Substance Strength Set

Substance-Strength Set for the NTP

The set of active ingredient substance(s), when combined with an expression of their strength, is one of the definitional components of an NTP and therefore its correct description is an essential part of the human readable Formal Name for the NTP. The different components of the Substance-Strength Set, the precise active ingredient substance(s), basis of strength substance(s) and strength(s) have been documented in this section separately.

Describing and Naming Substances

To identify pharmaceutical substances that are acting as active pharmaceutical ingredients, Health Canada naming follows the International Non-proprietary Names (INN) or the United States Accepted Names (USAN). In rare cases, Health Canada naming follows a Canadian specific practice (Canadian Standard Drugs – CSD). When describing the active ingredient substance(s), the description used by Health Canada's DPD will be used, with some exceptions.

Canadian Substance Naming Examples:

INN	USAN	DPD (BDPP)
glyceryl trinitrate	nitroglycerin	nitroglycerin (nitroglycérine)
orciprenaline	metaproterenol	orciprenaline (orciprénaline)
paracetamol	acetaminophen	acetaminophen (acétaminophène)
salbutamol	albuterol	salbutamol (salbutamol)

Modifiers, such as salts and esters will also be described in the NTP formal name using INN or USAN as appropriate (e.g., "mesylate" rather than the full chemical name for the modifier "methanesulfonate"). In French, salt names often occur at the beginning of the drug name. These will be expressed without modification in CCDD French; alphabetical order of ingredients will follow the order of ingredients in English, so that corresponding ingredient names are in the same order within the NTP in both languages. Example:

English MP	French MP (note order of ingredients matches English alpha order, for consistency)
CLINDOXYL ADV GEL (benzoyl peroxide 3 % and clindamycin (clindamycin phosphate) 1 % cutaneous gel) GLAXOSMITHKLINE INC	CLINDOXYL ADV GEL (peroxyde de benzoyle 3 % et clindamycine (phosphate de clindamycine) 1 % gel cutané) GLAXOSMITHKLINE INC

Precise ingredient substances that include waters of hydration will not be described in the NTP formal names but will be described in the MP formal names: see Appendix F, Hydration and Solvation for detailed information.

Active ingredient substances are described using lower case, with upper case being used for letters within substance names if present in the official (INN) name, for example in 'polymyxin B' or 'abobotulinumtoxinA'.

Products supplied with carrier fluids

Some products, usually but not always infusion products, are supplied with a "carrier fluid" – the fluid that adds volume to the product without contributing to its therapeutic effect. In the DPD, there are examples (such as some lidocaine infusions) where the carrier fluid is listed as an active ingredient substance (e.g., lidocaine and dextrose). The CCDD will not describe the carrier fluid as an active ingredient substance in the NTP, although it may be described in the MP if the DPD product (brand) name includes it.

Vitamin substance naming

Vitamin terminology in Canada reflects a variety of naming patterns. Vitamins B12, C, D, E and K tend to be referred to by their alphanumeric "vitamin" names in practice; in contrast, folic acid (vitamin B9), niacin/nicotinic acid (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), riboflavin (vitamin B2), thiamine (vitamin B1), and vitamin D analogues such as alfacalcidol, calcifediol, calcipotriol and calcitriol tend to be known by their INNs or other common names.

The term "vitamin" is defined as a group of nutritionally essential organic molecules with similar structures (known as "vitamers"), which share the activity of the parent group (A,B,C,D,E or K); ingredient substances in pharmaceutical products are actually vitamers, with names that reflect internationally standardized terms such as INN (most common), USAN, or other common name. Therefore, it is these vitamer names that will be used to describe vitamin ingredient substances in the products in the CCDD; the alphanumeric names will not be used.

Precise Active Ingredient Substance(s)

The precise active ingredient substance is an accurate and granular description of the substance as it is used in the product (as it is presented by the manufacturer, before any dilution or transformation) but without any description of waters of hydration or solvates in the NTP, since these have no little clinical significance. The precise active ingredient is usually described in terms of the modified INN/USAN. If no modifier is stated, the precise ingredient substance is the base substance moiety.

Examples:

English Precise Ingredient	French Precise Ingredient
phenytoin sodium (in Pfizer's Dilantin capsule)	phénytoïne sodique
phenytoin (in Pfizer's Dilantin Suspension) [example of the base moiety being the precise ingredient substance]	phénytoïne
beclomethasone dipropionate (in Valeant's Qvar products)	dipropionate de béclométhasone
sumatriptan succinate (in GSK's Imitrex DF tablet)	succinate de sumatriptan
sumatriptan hemisulfate (in GSK's Imitrex Nasal spray)	hémisulfate de sumatriptan
potassium chloride (in Biomed's Slo-Pot)	chlorure de potassium

Basis of Strength Substance

The basis of strength substance (often referred to as the BoSS) is the substance against which the strength quantity(s) of the product is measured. It is usually described in terms of the INN or the modified INN, as appropriate.

