SURVEY OF STATE BOARDS OF PHARMACY ON THE COMPOUNDING OF NASAL SPRAYS			
State	Compound under Sterile Conditions?		Comment
	Yes	No	
California		1	
Delaware			DE Law is not specific. They would follow FDA guidelines and would probably require nasal sprays to be compounded under sterile product guidelines.
Iowa		1	
New Jersey	1		
North Dakota	1		
New Mexico	1		
Ohio			Rules do not specifically address the issue
Oklahoma	1		
Pennsylvania			PA Act and Rules do not specifically address the issue. The Board is in the process of promulgating compounding regulations. We expect these new regulations will require adherence to the current USP standards.
Rhode Island	1		
Totals	**5**	**2**	

VOLUME 7 NUMBER 1

Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Compounding Nasal Preparations

Loyd V. Allen, Jr., Ph.D., FACA, FAPhA

PHYSIOLOGY AND FUNCTION

The nose is a portion of the respiratory tract where air enters and leaves the respiratory system. It consists of bone and cartilage and is covered with skin. It contains hairs and mucosa (ciliated epithelium with goblet cells that produce mucus) which help to block the entry of dust and particulate matter. As the air passes through the nasal cavities, it is warmed by the blood supply immediately below the epithelium and humidified by the moisture content of the mucous. Another function of the nose is the sense of smell; olfactory receptors are located in the nasal mucosa.

A number of materials from various sources travel from the nose to the gastrointestinal tract. The mucous aids in entrapping dust, particulates, bacteria, etc.; these entrapped materials are continuously swept by the cilia toward the pharynx where they are eventually swallowed; any bacteria present is destroyed by the hydrochloric acid in the gastric juices. There are four paranasal sinuses that drain into the nasal cavities and, ultimately, into the gastrointestinal tract. Also draining into the nasal cavities are the lacrimal fluids that enter the nose by way of the nasolacrimal duct. Consequently, nasally administered drug products can result in systemic effects by either (1) local absorption through the nasal epithelium, or (2) as a result of being swallowed and absorbed via the gastrointestinal tract.

NASAL ADMINISTRATION

Nasal drug administration has been routinely used for administration of drugs for the upper respiratory tract, especially adrenergic agents, and is now also being used as a viable alternative for the delivery of many systemic therapeutic agents. A number of dosage forms are common and include solutions, suspensions and gels. Nasal solutions are solutions prepared for nasal administration either as drops or sprays. Nasal suspensions are liquid preparations containing insoluble materials for nasal administration, primarily as drops.

Nasal gels are semisolid preparations prepared for nasal application and can be for either local or systemic use, in a water soluble or water miscible vehicle. Nasal ointments are generally prepared from either water miscible/soluble or oleaginous bases.

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APPLICATIONS/USES

The advantages of nasal delivery include (1) lower doses, (2) rapid local therapeutic effect, (3) rapid systemic therapeutic blood levels, (4) rapid onset of pharmacological activity, and (5) relatively few side effects. In addition to the nasal decongestants, saline and other routine locally acting drugs, nasal administration is being investigated for the delivery of insulin, progesterone, metoclopramide, propranolol (for migraine headaches), dihydroergotamine, desmopressin, atropine, vitamin B_{12}, antihistamines, anti-obesity agents, narcotic analgesics and a host of other agents.

An example drug that shows effectiveness upon administration as a nasal gel, as compared to an oral tablet, is vitamin B_{12}, where clinical studies showed a six fold increase in maximum blood levels, a doubling of speed in entering the bloodstream, and a 2.5 fold increase in measurable vitamin B_{12} in the blood 48 hours after administration.[1] Similar results have been reported in other studies.[2-5]

Numerous drug substances can be prepared as nasal solutions or suspensions to be administered either as drops (solutions or suspensions) or sprays (solutions); other dosage forms may include nasal

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The risk of patient-to-patient contamination is very high with nasally administered products, patients should be advised that a nasal product is for ONE PATIENT ONLY.

gels, jellies or ointments. Some drugs are sufficiently volatile they can be carried into the nose through an inhaler.

COMPOSITION(S)

In addition to the active drugs, nasal preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity adjusting agents, gelling agents and possibly antioxidants. Important in the formulation process is the use of ingredients that are nonirritating and compatible with the nose as discussed within each category. In general, the same excipients used in ophthalmic formulations can also be used in nasal formulations.

