UPDATES

The State of Alabama vs. *SERRATIA MARCESCENS*

Discovered in 1819 by the Venetian pharmacist Bartolomeo Bizio and named in honor of the physicist Serafino Serrati, *Serratia marcescens* is a bacterium frequently responsible for catheter-associated bacteremia, urinary tract and wound infections. Flourishing in damp environments, it can be found in locations near tile grout, showers, faucets or even the toilet water line. In worst-case scenarios, *Serratia marcescens* can cause fatalities.

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The Case of the Contaminated TPN

In March 2011, the Alabama Department of Public Health was alerted by several local hospitals of an outbreak of *Serratia marcescens* bacteremia that apparently affected at least 19 hospital patients, of which at least 9 have since died.

Initial investigations linked the bacteremia with TPN (total parenteral nutrition) that all of the affected patients had received, and which had been delivered through an IV using a catheter.

Further investigations apparently confirmed that all of the suspected TPN had been supplied and manufactured by **Meds IV** of Birmingham, AL.

Meds IV, a Birmingham, AL, based pharmacy and in this instance also the manufacturer of the TPN, agreed to recall the product, and the Alabama Department of Public Health as well as Federal Centers for Disease Control and Prevention started their investigation.

Their preliminary findings suggest the following:

Staff at Meds IV's compounding room apparently used tap water to wash the product mixing vessels before rinsing them with sterile water. Samples taken from the water tap used were genetically fingerprinted and compared with the strains isolated in the TPN as well as 12 of the affected patients: it was a match. During the mixing of the TPN components, which included amino acids, residual *Serratia marcescens* bacteria may have been transferred from the mixing vessels to the product. In spite of an online filtration process, using 0.2-micron filters, the bacteria (or at least some of them) remained in the final TPN product before being filled into IV pouches.

What is "TPN"?

Total parenteral nutrition is indicated when a patient's gastrointestinal tract is non-functional or needs to be by-passed. It thus prevents the effects of malnutrition and provides the patient with nutrients, such as salts, glucose, amino acids, lipids, and vitamins.

Providing a patient with TPN is an *unnatural* way of feeding and can at times lead to complications, which may include infections, blood clots, fatty liver and/or liver failure, cholecystitis, and/or other hepatobuliary dysfunctions.

TPN is delivered using a medical infusion pump, which infuses a small amount of TPN from a sterile bag of nutrient solution (containing in volume between 500 ml to 4 liters). The infusion is delivered through a central intravenous catheter, usually through the subclavian or jugular vein with the tip of the catheter at the superior vena cava without entering the right atrium.

Enter: Meds IV

According to the records of the Alabama Secretary of State, **Meds IV LLC** is a Limited Liability Company with two members, namely **Edward Cingoranelli** and **William Rogers**. Not so according to the company's registration with the National Plan & Provider Enumeration System ("NPPES"), where "Meds IV" is shown as "Meds IV, Inc.", which in turn is identified as the "doing business as" name of Advanced Specialty Pharmacy LLC. According to the "Business Entity Annual Report 2010 filed with the Alabama Secretary of State, Advanced Specialty Pharmacy LLC has two members, namely **William Rogers** (who is shown as "President") and **Edward Cingoranelli**. Both of these companies appear to operate from premises at 102 Oxmoor Road, Suite 118, Birmingham, AL.

Next door (in Suite 120) is "PalliRx, Inc.". According to its website (www.pallirx.com), PalliRx offers "points-of-care" dispensing facilities. Records kept by the Alabama Secretary of State show that this company has an authorized capital of $15, and that the registered agent is: **Edward Cingoranelli**.

Suite 118 of the same building at 102 Oxmoor Road in Birmingham, AL, is listed as the registered address of "MedWorks RX LLC", of which **Anthony Cingoranelli** is a member. The Alabama Secretary of State was

informed that the business of this company is the sale of pharmaceuticals to physicians/healthcare providers.

Conspiracy Theorists at Work

As could be expected, some individuals have used the medium of anonymous Internet Blogs to "connect the dots", and infer from the existence of Meds IV, Advanced Specialty Pharmacy, and PalliRx, as well as the location from which each of these entities operate(d), and the involvement of William Rogers and Cingoranelli family members a sinister conspiracy (see, for instance, the "People-liking-People" Blog comments and "conclusions" at http://peoplelikingpeople.blogspot/2011/03/meds-iv-advanced-speciality-pharmacy.html).

The same individuals also claim that the current off-line status of www.medsiv.net and the removal of William Rogers' "LinkedIn' page support their view that blood is being "washed away" from guilty hands.

Whilst these "suspicions" can presently be cast aside as rather uninformed and at best speculative, the danger they pose becomes evident when the same individuals state that "*as people begin to make the connection* [they] *will steer clear of everything relating to Rogers and Cingoranelli*".

These "conspiracy theorists" completely ignore the fact that it is neither illegal nor unusual for several individuals (or entities) to be involved in, and operate, separate companies; they also ignore the more important fact that even the most conscientious and reputable manufacturers of pharmaceutical and/or life-science products can, unfortunately, experience a manufacturing issue that may ultimately result in a product recall.

In the month of March 2011 alone, the US Food and Drug Administration published a total of 41 recall notices, of which 15 concerned pharmaceutical and life-science products. Therefore, would anyone seriously suggest that Del Monte is involved in dubious and/or suspicious activities because it recalled potentially salmonella-infected cantaloupes from Panama, or Eli Lilly because it recalled Forteo Starter Kits when it became aware of possibly bacillus cereus infected preparation pads?

These "conspiracy theorists" operate on the principle that, regardless of the facts, anyone deserves a fair trial before being hung.

