

And Then There Was One: Comments on the Price Rise for MAA and DTPA

On February 25, Jubilant DraxImage (Kirkland, Québec), the sole North American manufacturer of both macroaggregated albumin (MAA) and diethylenetriamine pentaacetic acid (DTPA), announced large price increases for both agents. This has caused considerable concern among some SNMMI leaders and nuclear medicine physicians about the viability of the radionuclide lung scan as a primary diagnostic study for pulmonary embolism.

Gary Dillehay, MD, then SNMMI president, stated in an April 17 letter to the membership the society's opposition to the price increase and its concern over the possible impact on the volume of radionuclide lung scans. A survey compiled by Arlington Medical Research (AMR; Exton, PA) has already documented a 40% drop in ventilation/perfusion (V/Q) study volumes in the past decade, primarily in favor of CT pulmonary angiography (CTPA) (Fig. 1). DraxImage has justified these large price increases by citing the need to ensure supply sustainability and reliability. The company indicated that the choice was between maintaining the existing price structure, which would have forced its exit from this market, or undertaking this one-time (albeit large) price adjustment to allow continued production and re-investment to ensure long-term sustainability and reliability of MAA as well as DTPA for ventilation studies (note that this is an off-label use of ^{99m}Tc -

DTPA for this clinical application). DraxImage chose the latter pathway. Although pricing structures differ geographically and/or by radiopharmacy supplier, the general increase for MAA and DTPA multidose vials is from \$15–\$20 up to \$411 and from \$17 up to \$121, respectively. Unit doses rose from ~\$15–\$20 to \$110 for MAA and from \$18–\$20 to \$65 for aerosol DTPA.

Although this represents a significant impact on most hospital budgets, it does not seem greatly out of line when compared with other commonly used radiopharmaceutical unit doses. In the greater New York area, for example, kidney agents such as MAG-3 and DMSA are \$260 and \$430, respectively, and other agents such as Ceretec, ^{111}In -DTPA, and OctreoScan range from \$1,500 to \$3,000. In fact, some individuals believe that MAA has been underpriced for years when compared with these other agents. The timing of the increase presented a problem because most hospital budgets for materials such as radiopharmaceuticals are set in October of the prior year. Therefore, putting these increases into effect on May 1 had a budget timing impact on many hospitals. One helpful factor is that Medicare's Hospital Outpatient Prospective Payment System has raised reimbursement for V/Q imaging from \$336.40 in 2013 to \$430.87 in 2014. Although this softens somewhat the DraxImage price increase, it does not remove the subjective concern that fewer V/Q exams will be performed in favor of CTPA studies.

In the United States, >95% of end user patient doses are provided by commercial radiopharmacies, and prices are negotiated directly from the manufacturer by large private radiopharmacies. Examples include Cardinal Health and United Pharmacy Partners Inc. (UPPI), a commercial pharmacy network and trade association with 83 member nuclear pharmacies acting as group purchasing organizations. UPPI provides purchasing power and customer service, such as reimbursement specialists and continuing education support. UPPI has expressed its own concern about the impact of these price increases on the future of V/Q imaging. Several medical centers have canceled standing orders of reserve MAA and have opted to obtain it on a "need only" basis.

To better understand the overall dilemma and reasons for the price increase, it is helpful to review the history of radionuclide lung scanning, the problems associated with its production, and possible alternatives.

History

Following early biodistribution studies by George Taplin, MD, in the early 1960s, MAA was introduced into



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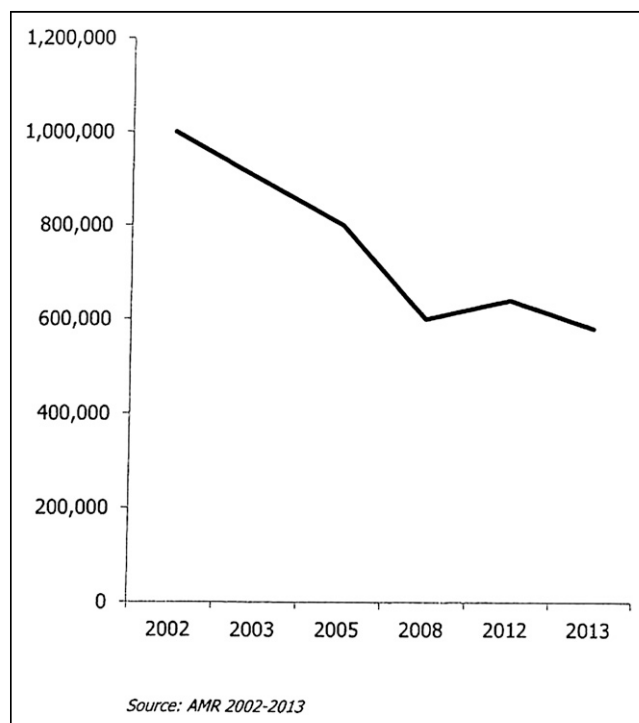


