies of scale in NDF-RT™ result from describing and modeling a limited universe of approximately 4,000 *active* ***single ingredient*** *generic preparations*, rather than more than 10,000 orderable medications and 100,000 packaged drug products. Described characteristics of a generic single ingredient or combination preparation can be inherited into any pharmaceutical product formulated from it.

Goals

All *active* ***single ingredient*** *generic ingredient preparation* concepts in the "Pharmaceutical Preparations" hierarchy should be modeled to a uniform desirable level of quality. Characteristics of *active* ***multiple ingredient*** generic preparation concepts usually can be computed from their individual ingredients and need not be modeled at this time. However, any therapeutic characteristics that differ will need to be distinguished by future modeling efforts.

Semantic modeling should assure that all definitional characteristics (*role relationships*) for each active generic ingredient concept are *correct* and *complete***,** according to authoritative drug knowledge in one or more VHA-specified references.

NB: Throughout this NDF-RT™ semantic modeling section, so-called *active* or *generic ingredient preparation* concepts specifically refer to **DRUG_KIND** "Generic Ingredient" concepts, where **Level** = "Ingredient", which appear in the "Pharmaceutical Preparations" hierarchy. These are drug formulations which contain chemicals that are named in the **INGREDIENT_KIND** "Chemical Ingredients" reference hierarchy via a distinguishing suffix tag "[Chemical/Ingredient]" and are explicitly linked from the generic ingredient concept by a **has_Ingredient** role relationship. As of December 2009, only single ingredient **DRUG_KIND** "Generic Ingredient" concepts have been modeled.

Tasks

- Review and assign Mechanisms of Action (**has_MoA**) role relationship(s) and Physiologic Effects (**has_PE**) role relationship(s) to every *active single ingredient* generic ingredient
- Review and assign clinically-significant therapeutic/preventive/diagnostic use or indication role relationships (**may_treat, may_prevent, may_diagnose, induces**) to every *active single ingredient* generic ingredient, at an appropriate level of clinical granularity

- Review and assign clinically-significant contraindication role relationships (**CI_with, CI_ChemClass, CI_MoA, CI_PE**) to every *active single ingredient* generic ingredient, at an appropriate level of clinical granularity, according to the **KIND** of the target concept
- Review and assign to-be-specified role relationships relevant at this level
- Delete incorrect role relationships *only if* among those types listed above
- Model "base" generic ingredient preparations differently from their "salt/ester" child concepts as needed
- Alert managing editor of missing reference concepts required for semantic modeling
- Alert managing editor of incorrect, inappropriate, or duplicate concepts to be deleted
- Set each concept's internal **Review_Status** property appropriately when finished

NB: This guide assumes that an automated update or New Drug Transaction (NDT) process would instantiate new **DRUG_KIND** concepts in the NDF-RT™ knowledge base in a consistent, principled manner. Updates should correctly place drugs or generic ingredients in the drug polyhierarchy, instantiate essential basic roles (**has_Ingredient, has_DoseForm**) and associations, set certain VHA NDF-specific property values (**VANDF_Record, VUID,** etc.), and set other NDFRT-specific properties (**Level, Review_Status**, etc.). External source associations and property values would also be initialized automatically, as feasible. Semantic modeling would then be required only for appropriately flagged new or revised **DRUG_KIND** concepts.

Desiderata

Choose the most precise reference concept at the same level of specificity as the stated concept in the authoritative reference. For example, an active ingredient preparation which may treat Malignant Hypertension should be modeled as such. However, other ingredient preparations that treat the more general concept Hypertension should use only that general concept in their descriptions, rather than more specific descendants farther down the Disease concept reference hierarchy.

> **NB:** The TDE Hierarchy Tree and Concept Walker panels facilitate browsing concepts and their descendants in the reference hierarchies.

