

Table 1. ISO Classification of Particulate Matter in Room Air (limits are in particles of 0.5 μm and larger per cubic meter [current ISO] and cubic feet [former Federal Standard No. 209E, FS 209E])*

ISO Class	Class Name	Particle Count	
		ISO, m^3	FS 209E, ft^3
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

* Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3,520 particles of 0.5 μm or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) ($1 \text{ m}^3 = 35.2 \text{ ft}^3$).

The standards in this chapter are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared (e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, physicians' practice facilities, and other locations and facilities in which CSPs are prepared, stored, and transported). Persons who perform sterile compounding include pharmacists, nurses, pharmacy technicians, and physicians. These terms recognize that most sterile compounding is performed by or under the supervision of pharmacists in pharmacies and also that this chapter applies to all healthcare personnel who prepare, store, and transport CSPs. For the purposes of this chapter, CSPs include any of the following:

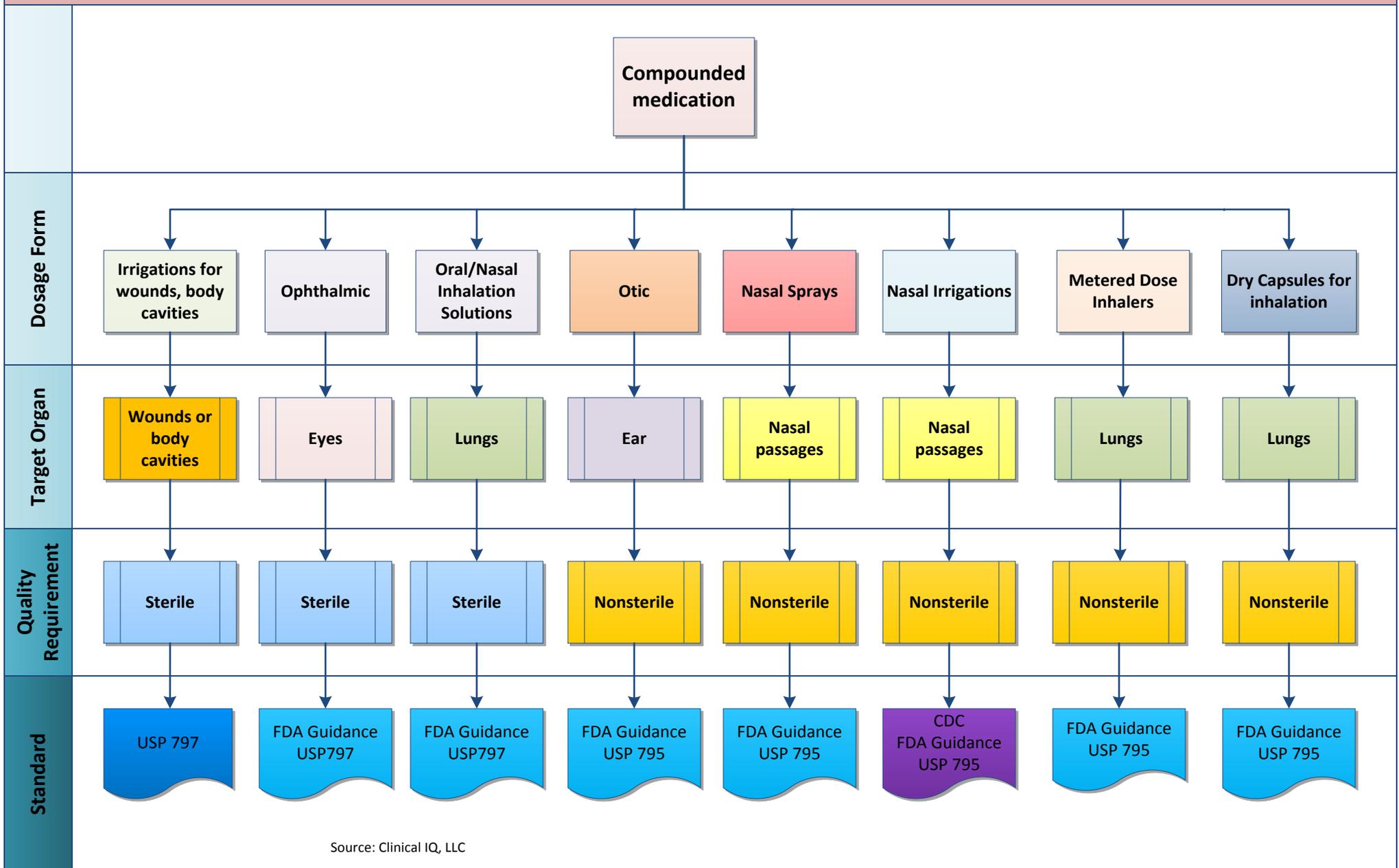
- (1) Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.
- (2) Manufactured sterile products that are either prepared strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) or prepared differently than published in such labeling. [NOTE—The FDA states that "Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling" [21 USC 321 (k) and (m)]. However, the FDA-approved labeling (product package insert) rarely describes environmental quality (e.g., ISO Class air designation, exposure durations to non-ISO classified air, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be prepared for administration). Beyond-use exposure and storage dates or times (see *General Notices and Requirements and Pharmaceutical Compounding—Nonsterile Preparations (795)*) for sterile products that have been either opened or prepared for administration are not specified in all package inserts for all sterile products. Furthermore, when such durations are specified, they may refer to chemical stability and not necessarily to microbiological purity or safety.]