Let's stick with the facts instead: The investigations by the Alabama Department of Public Health and other agencies are not yet concluded. Litigation has been started against the hospitals where the contaminated TPN was dispensed as well as Meds IV. Additional as well as new facts may emerge as time goes by that may assist in the determination how *Serratia marcescens* materialized at the manufacturing premises of Meds IV, what was done to maintain a sterile manufacturing environment, and/or why the filtration process did not capture the bacteria.

"Operation Sea Spray"

Serratia marcescens has an illustrious history. Leonard Cole (in "Clouds of Secrecy", Rowman & Littlefield 1988) and Ed Regis (in " The Biology of Doom", Holt Paperbacks, 2000) both claim that on September 26 and 27, 1950, the US Navy conducted a secret experiment named "Operation Sea Spray" during which *Serratia marcescens* was released from bursting balloons over suburban areas in the San Francisco Bay, causing 11 persons to be hospitalized and 1 fatality (named as Edward J. Nevin). They also allege that there was an increase in pneumonia cases following the release.

Blood on the Eucharist?

Since *Serratia marcescens* can manifest itself as a pink discoloration on surfaces and has an ability to grow on bread, claims have been made that the "miraculous" appearance of blood on the Eucharist that let Pope Urban IV to instituting the Feast of Corpus Christi in 1264 was in reality attributable to the use of *Serratia marcescens*-infected bread.

Previous Cases

There is at least one previous case of a known *Serratia marcescens* contamination: In 2008, a nationwide recall was made when pre-filled Heparin IV flush syringes were found to be contaminated by *Serratia marcescens*, resulting in patient infections.

Product Contamination

Instances of the contamination of pharmaceutical and life-science products – fortunately – do occur infrequently. Several distinctions have to be made:

(a) "Harmless" contamination: is an accidental contamination of the pharmaceutical or life-science product by one or more substances that neither affect the efficacy nor the safety of the product itself, but still leads to an impurity that was neither intended nor desired;

(b) "Harmful" contamination: is an accidental contamination by one or more substances that affect either the efficacy or the safety of the product itself (or both), and leads to an unintended and undesired impurity;

(c) "Adulteration": is a deliberate and intentional contamination of the product by one or more substances, irrespective of the consequences (which may either be harmless or harmful).

Regardless of the reasons why a contamination occurred, *current Good Manufacturing Practices* ("cGMP") call upon the drug manufacturer to have a procedure in place (usually in the form of a *Standard Operating Procedure*) for the investigation of such contamination incident (or, in fact, any other irregularity or *deviation*), to investigate the incident, to determine the root cause, and to consider possibilities of corrective action. In addition, the contaminated product should be withheld from further distribution, and in appropriate instances, recalled.

Standard Operating Procedures

The manufacturing process, the handling and storage of finished and unfinished drug products, the packing and shipping, as well as the criteria applied before the product is released for distribution are all governed by Standard Operating Procedures ("SOPs") that the drug manufacturer will have created with specific reference to a drug product.

Even though well-established drug manufacturing companies have been operating for many years, especially new drugs must invariably trigger a complete review of all SOPs to ensure both product safety and integrity. Drugs requiring storage at +2/+8 degrees C have to be treated differently from those that can be exposed to ordinary room temperatures. Deep frozen drugs (at -60 degrees C or less) have their own storage, handling, and transport requirements. There is no such thing in SOPs as "one fits all".

Drafting SOPs is both a complex and complicated process, and requires extensive inter-departmental cooperation. The draftsman has to consider each step of the manufacturing process (beginning from the moment raw materials are purchased and shipped to the manufacturing site), have intrinsic knowledge of the drug specifics, characteristics, and requirements, and essentially consider an endless number of hypothetical scenarios to create all of the needed safeguards to allow the ultimate patient to receive the final product at the dispensing pharmacy.

Not unlike Frederic the Great, King of Prussia, in his desire to create an all-encompassing body of constitutional, administrative, civil, and criminal law codex that left nothing to chance (or, as he allegedly claimed, to misconstruction by lawyers), a body of SOPs will often be a "work in progress", leading to revisions and updates as the passage of time provides new and previously unexpected learning experiences.

By way of example: Drug products sold in the US are at times manufactured elsewhere, for instance in Europe, and may thus be shipped to the US, nicely stacked, on Euro pallets, which have different dimensions than US pallets.

The product distribution in the US may thus require the drug product to be transferred from Euro pallets to US pallets, which is likely to result in a different quantity of drug cartons from more than one Euro pallet ending up on a US pallet. *Prior to* such transfer, the incoming drug product must be checked and examined, for instance for potential adverse temperature exposures during earlier transit stages because once the pallet transfer has taken place, it may no longer be possible to determine which products were potentially affected by temperature abuse, and which were not. Hence, the "Shipping" SOP should provide for this step to take place *before* the re-stacking of the drug shipping cartons on US pallets. An omission to require this step has the potential of turning into an expensive mistake, requiring the possible destruction of the entire consignment instead of a small proportion that can be traced back to the potential temperature abuse.

Back to Alabama…

Meanwhile, the Alabama Department of Public Health and other agencies are continuing their investigations as to how and why *Serratia marcescens* was present at the TPN manufacturing site, and the pending litigation will no doubt bring to light whether Meds IV took all appropriate steps to prevent bacterial presence and/or eliminate potentially present contaminants.

It is also to be expected that Meds IV's cleaning supply purchase records will be scrutinized diligently since apparently, the most effective way to prevent the presence or spread of *Serratia marcescens* is extensive use of – common household bleach.

….and *FINALLY:*

The Food Safety Modernization Act has come into force, extending registration requirements with the FDA, record keeping rules, and introducing foreign food manufacturer verification processes apart from bestowing a recall authority on the FDA.

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