PREPARATION METHODS/TECHNIQUES

Solutions:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, clarity and other quality control factors from a sample of the solution.
5. Filter through a sterile 0.2 µ filter into a sterile nasal container.
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Suspensions:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve/mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, and other quality control factors from a sample of the suspension.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Suspensions (alternate method):

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Dissolve/mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
4. Add sufficient Sterile Water for Injection to volume and mix well.
5. Determine the pH, and other quality control factors from a sample of the suspension.
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Ointments:

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Mix each of the ingredients with the sterile vehicle.
4. Determine the quality control factors from a sample of the product.
5. Package and label.
6. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Gels:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Filter through a sterile 0.2 µ filter into a sterile container.
4. Add the gelling agent (previously sterilized) and mix well.

5. Add sufficient Sterile Water for Injection to volume/weight and mix well.
6. Determine the pH, clarity and other quality control factors from a sample of the gel.
7. Package and label. (Sterile 1 mL syringes preloaded with individual doses work well).
8. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

PHYSICOCHEMICAL UNIQUENESS OF COMMON INGREDIENTS

The attributes of a vehicle for a nasal solution include:
(1) pH generally in the range of 5.5-7.5,
(2) mild buffer capacity,
(3) isotonic,
(4) not modify the normal mucus viscosity,
(5) compatible with normal ciliary motion and ionic constituents of nasal secretions,
(6) compatible with active ingredient,
(7) stable,
(8) sterile,
(9) and preserved.

pH- Nasal preparations are ordinarily prepared at the pH of maximum stability for the drug(s) they contain; generally in the range of 4-8 is considered optimum. Sometimes it may be necessary to adjust outside this range.

Buffers-The buffers are included to minimize any change in pH during the storage life of the drug. Any changes in pH can affect the solubility and the stability of drugs, consequently, it is important to minimize fluctuations in pH. The buffer system should be designed sufficient to maintain the pH throughout the expected shelf-life of the product but with a low buffer capacity. Phosphate buffer systems are widely used and are generally compatible with most nasal medications.

Tonicity Adjustment-The preferred agents for adjusting the tonicity of nasal solutions include sodium chloride, boric acid and dextrose. Severely hypertonic solutions should be avoided. Nasal fluid is isotonic with 0.9% sodium chloride solution. A value of 300 mOsm/L is ideal with a range of 200-600 mOsm/L being acceptable. If a product is applied that is outside of the proper range, the nasal ciliary movement may slow or even stop. Tonicity values in the range of 0.6% to as high as 1.8% sodium chloride equivalency are generally acceptable. If the solution of the active drug is hypotonic, it may be necessary to add a substance to attain the proper tonicity range. Sodium chloride, boric acid and dextrose are commonly used.

Normal mucous viscosity-Most nasal preparations are aqueous based and generally will not significantly alter the viscosity of the mucous. A strongly hypertonic product, however, may result in a slight "drying" effect and thickening of the mucous. The opposite may occur for a strongly hypotonic product. This can have an adverse effect on the efficiency of the cilia in mucous and particulate removal.

Compatibility-Strict attention must be paid to the compatibility of all the various ingredients, including all the excipients, of the product to ensure a safe, effective and esthetic product.

Stability-Stability is largely influenced by pH, temperature, light, oxidation and other factors. In addition to proper formulation, proper packaging is essential. Occasionally, antioxidants may be required for selected active drug ingredients. The same antioxidants used in ophthalmic products can usually be used in nasal products.

Sterility-Nasal preparations should be sterile. Sterility is conveniently achieved through sterile filtration using a sterile membrane filter of 0.45 or 0.2 μ pore size and filtering into a sterile container. Other methods of sterilizing ingredients include dry heat, steam under pressure (autoclaving) and gas sterilization (ethylene oxide).

Preservation-Since most nasal preparations are prepared in multiple use containers, they must be preserved (unless individual doses are separately packaged). The selected preservative must be compatible with the active drug as well as all the other excipients in the product. Common preservatives that can be used for nasal products are shown in Table 1. Generally, the same preservatives used in ophthalmic formulations can be used in nasal formulations.

Specific Quality Control
Sterility checks, clarity (solutions), pH, volume/weight.

PACKAGING/STORAGE/LABELING

Most nasal preparations are packaged in glass dropper bottles or plastic spray bottles, usually containing 15 to 30 mL of product. Gels are packaged in either tubes or syringes for ease of administration.

Generally, nasal preparations should be stored at either room or refrigerated temperatures and should not be frozen.

STABILITY

Beyond-use dates for water-containing formulations are not later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids, the beyond-use recommendation is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier. For all others, the recommended beyond-use recommendation is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recommendations can be extended if there is supporting valid scientific stability information.

COUNSELING

The risk of patient-to-patient contamination is very high with nasally administered products, consequently, patients should be advised that a nasal product is for ONE PATIENT ONLY and should not be passed around.