ORGANIZATION OF THIS CHAPTER

The sections in this chapter are organized to facilitate the practitioner's understanding of the fundamental accuracy and quality practices for preparing CSPs. They provide a foundation for the development and implementation of essential procedures for the safe preparation of low-risk, medium-risk, and high-risk level CSPs and immediate-use CSPs, which are classified according to the potential for microbial, chemical, and physical contamination. The chapter is divided into the following main sections:

- Definitions
- Responsibility of Compounding Personnel
- CSP Microbial Contamination Risk Levels
- Personnel Training and Evaluation in Aseptic Manipulation Skills
- Immediate-Use CSPs
- Single-Dose and Multiple-Dose Containers
- Hazardous Drugs as CSPs
- Radiopharmaceuticals as CSPs
- Allergen Extracts as CSPs
- Verification of Compounding Accuracy and Sterility
- Environmental Quality and Control
- Suggested Standard Operating Procedures (SOPs)
- Elements of Quality Control
- Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding
- Finished Preparation Release Checks and Tests
- Storage and Beyond-Use Dating
- Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs
- Patient or Caregiver Training

Compounded Doses and their respective Quality Requirements



Nasal formulations and their quality requirements

Presented to Nevada Board of Pharmacy
on behalf of Maple Pharmacy

Las Vegas, Nevada

July 24, 2014

Introductions

John L. Quick

Mr. Quick holds an Undergraduate degree in Chemistry from Indiana University with a Masters from Northwestern Kellogg School of Management. He has 47 years experience in drug and pharmacy compounding including 37 years with Baxter International with the last 10 years as the Corporate Worldwide VP Quality/Regulatory. He was responsible for Baxter's Pharmacy compounding operations during that period of time which were sold to PharMEDium. He is currently associated with Maple Pharmacy, Las Vegas, NV.

Introductions

Eric Kastango

Mr. Kastango holds a bachelor of Pharmacy from Massachusetts College of Pharmacy and Health Sciences with a Masters from the University of Phoenix. He was elected member of the USP Sterile Compounding Committee from 2005-2010. He was recently re-elected to the 2010-2015 USP Compounding Expert Committee and is currently the chairperson of the USP Chapter subcommittee. In May, 2014 he was recognized by the NABP with the Henry Cade Memorial Award at the NABP meeting in Phoenix. He publishes extensively in the area of pharmacy compounding.

Introductions

Dr. Alan Shikani

Dr. Shikani is a clinician, researcher, teacher and inventor and is an accomplished physician in the field of Otolaryngology. He did his residency and fellowship training at Johns Hopkins. Dr. Shikani is the founder and director of the Maryland Ear, Nose and Throat Center. Physicians from around the world come to Maryland to spend a year with specializing in diseases of the nose and sinuses. Dr. Shikani has received numerous awards and recognitions in his area of specialty.

Dr. Shikani is present today to specifically address any questions in regard to the ENT medical practice and the use of nasal sprays.