FIGURE 1. ^{99m}Tc -MAA perfusion imaging procedures performed in the United States, 2002–2013. Reprinted with permission from DR/Decision Resources, LLC. (4)

clinical medicine by James Quinn, III, MD, and Henry Wagner, Jr., MD (1–3). The original agent was ^{131}I -MAA. Of note, Wagner performed the first human study on himself.

I was fortunate to use ^{131}I -MAA under the Investigational New Drug process with E.R. Squibb. After U.S. Food and Drug Administration (FDA) approval, many companies in the early 1970s started marketing MAA for labeling with $^{99\text{m}}\text{Tc}$. These included Squibb, New England Nuclear/DuPont, Mallinckrodt, CIS/Syncor, Diagnostic Isotopes, and Merck–Frost in Canada. The latter has become Jubilant DraxImage. The difficulties of manufacturing the product, with its many failed lots and lack of profitability, have led progressively to abandonment by most of these companies. In 2011, Pharmeducense also permanently ceased production because of poor particle counts. Mallinckrodt, which distributes MAA in Europe, ceased U.S. production because of its assessment that this was a non-profitable business venture. In addition to manufacturing challenges, these responses were also related to negative perspectives about V/Q imaging following the 1990 Prospective Investigation of Pulmonary Embolism Diagnosis study report and the introduction of CT angiography in the mid 1990s.

The shrinkage of the MAA manufacturing market has resulted in Jubilant DraxImage becoming the sole supplier of MAA for all of North America. They also are the sole suppliers of DTPA used for off-label aerosol ventilation studies. This trend is not unique; single sources currently produce 16 of 24 of the most commonly used radiopharmaceuticals (4). As in the MAA situation, the lack of competition has been caused by difficulties adhering to strict FDA guidelines and the relatively low profit margins associated with the price structure of radiopharmaceuticals. Also pertinent is documentation by the FDA that 40 radiopharmaceuticals have been discontinued (5). Changing clinical relevance contributes to the decision to discontinue, but lack of profitability is also an important factor.

Difficulties in Manufacturing MAA

MAA is one of the more difficult agents to prepare. The basic human serum albumin (HSA) must be obtained from an FDA-approved human donor pool. This was of particular concern in the 1980s at the height of HIV concerns. Companies producing MAA subcontracted acquisition of the albumin. Because of strict donor selection criteria and FDA oversight approval, no problems related to HSA have been reported. The aggregated particles from HSA are prepared with meticulous and controlled heating, pH adjustment, and cooling to produce aggregated particles in the appropriate total number per vial and mandatory narrow size range of 10–70 μm (FDA-approved product specifications). Several dozen quality release specifications, including testing and biodistribution in mammals, require up to 30 days to complete. A significant number (10%–30%) of batches fail and must be discarded. Jeffrey Norenberg, PharmD, PhD, and William Hladik, III, MS, RPh, provide an excellent overview of MAA production (6).

Alternatives to the Price Rise

It is unlikely that other manufacturers will consider entering or re-entering the marketplace. Cost would be prohibitive. Mallinckrodt supplies MAA in Europe. A spokesperson indicated to me that “Mallinckrodt made the decision to discontinue production of our MAA product a few years ago after a careful and thorough assessment. We determined we could not continue to offer the product in a financially viable manner that would not be cost prohibitive to the customers. That assessment remains the same, with even more cost that would be incurred in re-entering the market, and we have no plans to resume MAA production.” This viewpoint is apparently shared by other former U.S. as well as non-U.S. manufacturers.