Containers for dispensing include dropper bottles, spray bottles and syringes (for gels). For systemic therapeutic drugs, it may be necessary to calibrate a dropper or spray container to deliver a consistent and uniform dose. Therapeutic drugs, such as dihydroergotamine mesylate or morphine sulfate, among others, can be administered after the administration device is calibrated and the patient is taught to use it properly. For potent drugs, it may be advantageous to pre-load individual nebules or 1 cc syringes with each individual dose. After application or administration of the accurately measured dose, the container would be discarded.

It may be necessary to calculate the quantity of drug actually administered per drop or per spray of nasal product. This can be done as follows.

1. Calculation of medication administered per drop of product.
   Using the dropper that will be used by the patient, dropwise, drop the product into a cylindrical graduate until 2 mL of product has been measure, counting the number of drops required. Dividing this number by two, will give the number of drops per milliliter of product. From this information, the required number of drops that will deliver quantity of product can be calculated.

2. Calculation of medication administered per spray of product.

The calibration can be easily accomplished by weighing the container with the solution. keeping in mind the variables of pressure on the container sides, the time the pressure is applied, etc., hold the container in the usual upright position and deliver 10 sprays into a disposable plastic bag. Weigh the container again, subtract from the original weight and divide by 10. This would give an "approximate" volume delivered per squeeze, assuming a specific gravity of 1.0. Obviously it would be best to also have the patient do this to refine the quantity administered under actual use conditions. To accommodate for the differences in specific gravity, viscosity, etc., it may be beneficial to prepare a "blank" solution for practice containing all the ingredients except for the active drug.

EXAMPLE FORMULATIONS

Rx	**General Nasal Solution Vehicle (pH 6.5 and isotonic)**		
	$NaH_2PO_4.H_2O$		0.65
	$Na_2HPO_4.7H_2O$		0.54
	NaCl		0.45
	Benzalkonium chloride		0.05-0.01%
	Distilled Water	qs ad	100 mL

Rx	**Isotonic Sodium Chloride Solution**		
	Sodium Chloride		0.9 g
	Benzalkonium Chloride		1:10,000
	Sterile Water for Injection	qs	100 mL

Rx	**Atropine sulfate 0.5% nasal solution**		
	Atropine sulfate		500 mg
	Sodium chloride		835 mg
	Sterile water for injection	qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the atropine sulfate and the sodium chloride in about 95 mL of water for injection.
4. Add sufficient water for injection to make 100 mL.
5. Filter through a 0.2 µ filter into a sterile container.
6. Package and label.

Rx	**Desmopressin acetate nasal solution 0.033 mg/mL**	
	Desmopressin solution 0.1 mg/mL	2.5 mL
	0.9% Sodium chloride solution	5 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Mix the two solutions together and mix well.
4. Filter through a 0.2 µ filter into a sterile container.
5. Package and label.

Rx	**Saline Nasal Mist**		
	Sodium chloride		650 mg
	Monobasic potassium phosphate		40 mg
	Dibasic potassium phosphate		90 mg
	Benzalkonium chloride		10 mg
	Sterile water for injection	qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the ingredients in sufficient sterile water for injection to make 100 mL of solution.
4. Filter through a 0.2 µ filter into a sterile solution.
5. Package in a nasal spray bottle.

Rx	**Xylometazoline hydrochloride nasal drops**	
	Xylometazoline hydrochloride	100 mg
	Sodium chloride	850 mg
	Benzalkonium chloride	10 mg
	Sterile water for injection qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve all the ingredients in sufficient sterile water for injection to make 100 mL.
4. Filter through a sterile 0.2 µ filter into a sterile container.
5. Package and label.

Rx	**Progesterone nasal suspension**	
	Progesterone	20 mg
	Dimethyl-β-cyclodextrin	62 mg
	Sterile water for injection	1 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the dimethyl-β-cyclodextrin in 0.9 mL of sterile water for injection.
4. Add the progesterone and stir until dissolved.
5. Adjust the pH to 7.4 using either dilute hydrochloric acid or dilute sodium hydroxide solution.
6. Add sufficient sterile water for injection to make 1 mL.
7. Package and label.

Rx	**Scopolamine hydrobromide 0.4 mg/0.1 mL nasal solution**	
	Scopolamine hydrobromide	400 mg
	pH 5.0 buffer	5 mL
	in 0.9% Sodium chloride solution qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the scopolamine hydrobromide in about 50 mL of the 0.9% sodium chloride solution.
4. Add the pH 5.0 buffer and mix well.
5. Add sufficient 0.9% sodium chloride solution to volume and mix.
6. Filter through a 0.2µ sterile filter into a sterile container.
7. Package in a metering nasal spray container and label.