Examples:

English BoSS	French BoSS
Coversyl: 4 mg of perindopril erbumine per tablet	périndopril erbumine 4 mg par comprimé
Dilantin: 50 mg of phenytoin sodium per capsule	phénytoïne sodique 50 mg par capsule
Dilantin: 125 mg of phenytoin per 5 mL	phénytoïne 125 mg par 5 mL
Qvar: 50 mcg of beclomethasone dipropionate per actuation	dipropionate de béclométhasone 50 mcg par actionnement
Imitrex DF: 50 mg of sumatriptan per tablet	sumatriptan 50 mg par comprimé
Imitrex Nasal spray: 5 mg of sumatriptan per actuation	sumatriptan 5 mg par actionnement
Norvasc: 10 mg of amlodipine per tablet	amlodipine 10 mg par comprimé

Describing the NTP using Precise Ingredient Substance and BoSS

1) Where the precise active ingredient substance is the basis of strength substance, only the precise active ingredient substance is required for the NTP:

Examples:

NTP Formal Name (with precise ingredient and BoSS)	FR Description (with precise ingredient and BoSS)
Coversyl: perindopril erbumine 4 mg oral tablet	périndopril erbumine 4 mg comprimé oral
Dilantin: phenytoin sodium 50 mg oral capsule	phénytoïne sodique 50 mg capsule orale
Dilantin: phenytoin 125 mg per 5 mL oral suspension	phénytoïne 125 mg par 5 mL suspension orale
Qvar: beclomethasone dipropionate 50 mcg per actuation pressurized inhalation	dipropionate de béclométhasone 50 mcg par actionnement inhalation en flacon pressurisé

2) Where the precise active ingredient substance is not the basis of strength substance, both the precise active ingredient substance and basis of strength substance are required to define the NTP. In the formal name, the basis of strength substance will be stated first, outside the brackets and the precise active ingredient substance will be stated second within brackets (parentheses).

Examples of precise active ingredient substance when NOT the basis of strength:

English Precise Ingredient Substance	French Description of Precise Ingredient Substance
Norvasc: amlodipine (amlodipine besylate) 10 mg per tablet	amlodipine (bésylate d'amlodipine) 10 mg par comprimé
Imitrex DF: sumatriptan (sumatriptan succinate) 50 mg per tablet	sumatriptan (succinate de sumatriptan) 5 mg par comprimé
Imitrex Nasal spray: sumatriptan (sumatriptan hemisulfate) 5 mg per actuation	sumatriptan (hémisulfate de sumatriptan) 5 mg par actionnement

Absence of specific excipient substances

The absence of a specific excipient substance that may have some clinical considerations such as sugar, dye, preservatives etc. (i.e., “freeness”) will not be part of the consideration for an NTP and will not be included in the NTP formal name or FR description. However, for the MP, if the DPD product (brand) name contains information regarding “freeness”, then this will be included in the MP formal name and MP FR description.

Example: (where the “freeness” is highlighted for illustration in italics):

MP Formal Name	MP French Description
AMOXICILLIN *SUGAR-REDUCED* GRANULES FOR ORAL SUSPENSION (amoxicillin (amoxicillin trihydrate) 250 mg per 5 mL oral suspension) SIVEM PHARMACEUTICALS ULC	AMOXICILLIN *SUGAR-REDUCED* GRANULES FOR ORAL SUSPENSION (amoxicilline (trihydrate d’amoxicilline) 250 mg par 5 mL suspension orale) SIVEM PHARMACEUTICALS ULC

Description of Strength (as part of the Strength-Set) in the NTP

The strength of a therapeutic product is the amount (quantity) of (each) active ingredient substance per presentation unit (see below). Representation of strength is a safety issue, and the Institute for Safe Medication Practices Canada (ISMP Canada) has made several recommendations that have been considered.

An amount is a physical quantity – it is expressed as a value and the unit of measure for that value, but for a therapeutic product, the strength is actually a “ratio concept” – a numerator quantity and denominator quantity (an amount per unit – where the unit is also a physical quantity per unit of presentation).

Presentation Strength and Concentration Strength (See also Unit of Presentation section)

For certain types of products, particularly continuous liquids, there are two options to describe the product strength: concentration strength, which describes strength with a standard (unitary) denominator (e.g., per mL); and presentation strength, which explicitly describes the amount of (each), active ingredient substance per presentation unit.