Introductions

Dr. William Kottmer

- Dr. Kottmer received his Doctor of Pharmacy Degree from Midwestern University College of Pharmacy – Glendale. His entire career has been based in compounding, starting as a hospital IV tech in 2004. He received his Authorized Nuclear Pharmacist certificate from the University of New Mexico and has worked as both a home infusion and nuclear pharmacist until joining Maple Pharmacy in Las Vegas.
- He is currently the Pharmacist-in-Charge at Maple.

Disclaimer

Eric S. Kastango, MBA, RPh, FASHP is Principal/CEO
Clinical IQ , LLC and CriticalPoint, LLC.

I am also an Consultant to NABP, many State Boards of Pharmacy and an Expert Consultant to the USP but am speaking today in my individual capacity and not for USP or other organizations.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP or any other organization I may be associated with, nor should they be construed as an official explanation or interpretation of USP Chapter <797>.

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".

Other Board of Pharmacy Positions

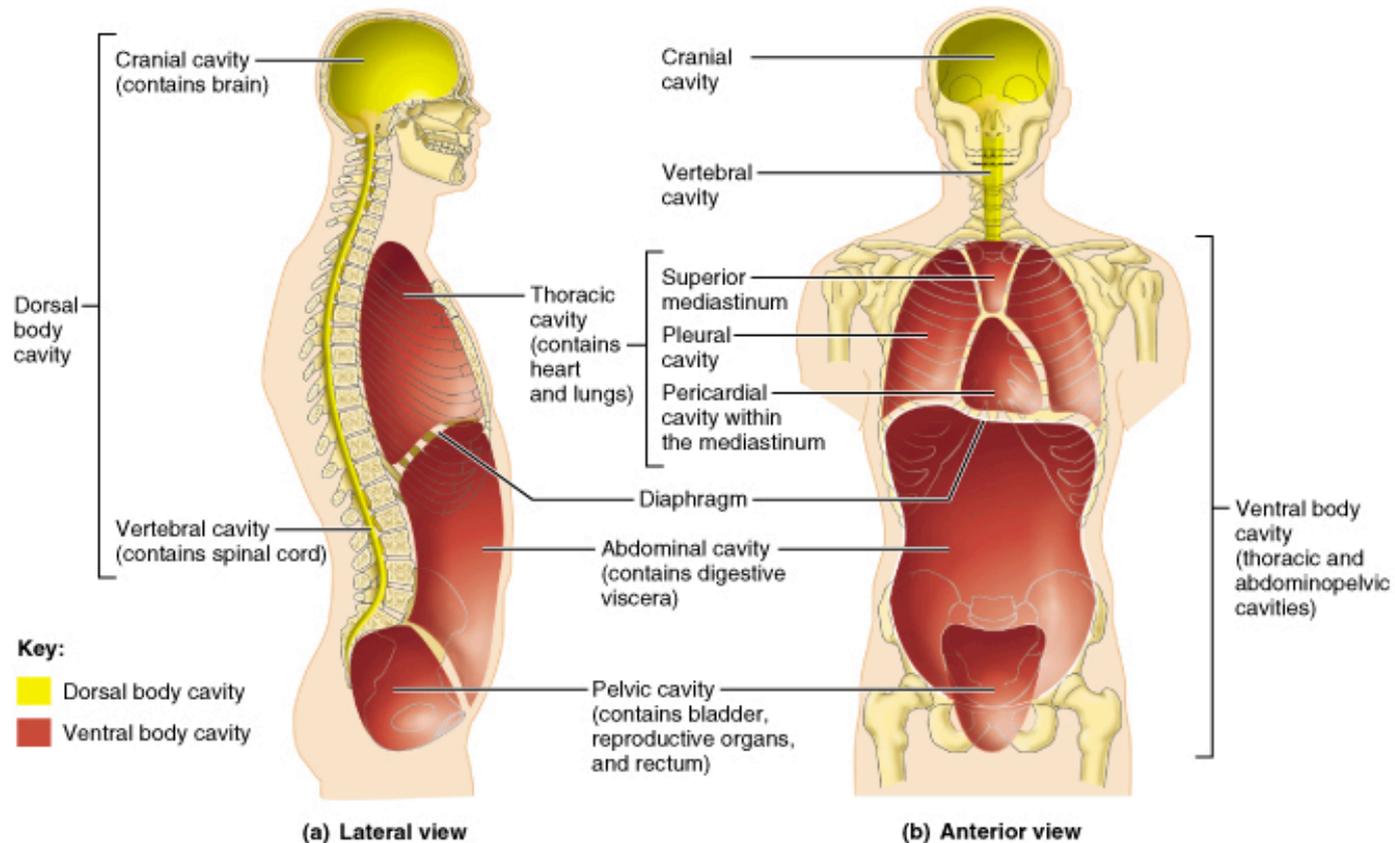
- Iowa Board of Pharmacy Rules and Regulation
 - "Nasal inhalation" means a drug product or preparation, including the delivery device if applicable, whose intended site of deposition is the respiratory tract or the nasal or pharyngeal region. Nasal inhalation does not include a topical nasal spray or irrigation that is deposited primarily in the nasal passages".