An alternative to obtaining FDA-approved MAA is the use of compounded radiopharmaceutical kits, but this option should be pursued only with great caution. It is prohibited when an approved drug is available for the same indication, with very uncommon and single-patient exceptions. The practice of compounding is often confused with manufacturing. Compounding is an FDA-approved practice that typically is performed for an individual patient by a licensed pharmacist as directed by a specific prescription order from a physician, maintaining the patient–physician–pharmacist triad (often termed more simply the “Triad”). The practice is regulated by state boards of pharmacy with some FDA oversight under the Food, Drug, and Cosmetic Act (FD&CA), 21 USC sections 353(a), 503A(7), and 503B (8). The process of compounding drug products differs greatly from manufacturing, in terms of the regulatory oversight and presence of extensive processes and quality and safety checks required for the latter. In some instances, however, pharmacies have moved away from compounding based on the “Triad” to performing large-scale compounding, with multiple units being produced in anticipation of need, response to drug shortages, or other factors, including cost. These large-scale compounding facilities are inconsistent with the traditional scope of practice of pharmacies and operate more akin to manufacturers. The practices of traditional pharmacies, whereby drugs are compounded to meet the needs of individual patients, have long been recognized by the FDA and protected under the safe harbors of the FD&CA, section 503A. The FD&CA was recently amended to clarify the FDA’s jurisdiction over nontraditional compounding manufacturers, creating a new category of large-scale compounding manufacturers termed “Outsourcing Facilities” (7,8).

Although compounding can play an important role in providing drug products for the end user, several disasters with this practice of large-scale drug compounding have been well publicized. In 2012, the New England Compounding Center bulk manufactured a steroid for epidural administration that was contaminated with a fungus that caused *Aspergillus* meningitis infections. This resulted in more than 750 cases of meningitis and 64 deaths in 20 states (9) and a \$100 million settlement against the company.

In the nuclear medicine community, some companies currently either perform large-scale compounding or are considering undertaking this practice. Any hospital contemplating the use of a compounding facility for their MAA supply or any other pharmaceutical product should do so in consultation with the Pharmacy and Therapeutics Committee responsible for oversight of medication use throughout the institution, as required by the Joint Commission and other accrediting entities. The SNMMI has a position statement on its website regarding the compounding of radiopharmaceuticals (10), which states “The compounded preparation should have justifiable patient care advantages over the commercial product, such as dosage form, availability/delivery timelines, or altered formulation related to patient allergy. Cost alone does not justify purchasing a compounded preparation instead of a commercial drug product.”

By ramping up to larger scale production without the stringent regulatory oversight that would be required in a manufactured product, the door is open for potential problems on a much larger scale for the end product. It is the responsibility of the end user to recognize the inherent risks and any potential differences between the compounded and manufactured products (11). On April 30, the Council on Radionuclides and Radiopharmaceuticals, Inc., wrote a letter to the FDA alerting them to what members believed are unlawful compounding practices of 2 nuclear pharmacies (12).

Alternatives to ^{99m}Tc -DTPA for Ventilation Studies

Before aerosolized ^{99m}Tc -DTPA came into use, ^{133}Xe gas was the standard of care ventilation agent and is still preferred to aerosolized particle studies at many medical centers. With the DTPA price increase, the costs of the 2 procedures are comparable. For those who prefer aerosols, a less expensive approach used at the University of Wisconsin is ^{99m}Tc -pyrophosphate (13). This agent actually clears a bit more slowly from the lungs, which may be helpful for those preferring SPECT V/Q imaging. ^{99m}Tc -sulfur colloid has also been proposed as an aerosolized ventilation agent. It should be noted that both of these approaches represent off-label uses, similar to DTPA. If and when Cyclopharma's Australian-produced Technegas becomes available in the United States, it may well prove to be the best ventilation agent of all.

Conclusion

Despite concern over the potential negative impact of the recent price increase for both MAA and DTPA, it is essential that nuclear medicine physicians remain focused on continuing to educate clinicians and our diagnostic radiology colleagues on the important role that V/Q studies play in accurately diagnosing clinically significant pulmonary emboli with considerably less radiation exposure than CTPA. In addition, MAA remains an essential diagnostic

predecessor to ^{90}Y -labeled selective internal radiation sphere therapy for liver malignancies. If MAA, in particular, were no longer available to us, it would be a very serious blow to our specialty.

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