Table 1. Common preservatives used in nasal products.

Name	Usual Concentration (%)
Chlorobutanol	0.5
Benzalkonium Chloride	0.004-0.02
Benzethonium Chloride	0.004-0.02
Phenylmercuric Acetate	0.001-0.01
Phenylmercuric Nitrate	0.001-0.01
Thimerosal	0.01
Parahydroxybenzoates	0.1

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Model Standards for Pharmacy Compounding of Non-hazardous Sterile Products

DRAFT 2 A

National Association of Pharmacy Regulatory Authorities

(adapted with permission from "Préparation de produits stériles non dangereux en pharmacie – Norme 2014.01," Ordre des pharmaciens du Québec, 2014)

3. REGULATORY FRAMEWORK

Many health care professionals prepare compounded sterile products, including nurses, physicians, pharmacists and pharmacy technicians. However, the majority of sterile compounding is performed by or under the supervision of pharmacists. Therefore, these standards pertain specifically to pharmacists, pharmacy technicians and pharmacies where compounded sterile products are prepared.

The preparation of medications has always been an integral part of the practice of pharmacy. It is essential to the delivery of health care and allows for personalized therapeutic solutions to improve patient care. However, it must always be carried out within an individual physician–patient–pharmacist relationship (i.e., from a prescription) or within a pharmacist–patient relationship for a specific need (e.g., with over-the-counter preparations). Provincial/territorial pharmacy regulatory authorities are responsible for verifying a pharmacy's preparation services in these situations.

In situations involving requests to compound preparations outside an individual physician–patient–pharmacist relationship, without a prescription, the compounding activities fall under the federal legislative framework. The same federal legislative framework applies to bulk preparation of compounded products and to shipments across provincial/territorial borders.

Health Canada is the federal department responsible for the *Food and Drugs Act* and the *Controlled Drugs and Substances Act* and their associated regulations. In January 2009, Health Canada developed its "Policy on Manufacturing and Compounding Drug Products in Canada"[5]. At the time these Model Standards were prepared, Health Canada was examining this policy with a view to creating new standards for situations not covered within the practice of pharmacy or under the current federal licensing framework.

The NAPRA professional competencies for Canadian pharmacists and pharmacy technicians at entry to practice provide guidance for developing an ethical, legal and professional practice. One of these competencies specifies that a pharmacist or pharmacy technician must seek guidance when uncertain about his or her own knowledge, skills, abilities or scope of practice. Therefore, individuals who do not have the training, expertise, facilities or equipment required to compound sterile products must refer patients to a pharmacist who does offer this service or, where permitted by provincial/territorial legislation, ask a colleague to compound the product for them.

Compounded sterile preparations include the following types of medications:

- nasal sprays
- respiratory therapy solutions
- solutions for live organ and tissue or graft baths
- solutions for injection (e.g., intramuscular, intravenous, intrathecal, intradermal, subcutaneous)
- irrigation solutions for wounds and body cavities
- ophthalmic drops and ointments
- otic drops for intratympanic administration
- parenteral nutrition solutions
- dialysis solutions
- solutions for intradermal injection (allergens)
- topical preparations

[5] Health Canada, Health Products and Food Branch Inspectorate. Policy on manufacturing and compounding drug products in Canada. POL-051. Ottawa, ON: Health Canada; 2009. Available from: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol_0051-eng.php

Nasal formulations and their quality requirements

Presented to Nevada Board of Pharmacy

on behalf of Maple Pharmacy

Las Vegas, Nevada

July 24, 2014

Sterile vs. Non-sterile

USP Chapter <797> (USP 37-NF 32) states:

"CSPs include any of the following: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants".

Body Cavities

Sterile

- Thoracic
- Spinal
- Abdominal
- Pelvic
- Abdominopelvic

Dosage forms administrated into these cavities need to be sterile

Nonsterile

- Alimentary canal (Mouth/Nose → Rectum)
  - Inherently and naturally contaminated and dosage forms need to be clean