Products that require sterility

- During development of the first USP 797 in 2001-2003, the USP sterile compounding committee asked FDA liaison, Dr. Kathy Anderson, for a list of administration routes that required therapies to be sterile. That list included body cavities that are normally sterile, e.g., urinary bladder and peritoneal space.
- Nasal passages were not included, because they are normally colonized with multiple types of microorganisms.
- Dr. Anderson's FDA list is the basis for the initial and current requirements for sterility of dosage forms and administration routes stated in the introduction to USP 797.

Source: Dr. David W. Newton, PhD, Chairman of USP Sterile Compounding Expert Committee, 2000-2010

Body Cavities



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Body Cavities

Sterile

- Thoracic
- Spinal
- Abdominal
- Pelvic
- Abdominopelvic



Dosage forms administered 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

Sterile vs. Non-sterile

USP Chapter <795> states:

- “The preparation is made in accordance with this chapter, other official standards referenced in this chapter, and relevant scientific data and information.”
- “*Purified Water* (see *Purified Water* monograph) shall be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water. *Purified Water* should be used for rinsing equipment and utensils.”

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.

FDA Position Continued

- Guidance for Industry – Sterility Requirement for Aqueous-Based Products for Oral Inhalation – Small Entity Compliance Guide
- FDA Q&A – Page 2 of Guidance
 - **“Is the product I manufacture subject to this rule”?**
 - “If you manufacture an aqueous-based oral inhalation drug product, your drug product is subject to this rule and must be manufactured sterile. This rule applies to drug products packaged in both single-dose and multiple-use primary packaging. ***Nasal spray drug products are not subject to this rule***”. (FDA emphasis).

FDA Position

FDA Consumer Update Resource: "Is Rinsing Your Sinuses Safe?"

- "What types of water are safe to use in nasal rinsing devices?"
 - *Distilled or sterile water you can buy in stores. The label will state "distilled" or "sterile."*
 - *Previously boiled tap water" or filter through a 1.0 micron filter*
 - *Neither of which results in "sterile".*

Is Rinsing Your Sinuses Safe?

Little teapots with long spouts have become a fixture in many homes for reasons that have nothing to do with tea.



Called neti pots, they are used to rinse the nasal passages with a saline (salt-based) solution, and have become popular as a treatment for congested sinuses, colds and allergies, and for moistening nasal passages exposed to dry indoor air.

However, the Food and Drug Administration (FDA) has concerns about the risk of infection tied to the improper use of neti pots and other nasal rinsing devices. The agency is informing consumers, manufacturers and health care professionals about safe practices for using all nasal rinsing devices, which include bulb syringes, squeeze bottles, and battery-operated pulsed water devices.

These devices are generally safe and useful products, says Steven Osborne, M.D., a medical officer in FDA's Center for Devices and Radiological Health (CDRH). But they must be used and cleaned properly.

Most important is the source of water that is used with nasal rinsing devices. Tap water that is not filtered, treated, or processed in specific ways is not safe

for use as a nasal rinse.

Some tap water contains low levels of organisms, such as bacteria and protozoa, including amoebas, which may be safe to swallow because stomach acid kills them. But these "bugs" can stay alive in nasal passages and cause potentially serious infections, according to the Centers for Disease Control and Prevention (CDC).

Improper use of neti pots may have caused two deaths in 2011 in Louisiana from a rare brain infection that the state health department linked to tap water contaminated with an amoeba called *Naegleria fowleri*.

Misleading, Missing Information

Information included with the device might give more specific instructions about its use and care. However, FDA staff has found that some manufacturers' instructions provide misleading or contradictory information, or lack any guidelines.