For example: dalteparin injection is a solution of dalteparin sodium whose unitary concentration is 25000 units per (1) mL. However, the product is “presented” for use in various volumes within a pre-filled syringe, such as 0.4 mL pre-filled syringes. These are the “presentation units” for the product. The presentation strength for the pre-filled syringe product is therefore 10000 units per 0.4 mL.(2)

Using presentation strength is particularly helpful when there are several different product sizes available. For example, a pre-filled syringe product containing 10000 units per 0.4 mL and a different pre-filled syringe product containing 12500 units per 0.5 mL both have the same concentration strength (25000 units per (1) mL).(2)

The Canadian Clinical Drug Data Set will use presentation strength for most product descriptions, with the exception of:

- insulin and related products, where a concentration strength is given (to allow the patient easy calculation of the amount to administer as this may change very frequently); similarly, products supplied in a “pen” with variable dosage
- bulk fluids: those expected to be used by healthcare professionals and which undergo further preparation prior to patient administration (e.g., bulk vials of nebuliser solutions or cytotoxics). However, please note that a bulk vial pattern NTP does not imply specific product characteristics, such as the presence or absence of a preservative
- large volume parenteral infusions (e.g., saline or dextrose) where it is the concentration and the volume that is clinically important
- liquids administered by "drops" or measured by a syringe (ophthalmic drops, nasal drops, oral drops, otic drops)
- semi-solid preparations (usually used topically) where a concentration strength expressed as a percentage shall be used

There may be other circumstances not listed above where concentration strength may be appropriate.

Often the “per” or “denominator” part of the strength description is implicit rather than explicit, especially when the unit of presentation uses the same term as the dose form, as is the case for solid dose forms. For example, the concept “amoxicillin 250mg capsule” is fully “amoxicillin 250 mg per 1 capsule oral capsule” where the unit of presentation is “capsule” and the dose form is “oral capsule”.

In other products, particularly those that are presented in a continuous phase, the “per amount” is stated explicitly (e.g., amoxicillin 250 mg per 5 mL oral solution) or almost explicitly (e.g., clotrimazole 1% topical cream, where the 1% represents 10 mg of clotrimazole per 1 g of the cream).

In CCDD for those strengths that do not require explicit statement of the denominator, the strength is expressed as a value then its unit, separated by a space.

Examples:

Strength	NTP Formal Name	NTP French Description
10 mg	clobazam 10 mg oral tablet	clobazam 10 mg comprimé oral
100 mcg	levothyroxine sodium 100 mcg oral tablet	lévothyroxine sodique 100 mcg comprimé oral

For those strengths where the denominator is stated explicitly, the numerator and denominator will *each* be expressed as a value then its unit, separated by a space and the numerator and denominator will themselves be separated by the word “per” with a space on either side.

Examples:

Strength	NTP Formal Name	NTP French Description
250 mg per 5 mL	clarithromycin 250 mg per 5 mL oral suspension	clarithromycine 250 mg par 5 mL suspension orale
100 mg per 4 mL	morphine sulfate 100 mg per 4 mL solution for injection ampoule	sulphate de morphine 100 mg par 4 mL solution injectable ampoule

For products with multiple active ingredient substances, the strength will be stated with the active ingredient it relates to, and therefore if the numerator and denominator must both be explicitly present, the denominator will be stated in each case:

Strength	NTP Formal Name	NTP French Description
250 mg per 5 mL and 125 mg per 5 mL	amoxicillin 250 mg per 5 mL and clavulanic acid (clavulanate potassium) 62.5 mg per 5 mL oral suspension	amoxicilline 250 mg par 5 mL et acide clavulanique (clavulanate de potassium) 62,5 mg par 5 mL suspension orale

For those products where the denominator is correctly unitary,

1. for parenteral products the “1” denominator value will be explicitly stated when the total volume (for continuous liquids) of the presentation is 1 mL; the presentation strength is therefore clearly stated and cannot misinterpreted as a concentration strength, as in the first example below
2. for metered dose presentations (where the strength is per 1 actuation) and for oral liquids (administered as drops or with an oral syringe) described using a concentration strength, the “1” does not need to be explicitly stated, as in the second and third examples:

Strength	NTP Formal Name	NTP French Description
1 mg per 1 mL	vincristine sulfate 1 mg per 1 mL solution for injection vial	sulfate de vincristine 1 mg par 1 mL solution injectable fiole
100 mg per actuation	fluticasone propionate 100 mcg per actuation pressurized inhalation	propionate de fluticasone 100 mcg par actionnement inhalation en flacon pressurisé
0.05 mg per mL	digoxin 0.05 mg per mL oral solution	digoxine 0,05 mg par mL solution orale

Representing Strength Values

The value of the strength will be represented using a whole number or a decimal number.

