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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane Room 1061
Rockville, Maryland 20852

CITIZEN PETITION: Docket No. FDA-2010-P-0179

We respectfully submit this Citizen Petition on behalf of radiologists whom administer gadolinium based contrast agents to patients as well as patients with sufficient renal impairment to put them at risk for NSF (collectively, the “Respondents”), pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act (“FDCA” or the “Act”) (21 U.S.C. §355), 21 C.F.R. Part 314, and 21 C.F.R. §10.30. This petition is filed in response to a petition filed on behalf of an anonymous client competitor submitted by the law firm of Stradley Ronon Stevens & Young, LLP (herein “Stradley Petition” or “Petitioner”) dated April 1, 2010, that was docketed under the number provided above. Below, we outline the action requested and relevant background information, as well as prior and current analysis of the issues for the Agency’s consideration and review.

I. Action Requested

We request that the Commissioner of Food and Drugs and the U.S. Food and Drug Administration (“FDA”) take the following action with respect to all approved New Drug Applications (“NDAs”) for gadolinium-based contrast agents (“GBCAs”):

A. Supplement the existing class boxed warning regarding NSF to include the following statements (or similar statements as FDA deems appropriate having reviewed the currently available scientific data and the recommendation of its advisory committees):

- Avoid the use of Omniscan™1 (gadodiamide), OptiMARK™2 (gadoversetamide) and

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1 Omniscan™ (gadodiamide) is a registered trademark of General Electric Healthcare.
2 OptiMARK™ (gadoversetamide) is a trademark of Covidien.

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FDA-2010-P-0179

CP
Magnevist (gadopentetate dimeglumine) in patients with severe kidney disease.

- The molecular structure of macrocyclic contrast agents, for example ProHance (gadoteridol), essentially encapsulate the gadolinium such that there is negligible release of gadolinium.

- The molecular structure of MultiHance (gadobenate dimeglumine) includes a C substitution on the backbone of the molecule, making it more kinetically stable than Omniscan, OptiMark and Magnevist which safeguards patients who have renal failure by providing an alternative route of elimination. Additionally, MultiHance® has a dual route of excretion (renal and biliary) and because of its higher relaxivity, there is no reason to ever administer a greater dose than approved, and, in fact, a lower dose than approved is frequently diagnostically sufficient.

B. Review and update the class boxed warning and class "WARNINGS" labeling as new evidence becomes available and as new GBCAs are reviewed for approval.

C. Issue an updated "FDA Alert" for health care professionals reflecting the new agency findings on differential product risk for NSF.6

II. Statement of Grounds

A. Background Information

The Stradley Petition, which was submitted by a law firm "on behalf of an interested party client," requests that FDA blindly continue "class labeling" for GBCAs relating to the risk of NSF and refrain from differential NSF risk-based labeling among the GBCA products. It is the Respondents' position that providing a differential NSF risk based labeling between GBCA products is a critical part of FDA's responsibility and an important factor for patient safety. The current "class labeling" boxed warning appearing on the FDA-approved labeling of all GBCAs is as follows:

**WARNING: NEPHROGENIC SYSTEMIC FIBROSIS**

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m2),
- or acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

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3 Magnevist (gadopentetate dimeglumine) is a registered trademark of Bayer Healthcare.
4 ProHance (gadoteridol) is a registered trademark of Bracco Diagnostics Inc.
5 MultiHance (gadobenate dimeglumine) is a registered trademark of Bracco Diagnostics Inc.
7 Stradley Petition at 1.
In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with noncontrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (See WARNINGS).

In addition, FDA directed each GBCA to include the following class labeling in the "WARNINGS" section of the respective Prescribing Information:

**Nephrogenic Systemic Fibrosis (NSF)**

Nephrogenic systemic fibrosis (NSF) may arise in patients who receive gadolinium based contrast agents and who have acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²) and in patients with acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with noncontrast enhanced MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.

Post-marketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following sequential administrations of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.

The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the
estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006; 17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION)."a

The Stradley Petition advocates blindly maintaining undifferentiated class labeling between gadolinium-containing contrast drugs. These Respondents urge the FDA to reject that approach and provide for critical differentiation of these contrast drugs based on the recommendations of the FDA advisory committees' review and analysis of the scientific literature as described below. The boxed warning for all U.S. marketed GBCAs has been helpful. However, failure to distinguish at all among GBCAs in the prominent boxed warning regarding the differential product risk for NSF runs counter to: (1) substantial scientific evidence; (2) prevailing clinical practice guidelines; (3) the recommendations of other governmental entities; (4) recommendations of FDA reviewers; and (5) recent recommendations of FDA's Joint Cardiovascular and Renal Drugs Advisory Committee, and Drug Safety and Risk Management Advisory Committee ("Advisory Committees"). Furthermore, the agency has already mandated differential labeling, as highlighted above, for placement in the WARNINGS section of GBCA Prescribing Information. As more evidence is available today than in 2007 when FDA last updated the class warning information for GBCAs, the scientific information warrant more prominent placement of and update to the differential risk information currently featured only in the WARNINGS section of the Prescribing Information. Undeniably, the different product risks between the GBCA products for NSF, is information critical to health care providers and patients from the standpoint of safety. It is much more critical given some sponsors' efforts to attempt to explain away the significant differences seen in the number of unconfounded cases of NSF, with different GBCA complexes. This situation creates confusion as to the real differential risks between the various GBCAs and the FDA must act to avoid potential unnecessary injury due to lack of such meaningful data.