1. Model all <u>important</u> characteristics (MoA, PE, and clinically-significant therapeutic indication or contraindication information) for *active **single ingredient** preparations*, where "important" is defined as it appears in relevant subsections of the medication entry in the designated primary reference. Other reference texts or drug web sites may be consulted to clarify issues or rectify omissions in this primary reference. Balance the goal of completeness with any productivity requirements.

    a. <u>Mechanisms of Action (**has_MoA** role)</u>
    How an active ingredient preparation acts at the cellular, subcellular, or molecular levels. Includes receptor interactions and physiochemical activity. *Examples: Angiotensin Converting Enzyme Inhibitor, Adrenergic beta1-Antagonist.*

b. Physiologic Effects (**has_PE** role)
How an active ingredient preparation affects organ systems, organs, or tissues within the body. *Examples: Bronchodilation, Acid Secretion Inhibition.*

c. Clinically-significant Uses or Indications (**may_treat, may_prevent, may_diagnose, induces** roles)
Which diseases or pathophysiologic states would this active ingredient preparation have as *clinically-significant* indications or uses (either on- or off-label) for *treatment*, *prevention*, or *diagnosis*. Consider whatever meets the following criteria:

> "Medication X is *appropriate* for the diagnosis, prophylaxis, or treatment of disease Y, its associated symptoms, or closely associated diseases (e.g., specific opportunistic infections in AIDS), given the usual course of the disease being treated, the usual risks of the medication, and the usual benefits derived from that medication."

Examples: Atenolol may treat Hypertension, Atorvastatin may treat Hypercholesterolemia, Medroxyprogesterone Acetate may prevent Pregnancy.

d. Clinically-significant Contraindications (**CI_with, CI_ChemClass, CI_MoA, CI_PE** roles)
Which contraindications would be *clinically-significant* for this active ingredient preparation. Contraindications can be described in one of four ways by reference to different **KIND**s of NDF-RT concepts.

- Contraindicated in the presence of specified diseases or pathophysiologic states:
  CI_with role → DISEASE_KIND concept
  Examples: Atenolol contraindicated with Bradycardia, Azathioprine contraindicated with Pregnancy.

- Contraindicated in the presence of any active ingredient prep in the specified structural chemical class:
  CI_ChemClass role → INGREDIENT_KIND concept
  Example: Chlorothiazide contraindicated in the presence of Sulfonamides.

- Contraindicated in the presence of any active ingredient preparation having the specified mechanism of action:
  CI_MoA role → MECHANISM_OF_ACTION_KIND concept
  Example: Bupropion contraindicated in the presence of Monoamine Oxidase Inhibitors.

- Contraindicated in the presence of any active ingredient preparation having the specified physiological effect:
  CI_PE role → PHYSIOLOGIC_EFFECT_KIND concept
  Examples: Aldesleukin contraindicated in the presence of Cardiac Rhythm Alteration.

  NB: Lacking drug-specific concepts for toxicity or hypersensitivity, these drug-specific contraindications should be modeled **CI_with** either of the general disease concepts "Drug Toxicity" or "Drug Hypersensitivity", using a drug-specific concept if available.

2. Only the "base" chemical structural form of an active ingredient preparation (e.g., erythromycin) should be modeled *unless* there are important differences in chemical function (MoA, PE) or therapeutics (indications, contraindications) for a salt or ester form (e.g., erythromycin estolate). In such cases, model the commonalities in the base chemical parent concept, and model only the differences in various salt or ester descendent concepts. In the usual case where base and salt/ester concepts have identical MoA, PE, indications, and contraindications, the salt or ester concepts need not contain any of the aforementioned roles, although the **has_Ingredient** role relationship, which always differs, must be present in all concepts.

3. If any functional characteristics (MoA or PE) of an active ingredient preparation are unknown or not specified, model with the default unknown reference concept (e.g., "Unknown Cellular or Molecular Interaction") to note that fact.

4. If any active ingredient preparation concept has previously assigned MoA, PE, indication, or contraindication role relationships that are *incorrect*, delete those role relationships.

5. Modelers should *not* add, delete, or rename any NDF-RT™ concept. If naming (spelling, duplication, etc.) issues are detected, notify the managing editor. If an important reference concept is missing and must be added so one can correctly model this and other active ingredient preparations, suggest an appropriate name for the concept, and where it should be placed in the reference hierarchies (i.e., its parent concept[s]). Finish modeling everything else in that concept before moving on, setting the **Review_Status** property as explained below.

6. After modeling each ingredient prep concept, always reset the value of the **Review_Status** property to reflect its current modeling state before saving any changes to the concept. Choose the appropriate **Review_Status** value from the TDE pick list, namely:
   Unreviewed - never modeled (default for new concepts).
   Needs Review - incompletely modeled with issues or problems.
   Reviewed - completely modeled without remaining issues or problems.
   Approved - assigned only by the managing editor after resolving issues.