Products that don't require sterility

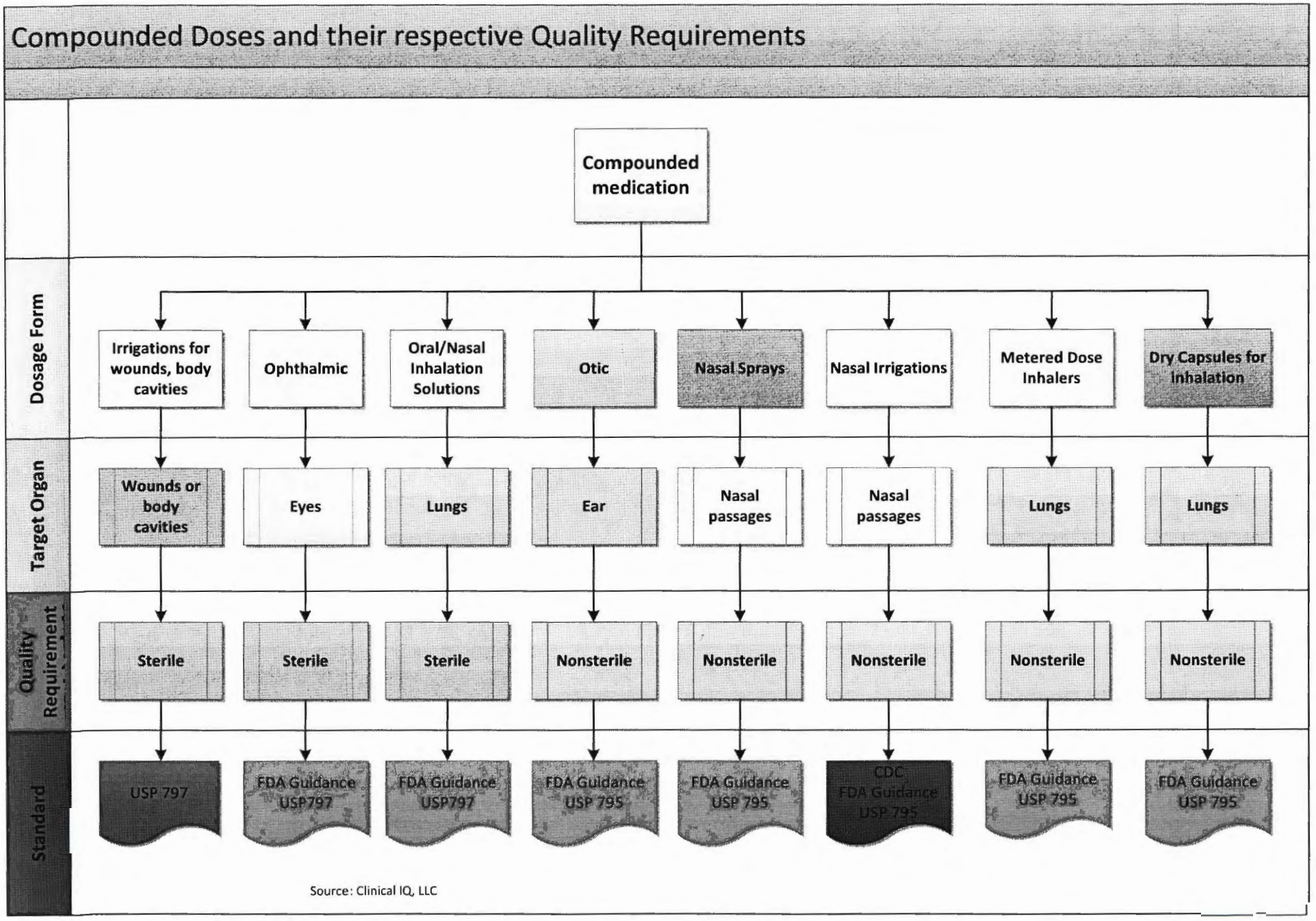
- Topicals, oral solid and liquid dosage forms, otics and nasal solutions.
- These formulations are compounded according to USP Chapter <795> Pharmaceutical Compounding-Nonsterile Preparations

FDA Position

- 2002 FDA Industry Guidance Document-Nasal sprays are not required to be sterile
  - Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51)
  - Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer.
  - Nasal Sprays are not subject to this rule.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf

- This position has not changed according to correspondence with a FDA Senior Microbiologist at CDER on June 26, 2014.


Compounded Doses and their respective Quality Requirements
Compounded medication
Dosage Form
Irrigations for wounds, body cavities
Ophthalmic
Oral/Nasal Inhalation Solutions
Otic
Nasal Sprays
Nasal Irrigations
Metered Dose Inhalers
Dry Capsules for Inhalation
Target Organ
Wounds or body cavities
Eyes
Lungs
Ear
Nasal passages
Nasal passages
Lungs
Lungs
Quality Requirement
Sterile
Sterile
Sterile
Nonsterile
Nonsterile
Nonsterile
Nonsterile
Nonsterile
Standard
USP 797
FDA Guidance USP797
FDA Guidance USP797
FDA Guidance USP 795
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CDC FDA Guidance USP 795
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