B. GBCAs and NSF

GBCAs are contrast agents used in magnetic resonance imaging ("MRI") to improve the visualization of body structures or vasculature. To date, FDA has approved seven GBCAs. They contain gadolinium, a paramagnetic metal which must remain chelated within the contrast agent to

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b See Transcript of Advisory Committee Meeting, December 7-8, 2009 at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommitteeUCM197768.pdf ("Meeting Transcript").
avoid toxic effects from the gadolinium.\textsuperscript{10}

As reported by FDA in its Briefing Document released prior to the December 8, 2009 joint meeting of its advisory committees,\textsuperscript{11} the association between GBCAs and NSF was first reported in the medical literature in 2006. In particular, NSF was associated with the use of GBCAs in patients with severe renal insufficiency. Observational studies found that NSF, a scleroderma-like disease, produces characteristic skin lesions and a fibrotic process within multiple body organs which may result in death.

C. **FDA and Boxed Warning**

In June 2006, the FDA issued a Public Health Advisory informing the medical community about the association of GBCAs and NSF, reporting on 25 cases of NSF in patients with kidney failure who were administered Omniscan, and providing recommendations, including that GBCAs be used, especially at high doses, only if clearly necessary in patients with advanced kidney failure and that prompt dialysis be considered.\textsuperscript{12} In December 2006, FDA updated its Advisory and Information for Healthcare Professionals, reporting on a total of 90 cases reporting these adverse events to FDA. All reported cases involved Omniscan, Magnevist, or OptiMARK.\textsuperscript{13}

In May 2007, FDA announced in a Press Release that it had asked all manufacturers of GBCA related products to include voluntarily a new boxed warning and additional warning language on the product labeling of their GBCAs. The language of the boxed warning across this class of drugs was dictated to state that patients with severe kidney insufficiency who receive GBCAs are at risk of developing a debilitating, and potentially fatal disease known as nephrogenic systemic fibrosis (NSF). It further was to provide that patients just before or just after liver transplantation, or those with chronic liver disease, are also at risk for developing NSF if they are experiencing kidney insufficiency of any severity.\textsuperscript{14}

The Press Release further provided that:

Gadolinium-based contrast agents are commonly used to improve the visualization of internal structures when patients undergo a MRI. Five gadolinium-based contrast agents have been approved for use in the United States: Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide); OptiMARK (gadoversetamide); MultiHance (gadobenate dimeglumine); and ProHance (gadoteridol).

Reports have identified the development of NSF following single and multiple administrations of the gadolinium-based contrast agents. The reports have not always


\textsuperscript{12} See Public Health Advisory at http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124344.htm (December 2006).

identified a specific agent. Omniscan was the most commonly reported agent, when a specific agent was identified, followed by Magnevist and OptiMARK.

NSF also has developed after the sequential administration of Omniscan and MultiHance and Omniscan and ProHance. Because reports incompletely describe exposure to gadolinium-based contrast agents, it is not possible to know if the extent of risks for developing NSF is the same for all agents.

Bayer Schering Pharma, Berlin, Germany, manufactures Magnevist; GE Healthcare, Chalfont St. Giles, U.K., is the maker of Omniscan; OptiMARK is manufactured by Mallinckrodt, Inc., Hazelwood, Mo.; and ProHance and MultiHance are made by Bracco Diagnostics Inc., Princeton, N.J.15

Underlying this action by FDA were, among other things, the findings of the agency's Medical Reviewer in the Division of Medical Imaging and Hematology Products, Dr. Melanie Blank.16 In a Memorandum to File completed only days before the agency issued its Press Release, Dr. Blank summarized "the evidence for the causative role of gadolinium-based contrast agents in the development of NSF" and proposed "to request revised class labeling from the drug manufacturers that includes a warning.