If the value is a whole number, (integer) there will be no decimal point or trailing zeros (e.g.,10 mg not 10.0 mg).

If the value is a decimal, there will be a leading zero, avoiding naked decimals (e.g., 0.75 mg not .75 mg). In CCDD French, the decimal will be represented by a comma.

If the value is greater than a thousand, commas or spaces will not be used to separate the thousands (e.g., 1000 rather than 1,000 or 1 000). Although the ISMP recommends the use of commas, the DPD does not use spaces or commas in strength description, due to the subtle differences in what these represent between English and French and the risks that this introduces. In order to enhance readability of larger numbers, any strength value greater than or equal to 1×10^9 will be expressed using scientific notation in the following format, 1e9. See also the guidance "Good Label and Package Practices Guide for Non-prescription Drugs and Natural Health Products" published by Health Canada, which can also be applied to prescription medicinal products.

Representing Units of Measure

The unit of measure should be in the metric system whenever possible.

The unit of measure should be stated in the singular.

The Standard International (SI) abbreviations are to be used, without a terminal period (e.g., 1 mg not 1 mg.). Volume should be expressed using litres (L) or millilitres (mL) not cubic centimetres. One exception is that micrograms should be abbreviated to mcg not µg or ug. Although the SI system supports both ml and mL (and indeed l and L for litres) and both are used in science and in medicine, the convention in medicinal product terminology appears to be moving towards mL to try to avoid any possibility of confusion between lower case l and the numeric 1.

For those products whose strength is stated as "international units", the term "unit" will be used and must be stated in full, not as the abbreviation "u" or "U" or "iu" or "IU". (E.g., insulin lispro 100 unit per 1 mL).

For those products that are supplied in some form of metered-dose packaging, the unit of measure (for the denominator) should be "actuation" (e.g., beclomethasone dipropionate 50 mcg per actuation nasal spray).

For those products whose strength is presented as a percentage (where the denominator is in the unit of measure), the type of percentage (weight in weight (w/w), weight in volume (w/v) or volume in volume (v/v)) will not be stated. For example, Spectro Eczemacare Medicated Cream is described with a strength of 0.05 % w/w, meaning that there is 5 mg of clobetasone butyrate per 10 g of cream base; however, the NTP or MP strength description will be just "0.05 %".

Consistency of Strength Units and Alternative Strength Descriptions

Consistency of representation of strength units is also an important safety issue.

Some products have more than one type of units to describe their strength; for example, Epinephrine 1 mg per 1 mL solution for injection may also be described as Epinephrine 1:1000 (as in the Efra Adrenalin product). Similarly, epoetin products may be described either using mass or using units: Janssen's Eprex product uses units (e.g., 1,000 unit per 0.5 mL of epoetin alfa) whereas Roche's Mircera product uses mass (e.g. 600 mcg per 0.6 mL). Lidocaine local anaesthetic products may be described using a percentage strength (e.g., 2 %) or as 20 mg per 1 mL. Sometimes, a product or monograph will reference both strength descriptions. For those products with alternative strength descriptions, the NTP formal name will use mass in SI units wherever possible. Units (international units) should only be used if the manufacturer consistently describes both the product and the dosage schedule using units (as is the case for Eprex or dalteparin products) and no mass strength is provided.

Where products from different manufacturers use different representations of SI units (e.g. 0.02 mg vs 20 mcg) the NTP formal name will use one standard unit. The choice of representation for the unit will consider the following:

- any recommendation by ISMP Canada
- the unit which avoids using a decimal in the strength value
- the unit most commonly used for describing the dosage of the product in the monograph
- the unit most commonly used for describing the strength on the product label and packaging
- the unit used for the product in other national and international terminologies.

For example: combined oral contraceptives as described in DPD have a mix of milligram strengths (with decimals) and microgram strengths; to bring consistency, the estrogenic component will always be described using micrograms and the progestogen component will be described using micrograms or milligrams as appropriate to give whole numbers (e.g., norgestimate will use micrograms and norethindrone acetate will use milligrams). Digoxin products and clonidine products are described and dosed using decimals of milligrams; the NTPs for these products will continue to use milligrams for CCDD representations.

(2) Note that in CCDD NTPs, the term "unit" (and all strength units) will be in the singular form.