For example, some manufacturers have recommended using plain tap water; others warn against using it in printed directions, but show its use in pictures or videos.

CDC Position

- CDC website: Sinus Rinsing & Neti Pots
 - Distilled or sterile water is used to prevent infections. The solution does not have the requirement to be sterile

The screenshot shows the CDC website page for *Naegleria fowleri* - Primary Amebic Meningoencephalitis (PAM). The page is titled "Sinus Rinsing & Neti Pots" and includes a navigation menu on the left with options like "General Information", "Illness & Symptoms", "Pathogen & Environment", "Sources of Infection & Risk Factors", "Diagnosis & Detection", "Treatment", "Prevention & Control", "Swimming", "Tap & Faucet Water", "Sinus Rinsing & Neti Pots", "Ritual Nasal Rinsing & Ablution", "Public Drinking Water Systems", "Naegleria fowleri in Louisiana Public Water Systems", "Public Health & Medical Professionals", "Publications, Data, & Statistics", "Health Promotion Materials", "CDC at Work: Naegleria fowleri", "Policy & Recommendations", "Related Links", "Parasites A-Z Index", "Parasites Glossary", "Index of Water-Related Topics", and "Laboratory Diagnostic Assistance [DPDX]".

The main content area includes a search bar, a navigation breadcrumb "Parasites Home > Naegleria fowleri > Prevention & Control > Tap & Faucet Water", and social media sharing options. The title "Sinus Rinsing & Neti Pots" is followed by a paragraph: "Very rarely, *Naegleria fowleri* infections have been reported when people submerge their heads¹⁻² or irrigate their sinuses (nose)²⁻³ using contaminated tap water. If you are making a solution for irrigating, flushing, or rinsing your sinuses (for example, by using a neti pot, sinus rinse bottle, or other irrigation device), use safe water to protect yourself."

Below this is a section titled "Take at least one of these actions to lower your risk of becoming infected:" followed by a list of actions:

- **Boil:** Use water that has been previously boiled for 1 minute and left to cool.
 - At elevations above 6,500 feet, boil for 3 minutes.
- **Filter:** Use a filter designed to remove some water-loving germs.
 - The label may read "NSF 53" or "NSF 58."
 - Filter labels that read "absolute pore size of 1 micron or smaller" are also effective.
- **Buy:** Use water with a label specifying that it contains distilled or sterile water.
- **Disinfect:** Learn how to disinfect your water to ensure it is safe from *Naegleria*.
 - Chlorine bleach **used at the right level and time** will work as a disinfectant against this germ.

Additional text includes: "Rinse the irrigation device after each use with safe water, and leave the device open to air dry completely." and "For more information on neti pots and other nasal rinsing devices, see FDA's Consumer Update: [Is Rinsing Your Sinuses Safe?](#)"

There is a section for "References" with three numbered items:

1. Louisiana Department of Health & Hospitals. [LHH Confirms Death of a Child Associated with Rare Amoeba Found in St. Bernard Parish Home](#). 6 September 5, 2013.
2. Dorosh MM, Cameron AC, Robinson DG. [The epidemiology and control of primary amebic meningoencephalitis with particular reference to South Australia](#). *Trans R Soc Trop Med Hyg*. 1993;77(1):172-7.
3. Yoder JS, Steif-Bourgeois S, Roy SL, Moore TA, Viveiros GS, Retard RC, Hill V, Wilson JD, Linscott AJ, Croger R, Kozak NA, Stram R, Narayanan J, Mull B, Kahler AM, Schneebarger C, da Silva AJ, Beach MJ. [Deaths from *Naegleria fowleri* associated with sinus irrigation with tap water: a review of the changing epidemiology of](#)

On the right side of the page, there is a "Contact Us" section with the following information: "Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, 800-CDC-INFO (800-232-4636), TTY: (888) 232-6348, [Contact CDC-INFO](#)". There is also a "Neti pots look like little teapots with long spouts and are used to rinse the nasal passages with a saline (salt-based) solution. They have become popular as a treatment for congested sinuses, colds, and allergies, and for moistening nasal passages exposed to dry indoor air." and a note: "If you are making a solution for irrigating, flushing, or rinsing your sinuses (for example, by using a neti pot), use the right kind of water to protect yourself."

Thank you for your consideration