Among her listed findings were the following:

- 2006: GBCA implicated in 5/9 dialysis patients (~55%).
- 2006: Danish reports of 5% incidence (20 cases) among 400 renal failure patients undergoing MRI with Omniscan.
- 2007 CDC reports a cluster of cases at a Missouri hospital; GBCA only definitive correlate for development of NSF.
- Peer reviewed literature and adverse event reports (AERS) suggest higher or repeated GBCA doses used in NSF cases.
- All of the cases of NSF in the peer reviewed literature and AERS database have severe renal failure. The major operative theory is that renal failure prolongs GBCA retention in the body, allowing free gadolinium to be released from GBCAs that are structurally weak.
- There are two factors necessary for the development of NSF—severe renal failure and exposure to GBCAs. Acute renal dysfunction in the perioperative liver transplantation and hepatorenal syndrome may confer a greater risk for development of NSF. Other potential risk co-factors which may affect the development of NSF may include: acidosis, erythropoietin use, concomitant surgery or inflammation.

15 Id.
16 Memorandum to the File - Gadolinium-Based Contrast Agents (GBCAs) and Nephrogenic Systemic Fibrosis (NSF) (May 15, 2007), available at http://s3.amazonaws.com/propublica/assets/omniscan/blankmelanie-review-omniscan2.pdf.
17 Id. at 1.
18 Id. at 2-4.
• Peer-reviewed Literature: To date the vast majority of cases of NSF are associated with Omniscan in the peer reviewed literature and 2 cases of NSF associated with Magnesvist. There have been no carefully reselm;lhed publications in which the use of other agents alone, have been reported to be associated with NSF.

• Adverse Event Reports System (AERS) with market share data from Arlington Medical Resources (data are from February 2007):

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>MPR</th>
<th>Appx</th>
<th>NSF cases</th>
<th>% Market share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omniscan</td>
<td>GB</td>
<td>192K</td>
<td>7%</td>
<td>30%</td>
</tr>
<tr>
<td>Magnesvist</td>
<td>GB</td>
<td>1996</td>
<td>2%</td>
<td>50%</td>
</tr>
<tr>
<td>Optima</td>
<td>Maltese</td>
<td>1998</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>ProHance</td>
<td>GB</td>
<td>1999</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>MultiHance</td>
<td>GB</td>
<td>2006</td>
<td>0%</td>
<td>50%</td>
</tr>
</tbody>
</table>

It is also noteworthy, and consistent with FDA's own internal review, that the industry's own practice guidelines, published in June 2007, conclude that “...patients with any level of renal disease should not receive Omniscan for their contrast-enhanced MR examinations.”

D. Advisory Committee Meeting

On December 8, 2009, two FDA Advisory Committees met jointly to review safety considerations related to FDA-approved GBCAs used with MRI scans. In particular, the Committees focused on reports of NSF among renal patients receiving GBCAs. They considered whether these data establish a differential safety risk for NSF among particular GBCAs. The sponsors of each GBCA presented the underlying data related to reports of NSF. Each sponsor provided FDA with data known to it regarding the reported incidence of NSF with its GBCAs.

Bracco Diagnostics Inc. ("Bracco") develops and markets a number of imaging agents for diagnostic purposes. Two such products are MultiHance (gadobenate dimeglumine) and ProHance (gadoteridol), each of which is a GBCA. At the meeting, Bracco presented an overview of all currently known NSF data and reports involving the use of ProHance and MultiHance. Namely, as of November 26, 2009, Bracco was aware of 20 confounded, and 2 unconfounded cases of NSF.

20 Final Meeting Agenda, Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting (December 8, 2009), available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteeMeetingMaterials/Drugs/ CardiovascularandRenalDrugsAdvisoryCommittee/UCM196212.pdf.
associated with ProHance, and 2 unconfounded cases of NSF associated with MultiHance reported to FDA with a low incidence of additional confounded cases of NSF reported in the literature for MultiHance.

Unconfounded vs. Confounded NSF Cases: It is difficult to determine which GBCA, if any, is associated with NSF when more than one GBCA is used and thus NSF cases occurring after the administration of one specific GBCA (unconfounded cases) allow for a higher significance of association to the disease.

Unconfounded NSF Cases for Omniscan - Population: GE Healthcare claims in their "Omniscan Advisory Meeting Briefing Document" (November 3, 2009)22 that: "Other than differences in the number of spontaneous reports, there is no clear evidence to indicate that any one GBCA is more or less safe than any other with respect to NSF". The same document noted that 16% of adverse reactions reported to GE Healthcare involved the skin and these were "mainly NSF". GE also state that: "currently NSF cases constitute about 14% of all Omniscan reactions reported to GE Healthcare".

GE Healthcare estimated that worldwide approximately 48 million units of Omniscan have been distributed from launch in February, 1993 to July, 2009. However, GE does not possess relevant data which reflects the number of patients in the population at risk for developing NSF who have been exposed to Omniscan. GE further noted that as of June 30, 2009 they were aware of 624 NSF cases after the administration of Omniscan. "The number of confounded cases is 119 out of 624 (19%)". Thus GE is aware of 505 NSF cases after the unconfounded use of Omniscan.

Unconfounded NSF Cases for MultiHance - Population: According to the Bracco "Advisory Committee Briefing Document for MultiHance"23 two cases of NSF have been reported to the FDA after unconfounded use of MultiHance; however, the company has not received definitive information that MultiHance was the sole product used in these cases or that NSF was confirmed by biopsy. Bracco is unaware of any other reports either in the peer-reviewed literature or reported to Bracco associating use of MultiHance with unconfounded cases of NSF. Bracco noted that as of October 26, 2009, approximately 8 million patients have received at least one dose of MultiHance.

Unconfounded NSF Cases for ProHance - Population: The Bracco "Advisory Committee Briefing Document for ProHance"24 noted that Bracco is aware of two possible unconfounded NSF cases for ProHance that have been reported to authorities. One case from Switzerland is for a male patient who received a high dose of ProHance six times over a two year period. NSF was diagnosed through skin biopsy and the reporter noted that the NSF case was "not severe". No additional information confirming the sole use of ProHance or the diagnosis of NSF was provided to Bracco, despite repeated requests. No publication or further information has been provided. The second case was reported in the United States after administration of a low dose of ProHance. The family physician provided a diagnosis of "beginning of NSF", although no biopsy was performed to confirm the NSF diagnosis and the patient's medical history did not include any known renal impairment that

23 MultiHance Advisory Committee Briefing Document Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee, December 8, 2009.
24 ProHance Advisory Committee Briefing Document Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee, October 30, 2009.
would normally be considered necessary for an NSF diagnosis. Bracco estimated that 13.2 million patients had received at least one dose of ProHance as of October 26, 2009.

**Population NSF Incidence - Omniscan vs. MultiHance vs. ProHance:** If one includes the questionable NSF cases for unconfounded use of the Bracco GBCA’s then based on the information from the manufacturers (sponsors) an estimation of the percentage NSF incidence for unconfounded use of each GBCA can be calculated. For Omniscan: 505 NSF cases from 48 million uses = 0.00111%; for MultiHance: 2 NSF cases from 8 million uses = 0.00025%; for ProHance: 2 NSF cases from 13.2 million uses = 0.00015%. These results indicate that NSF incidence for the population as a whole was 44-fold higher for unconfounded use of Omniscan compared to MultiHance and 73-fold greater than for unconfounded use of ProHance.

The incidence of NSF for unconfounded use of Omniscan based on their reported numbers is higher than the value claimed in their advisory meeting documents where they reported that in reference to NSF epidemiological data: “the overall incidence is extremely low, less than 0.00015% in 48 million doses”.

It is important to recognize that, in fact, none of the unconfounded cases claiming sole use of ProHance or MultiHance have ever in fact been confirmed. Thus, it is possible that the actual differential incidence of NSF between Omniscan and ProHance and/or MultiHance is indeed infinite.

**NSF Incidence in the at Risk Population (Omniscan vs. MultiHance):** GE Healthcare claimed in their Omniscan Advisory Meeting Briefing Document that “there are no reasonable head-to-head studies that could be used to establish a regulatory basis for any differentiation”. Such studies are not possible based on the regulatory recommendations, but retrospective studies can compare the relative NSF risk between the different GBCA’s. Population studies provide an overall risk association between GBCA use and NSF, but such studies will include individuals with normal or mild kidney disease that have little or no risk of contracting NSF. The most appropriate group to compare GBCA use is for individuals suffering end stage renal disease with the majority of these patients on dialysis. Since this is the “at risk” population then they are the most appropriate for comparison of NSF incidence levels for different GBCA products. Martin et al. (2010) recently updated an earlier article by Altun et al. (2009) with additional GBCA use and reported that a retrospective analysis of dialysis patients at one center found 8 patients who developed Omniscan out of 312 (2.6%) that received Omniscan, whereas there were 0 NSF patients out of 718 (0%) that received MultiHance. Furthermore, statistical analysis of the results indicated that at the 95% confidence level there was a statistically higher incidence of NSF after Omniscan compared to after MultiHance administration at the same institution in this at risk population on dialysis.

Similar to the Martin et al. study, The University of Wisconsin Radiology, Nephrology and Dermatology group reported on their website (updated 4/2009) that 6 out of 91 high risk patients (GFR < 30ml/min/1.73m² with pro-inflammatory conditions) who received Omniscan developed NSF (6.5%) whereas 0 out of 78 patients with the same high risk criteria developed NSF (0%) after

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the institution switched from Omniscan to MultiHance.

NSF Incidence in the at Risk Population (ProHance): Reilly (2008)28 performed a retrospective analysis of the risk of NSF in patients on long-term hemodialysis at a single institution after administration to ProHance only. A total of 141 patients were identified from the records with a total of 198 ProHance exposures. No cases of NSF were identified. The author compared the results with the published study of Deo et al. (2007)29, which found that the risk for NSF in hemodialysis patients was 2.4% for use of Omniscan and Magnevist. Note that the incidence is similar to the Omniscan incidence from Martin et al. 2010 (see above). Reilly observed that absence of NSF cases in hemodialysis patients administered ProHance could not be explained by chance alone.

Bracco’s Prospective Studies - MultiHance and ProHance: On September 27, 2007, Bracco commenced a prospective study of the effect of MultiHance on the prevalence of NSF, enrolling the first patient on January 21, 2008. As of November 2009, 234 high-risk patients have been studied. No cases of NSF have been reported to date. Bracco also commenced a similar NSF study for ProHance, enrolling 71 patients as of November 2009. This study has also detected no incidence of NSF to date using this GBCA. ProHance is currently the only FDA-approved GBCA that is macrocyclic in molecular structure, which is a configuration recognized as having greater chelate stability.

Table A30 below highlights the current FDA-approved linear (ionic, non-ionic and di-ionic) GBCAs on the U.S. market:

<table>
<thead>
<tr>
<th>GBCA (Brand Name (active ingredient))</th>
<th>Chemical Structure</th>
<th>Thermodynamic Stability Constant (logk, pH=0)</th>
<th>Conditional Stability Constant (logk, pH 7.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OmniscanTM (gadodiamide)</td>
<td>Linear, Non-Ionic</td>
<td>16.9</td>
<td>14.9</td>
</tr>
<tr>
<td>OptMARK(TM) (gadopentetate dimeglumine)</td>
<td>Linear, Non-Ionic</td>
<td>16.6</td>
<td>15.0</td>
</tr>
<tr>
<td>Magnevist® (gadopentetate dimeglumine)</td>
<td>Linear, Ionic</td>
<td>22.1</td>
<td>17.7</td>
</tr>
<tr>
<td>MultiHance® (gadobenate dimeglumine)</td>
<td>Linear, Ionic</td>
<td>22.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Generic® (gadoteric acid)</td>
<td>Linear, Di-Ionic</td>
<td>23.5</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

Bracco’s presentation was consistent with statistics reported by FDA. Included in FDA’s Briefing Document for the Advisory Committees is a report and recommendation by FDA’s Office of Surveillance and Epidemiology and Office of Translational Sciences, Center for Drug Evaluation

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30 Note that Table A is taken from the Bracco MultiHance Briefing Document for the Advisory Committee Meeting, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagement/AdvisoryCommitteesUCM192007.pdf. Footnotes and references cited in Table A are provided in the document available at this link.
and Research ("OSE Report"). That Report examined sales and use data, adverse event data, and the published literature. Its conclusion and recommendation are as follows:

The different lines of evidence cited in this review all have limitations, some of which are substantial. These limitations are described in the review. However, based on the preponderance of the evidence in this review, it is OSE’s judgment that different GBCAs are associated with varying risk of NSF. The highest risk is associated with Omniscan, and OptiMARK. There is an intermediate risk with Magnevist. The lowest risk is associated with ProHance and MultiHance. The other domestically-approved agents are not considered in this review as they do not yet have significant market exposure. ... The OSE joint recommendation is: Differential labeling of GBCAs for use in certain populations reflecting varying risk across products.31 ... OSE believes that the magnitude of NSF risk does not compel removal of specific GBCAs from the US market. However, based on the accumulated evidence, much of which has become available to FDA since the Agency recommended class labeling, differential risk-based labeling for GBCAs is warranted. OSE will work with the Division of Medical Imaging and Hematology Products and manufacturers to develop labeling that is consistent with the levels of risk and the benefits of the GBCAs.32

Upon consideration of the data presented to the Advisory Committees, members discussed the reported incidence of GBCAs. They considered the existing boxed warning and whether there is a need for a contraindication in patients with severe renal insufficiency for some or all GBCAs. The majority of Committee members recommended that Omniscan and OptiMARK be contraindicated "in patients with significant kidney disease" or severe renal disease.33 The majority of members also found that there was no clear evidence "that any one single agent was safe in this population."34 In addition, members found that "significant renal disease" is a concept that cannot be defined only using a creatinine or an estimated GFR level. They noted that prescribers also need to consider the difference between acute kidney disease and chronic kidney disease in terms of how these measures are assessed.35 The Committees also noted the importance of the lowest possible dosing be used, and development of a means for capturing cumulative dosing in patients.36

E. European Medicines Agency

As the OSE Report observed, the European Medicines Agency (EMEA) already stratified risk among the respective GBCAs based on extensive review of the literature, reported AERs and company data:

In February 2007 the EMEA issued a Direct Healthcare Professional Communication (DHPC) stating that 1) Omniscan should not be used in patients with severe renal impairment (glomerular filtration rate <30 ml/min/1.73m²) or who have had or are
awaiting liver transplantation and 2) careful consideration should be given to the use of other GBCAs in patients with severe renal impairment. A June 2007 DHCP added advice to consider carefully the use of Omniscan in patients with moderate renal dysfunction (glomerular filtration rate 30-59 ml/min/1.73m²) or in neonates. The June 2007 DHCP added similar contraindications and cautions for the use of Magnevist. Fewer strictures and cautions were administered for the use of the other GBCAs; the DHCP stated that careful consideration should be exercised for their use in patients with severe renal impairment.37

An EMEA Press Release dated November 20, 2009, provided the following classification scheme:

- **High risk** — Omniscan (gadodiamide), OptiMARK (gadoversetamide), Magnevist (gadopentetic acid)
- **Medium risk** — MultiHance (gadobenic acid), Primovist (gadoxetic acid), Vasovist (gadofosveset), Eovist.
- **Low risk** — Gadovist (gadobutrol), ProHance (gadoteridol), Dotarem (gadoteric acid).38

EMEA, therefore, differentiates among the available GBCAs on the market by determining a risk classification.

III. Discussion

Consistent with the FDA’s risk-based initiatives and desire to better identify post-market safety signals as they arise to facilitate regulatory action to protect the public health, the modification to the existing class boxed warning, which Respondents are requesting in this petition, would better communicate to health care professionals the differential safety risks observed among GBCAs for NSF in clinical experience. Given the debilitating, and sometimes fatal, nature of NSF, labeling based on the most current and meaningful available scientific evidence and data regarding incidence of NSF must be provided to health care professionals to minimize the risk to patients’ health in a clinician’s selection of a GBCA for a radiological procedure. Below, we highlight those reasons why, based on what is known to the agency and scientific community about GBCAs and incidence of NSF and differential classification schemes used abroad, a class boxed warning in the United States prominently featuring the differential NSF safety risk would best protect the public health.

A. Scientific Community and Agency Experts Recognize Differential Risk of NSF among GBCAs

As highlighted above, the FDA Advisory Committees and EMEA have each recognized the association between incidence of NSF and administration of at least certain GBCAs. In 2007, FDA

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37 Briefing Document at 44.
findings demonstrated a safety concern for NSF with certain GBCAs strong enough to merit class labeling of the differential risk of NSF in the "WARNING" section of the Prescribing Information. Since that time, reports of NSF cases in the literature and FDA's AERS reinforce the initial safety signals for Omniscan, Magnevist and OptiMARK and provide scientific evidence, both confounded and unconfounded, for the other GBCAs as well.

As presented in the OSE Report, AERS data as of September 3, 2009 indicated as follows:

<table>
<thead>
<tr>
<th>Product</th>
<th>Year</th>
<th>Risks reported</th>
<th>Severe</th>
<th>Cases reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>MultiHance</td>
<td>2007</td>
<td>Domestic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ProHance</td>
<td>2007</td>
<td>Domestic</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Notably, an examination of unconfounded NSF cases (as reported) identifying only a single GBCA revealed that MultiHance and ProHance had only 1 case of NSF reported in FDA's AERS for each (with one case for MultiHance being domestic and one case for ProHance being foreign). As Bracco presented to the Advisory Committees and highlighted above, virtually all of NSF case reports involving Bracco products have been confounded cases in which other GBCAs (Omniscan, Magnevist, OptiMark) were also administered to the patients.

As the Stradley Petition indicates, the OSE Report noted limitations to its findings in various respects. Multiple redundant large, prospective, multi-center, randomized, controlled trials ("RCT data") testing all GBCAs head-to-head have not been conducted. Notwithstanding the absence of RCT data, the totality of AERS data, the published literature, and individual company investigations provide significant and consistent data upon which FDA should act in its capacity as a public health agency responsible to protect the public. No doubt providing information in the label about the differential risks of NSF between various GBCAs for the at risk population is very important to health care providers and their patients. Such action will provide specific and meaningful data to properly inform medical providers and minimize future cases of NSF. These available data possess scientific merit and validity. The differential risk patterns are clear and consistent. RCT data is the standard used for product labeling by the manufacturer, but not the standard commonly adopted by FDA for safety warnings. In addition, the amount of time it would take to obtain the type of RCT data that would satisfy the unidentified Stradley Petitioner risks additional incidence of NSF that may be prevented by an update to the current class boxed warning based on data that has become available since the 2007 class label. Additionally, it is inconceivable that such a study would ever receive approval by any IRB given the legal and ethical implications, a fact that the anonymous Stradley Petitioner is without question fully cognizant. Any suggestion that such RCT data is necessary is equivalent to a petition that FDA wait for data that will simply never exist. Unfortunately, this strategy of delay only hurts those patients suffering renal impairment who need MR procedures.
Even with the limitations noted in the OSE Report, the data and patterns of NSF incidence with respect to specific GBCAs that clearly emerged cannot be overlooked. As best described by OSE:

As stated previously, these AERS data are subject to various limitations. Even with these limitations, however, it is noteworthy that the great majority of reports are associated with Omniscan and Magnevist, and that there are no domestic reports of NSF after administration of ProHance only (and only one foreign ProHance/NSF report). Among cases in which event dates were reported, the frequency of cases occurring after 2006, when the association of NSF with gadolinium administration became public, has greatly diminished.

Among MedWatch NSF cases where GFR is reported in the narrative, only one case reports GFR at the time of administration of a GBCA that would indicate less-than-severe renal dysfunction. This suggests that NSF occurs almost exclusively among patients with severe renal insufficiency.

The analysis of disproportional reporting from the AERS data within the gadolinium product class, shows safety signals for Omniscan and Optimark. This was not an analysis of absolute risk, but a comparison of reporting rates compared to reports of other adverse events associated with these products. Reports of nephrogenic system fibrosis (NSF) are more frequent than expected with these two contrast agent drugs, when compared to the other three.40

Notwithstanding that some cases are confounded by multiple agents, the trends among GBCAs examined by OSE are unmistakable, not only with respect to AERS data but also with respect to clinical study reports and registry data reviewed by FDA.41

The data evaluation performed by FDA, industry, and the medical community in assessing the risk of NSF with various GBCAs is also consistent with FDA's overall risk-based analysis and Sentinel Initiative, specifically, which is built on leveraging available data resources to identify safety signals generated at any point in the process to inform regulatory decision-making.42 FDA has recognized that "understanding a drug's risk-benefit profile necessarily evolves over the drug's lifecycle."43 FDA has, likewise, recognized the importance of "communicating scientific understanding to healthcare professionals, patients, and the public so that they can make prescribing decisions based on the best scientific information available."44 That is exactly what this Petition seeks.

40 Briefing Document at 53.
44 Id.
The new and more specific scientific findings from the OSE Report, Advisory Committee meeting, and EMEA classification scheme are "the best scientific information available" today. It is important, for the reasons outlined below, that this information be communicated to health care professionals on the front lines of patient safety and who make prescribing decisions every day for GBCAs.

B. Additional Cases of NSF May Be Prevented by Prominent Inclusion of Differential Risk Information in Class Boxed Warning

Contrary to the assertions of the Stradley Petitioner, there is unquestionably more than enough data and scientific evidence reported in the AERS, published literature, and company investigations to support an update to the current class boxed warning. It would be irresponsible not to inform clinicians of the consistent patterns observed in comprehensive and current available data. It would be contrary to the science-based recommendation of the Advisory Committees. It may unnecessarily endanger future patients to wait for RCT, or other data. Potentially, additional cases of NSF may arise if clinicians, because of FDA inaction here, are not made aware of the differential "WARNINGS", currently less conspicuously located within the Prescribing Information.

As noted above, in its review, OSE observed that "the frequency of cases occurring after 2006, when the association of NSF with gadolinium administration became public, has greatly diminished."43 This finding provides meaningful insight into the impact that risk communication, through label updates and FDA Alerts, can have in patient protection and disease prevention. As stated above, the official FDA Safety Alert concerning GBCAs has not been updated since May 2007 even though FDA has been in receipt of, and has reviewed, more current scientific evidence and reports of NSF.

Based on the evidence available in 2007, the agency determined that identification of differential NSF product risks was warranted in the "WARNINGS" section of Product Prescribing Information. Currently, FDA directs that the "WARNINGS" section of all GBCAs include the following statements: “[w]here a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK™). NSF has also developed following sequential administrations of gadodiamide46 with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®)." Based on the collective current evidence and publications today, an updated FDA Alert to health care professionals is necessary along with a label update to focus each clinician’s attention on the latest safety data and reports.

In undertaking any label update, more prominent placement of information regarding the NSF risk information available for individual GBCAs is necessary to help ensure that health care professionals review the more complete information. In addition, the current statements in the class boxed warning and class WARNING section must be updated accordingly to reflect the most recent findings of the OSE Report, Advisory Committees’ recommendations, and published literature. This update will ensure that FDA meets its obligation to provide health care professionals with "the best scientific information available" to aid in current prescribing decisions.

43 Briefing Document at 33.
46 GE’s Omniscan
A product’s FDA-approved Prescribing Information is its single most important product labeling. Its presentation of risk information is critical to health care professional understanding of risk information and prescribing decisions. In January 2006, FDA finalized the Physician Labeling Rule (PLR) which updates the past Structured Product Labeling scheme for Prescribing Information. The PLR provides that sponsors include a “Highlights” section of the FDA-approved Prescribing Information. FDA summarizes its requirements for the Highlights section as follows:47

The “Highlights” section will provide immediate access to the information that healthcare professionals most commonly refer to and view as most important. This summary typically will be one half pages in length.

Additional innovations provided in Highlights include:

- The date of approval of the original drug product.
- Recent Major Changes, a list of all substantive changes made within the past year to the following sections of the prescribing information: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions. These changes will be identified in the full prescribing information as well.
- Adverse drug reaction reporting contact information.

As a result, any update made to the FDA-approved labeling of GBCAs will not only communicate the updated scientific information, but also will prominently feature that information in the “Highlights” section of the product Prescribing Information. Since the “Highlights” section is the section to which healthcare professionals “most commonly refer” and “view as most important,” this will further ensure effective risk communication to healthcare professionals (and downstream communication of that information to patients). Updating of the class labeling and prominence of this risk information stands to further reduce incidence of NSF in patients with severe renal impairment.

It appears to be no coincidence, as noted by OSE in the FDA Briefing Document for the Advisory Committees' Meeting, that there was a reduction in reports of NSF following the agency’s 2006 and 2007 FDA Alerts to healthcare professionals and updated labeling. As such, and in line with FDA’s mission as a public health entity, delivery of updated scientific information to healthcare professionals through a class boxed warning reflecting the differential NSF product riskundyly inherent in the available data and observed by FDA, may and likely will further reduce incidence of NSF, particularly in the most at-risk patient population. Media attention concerning this labeling update will further focus attention of medical providers on the issue.

IV. Conclusion

In conclusion, we urge the agency to carefully consider the scientific data and reports it has received, as well as those reported in the literature, and ensure that the boxed warnings on GBCAs are reflective of these additional data. It is imperative that FDA-approved Prescribing Information contain the most meaningful product warnings for health care professionals. The current class labeling, in light of the scientific evidence, Advisory Committees' recommendations, and EMEA classification scheme, suggests that the across the board class labeling, advocated by the manufacturers of products with highest incidence of NSF, does not ensure meaningful communication of the safety warnings associated with individual GBCAs. Indeed, these sponsors offered from the very first reports of NSF, unsupported speculation as to why their products have more reported unconfounded cases of NSF than other GBCA sponsors, yet despite the passage of several years, the same speculative reasons are offered with no proof to support such claims. If such proof existed, it would have been offered. Only one conclusion can be reached, it simply does not exist.

Each GBCA is unique in important characteristics, such as chemistry, pharmacology, dosage and administration, and safety profile. One of the potentially relevant areas of difference is the stability of each GBCA. The most prevalent theory as to the mechanism of action is disassociation and the resulting risks of free gadolinim. Virtually all of the data are consistent with this theory, in which Omniscan and OptiMark are the least stable, followed by Magnevist. FDA and the scientific community can always benefit from additional information which may be forthcoming in the future, although possibly not for several years. However, that eventuality should not preclude FDA from acting and fully informing healthcare providers based on information known today.

The weight of the scientific evidence, and FDA’s current labeling approach relative to safety warnings, directs that a one-size-fits-all class labeling scheme going forward should be updated to more prominently reflect the differential risk. Failure to update product labeling to reflect the scientific information available today with respect to patterns of differential NSF risk among GBCAs runs the added risk of minimizing the perception of risk in the physician community for those GBCAs for which the scientific evidence indicate greater risk. Likewise, where these drugs are necessary to image high-risk patients, the physician should have easy access to know which drugs pose a lower risk of NSF. Moreover, the agency must, in accordance with its duties, update its FDA Alert to healthcare professionals on the prescribing of GBCAs in light of this new scientific information to ensure that healthcare professionals are armed with the best and most complete information they need to protect their patients and make informed prescribing decisions.

I, Richard Semelka, MD, have been designated by the plaintiffs as an MD expert in the In Re: Gadolinium-Based Contrast Agents Product Liability Litigation, MDL No: 1:08-mdl-50000-DAP. I, Diego Martin, MD, Ph.D, FRCP, have no conflict to disclose. We have concluded that ProHance and MultiHance are reasonably safe and available alternatives to the Omniscan, Magnevist and OptiMark.

NOTE: NSF can be a devastating disease. However, we recognize that the use of MR technology for the at risk population for critical diagnostic purposes is sometimes essential. Because we have seen documents and other evidence not available to FDA, we have concluded that ProHance
and MultiHance are the reasonably safe alternative to Omniscan, OptiMark, and Magnevist. Indeed, we strongly urge the FDA to seek access to these documents and deposition testimony, given the important health and safety issues involved.

We are available to discuss this information further should you have additional questions. We appreciate your time and attention to this important patient safety issue.

V. Certification

We certify that, to the best of our knowledge and belief this petition includes all information and views upon which the petition relies.

Sincerely,

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Vice Chairman of Clinical Research
Vice Chair of Quality and Safety

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