NSF and GBCA
Risk Modeling and CKD Screening

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Objectives

- Present a model for risk for NSF by stage of CKD based on cases reported in the literature.
- Present data on identification of patients with CKD at the point of care prior to GBCA-enhanced MR imaging at Yale - New Haven Hospital.

Nephrogenic Systemic Fibrosis (NSF): Review and Analysis of Published Papers: Methods

- Pubmed Search for Nephrogenic Systemic, Fibrosis, Nephrogenic Fibrosing Dermopathy and scleromyxedema, through May 2nd, 2009.
- No abstracts were included in the analysis.
- Level of evidence for NSF:
  - Biopsy-proven diagnosis in papers: Acceptable.
  - No-Biopsy or clinical findings only: Noted as such.
  - Gd-tissue testing: confirmatory of exposure if not known but not required for NSF diagnosis
- Many cases preceded the association with GBCA.
- Unique cases were included to the extent authors referred to prior partial reporting of their series, or if identical information from the same center is noted.

Nephrogenic Systemic Fibrosis: Published Papers and Reported Cases

- 11 case-series (10+ cases, same institution counted as one report) have been published (n=310 patients).
- 104 case reports (1-10) have been published (n=209 patients).
- Six large case-control series of dialysis-dependent patients, with biopsy-proven NSF, have been reported since the identification of an association with Gadolinium Based Contrast Agents (GBCA) administration.
- Breakdown of cases:
  - Unique cases 519
  - Biopsy-proven cases 479
  - Pediatric cases 9
  - Countries 20

AbuAlfa et al: Presented at the Third Annual Symposium on NSF and GBCA, Yale University, May 09

Nephrogenic Systemic Fibrosis: Published Literature: Cases per CKD stage and AKI

- Among all reported cases reported with relevant information, the following distribution of cases is noted:
  - 80.9 % Dialysis dependent with 9.1 % on PD.
  - 7.8 % CKD stages 4 and 5 (excluding AKI “eGFR”)

    eGFR = 12.2 ± 6.0 ml/min/1.73m^2 (31cases)

    (Range: 4 – 26 ml/min)

    eGFR < 15 (5 cases), < 30 (5 cases)

    (8 cases unknown stage but described as advanced)
  - 11.3 % AKI
  - 17.3 % had a prior or a functioning renal allograft.

AKI: Acute Kidney Injury **PD: Peritoneal Dialysis**

AbuAlfa et al: Presented at the Third Annual Symposium on NSF and GBCA, Yale University, May 09

Nephrogenic Systemic Fibrosis: Occurrence in AKI and CKD, non-Dialyzed Patients

- Non-dialysis patients accounted for about 10 to 20% of cases in the registry-reported and published cases.
- Estimated GFR (eGFR)[1-6] was < 30 ml/min/1.73 m^2 although 3 patients having AKI, with reportedly higher eGFR[2,7,8] at time of MR studies, were reported.
- One patient with an eGFR as high as 40 was mentioned in a review[9].
- Significant risk was found for patients with AKI, whose creatinine was rising and not dialyzed for at least 2 days post-exposure.[10]

1. Broome DR et al: *AJR* 2007: 188:586–592
2. Sadowski E et al: *Radiology* 2007; 243:148–157
3. Khurana A et al: *Invest Radiol* 2007; 42: 139–145
4. Swartz et al: *AmJ Med* 2003;114: 563–572
5. Maloo M et al: *American Journal of Transplantation* 2006; 6: 2212–2217
7. Saab and Abu-Alfa*: Radiology* 2007; 244: 930
6. Baron P et al *The American Journal of Dermatopathology* 2003; 25: 204–209
9. Swaminathan S and Shah S: *J Am Soc Nephrol* 2007; 18: 2636–2643
8. Wiginton et al: *AJR* 2008;190:1060-8
10. Prince M et al: *Radiology* 2008; 248: 807-816

Nephrogenic Systemic Fibrosis: CKD Stage 3: is there a risk?

- No cases in 88 exposed patients with CKD Stages 1-4.[1]
- No cases of NSF were noted among the HALT and CRISP cohorts of ADPKD patients with CKD stage 1 - 3 (n=1111 exposures).[2]
- No cases of NSF were seen in an estimated cohort of 592 exposed CKD patients, thought to have CKD 3 – 4.[3]
- No cases of NSF were seen in 50 CKD patients with CKD 3 – 4 and exposed to very high dose (median 80 ml) of the GBCA gadodiamide.[4]
- No cases of NSF were seen in an 168 CKD patients with CKD 3 and exposed to standard dose gadopentetate dimeglumine.[5]

1. Rydahl C et al: *Invest Radiol* 2008;43: 141–144
2. Chapman, *JASN*, 2007: PUB 021
3. Othersen J et al: *NDT* 2007, 22: 3179-85
4. Bridges M et al: *AJR* 2009; 192:1538–1543
5. Bryant BJ and Broome DR: *Clinical Radiology* 2009: 64, 706e713

Nephrogenic Systemic Fibrosis: CKD Stage 3: Medwatch Reported Cases

	Age	GBCA	GFR	Skin Bx	Comorbid conditions
Case 1	59	Omniscan x2/24 hrs	27.9 to 40	NSF	CKD RAS CVA
Case 2	49	Omniscan x2 Magnevist x2	12 to 24(pre Tx) 42 To 50 (post TX)	NSF	HRS Liver Tx
Case 3	59	Magnevist x2	> 60 (3 months prior)	No	RAS Renal cysts
Case 4	63	Magnevist x1	55 (Date unknown)	Yes	?
Case 5	93	Magnevist x1	43 (Date unknown)	Yes	CKD
Case 6	60	Magnevist Multihance (6 MRIs done)	30	? done Clin dx	Htn, DM, CAD, CKD

Nephrogenic Systemic Fibrosis: Model for Risk Estimation in CKD Stages 3 - 5

- **Assumptions:**
  - Proportion of patients on dialysis vs CKD 4-5 is 80.9% & 7.8%.
  - Highest reported risk is 2.4% (or 1 in 42) in exposed dialysis patients per exam is close to the true risk[1].
  - Utilization rate of MR with GBCA is at least the same in CKD stages 3 to 5 as CKD5 on dialysis.
  - NHANES prevalence data is used for patients at risk (0.33x stage 5, 2x stage 4 and 44x stage 3 as compared to prevalent dialysis).

- Risk would be at most 0.11% per exam or 1 in 908 exposed patients in CKD stage 4 or stage 5-not on dialysis.
  - CKD stage 5 patients may at significantly higher risk: 1 in 218.
  - CKD stage 4 patients are at a lower risk: 1 in 2492.
- *Assuming 5 cases occurred in CKD stage 3,* risk would range between 0.000725% per exam or 1 in 137,928 exposed patients[2].

1. Deo A et al: CJASN 2007: 2; 264-267
2. Ab u-Alfa A et al (Yale Meeting May 2009 and JACR 2008)

Cases stage 4/5: 2.7% and 5.1% respectively

Screening for Chronic Kidney Disease at the Point-of-Care Prior to GBCA Administration

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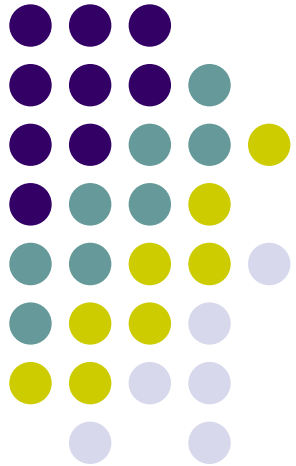
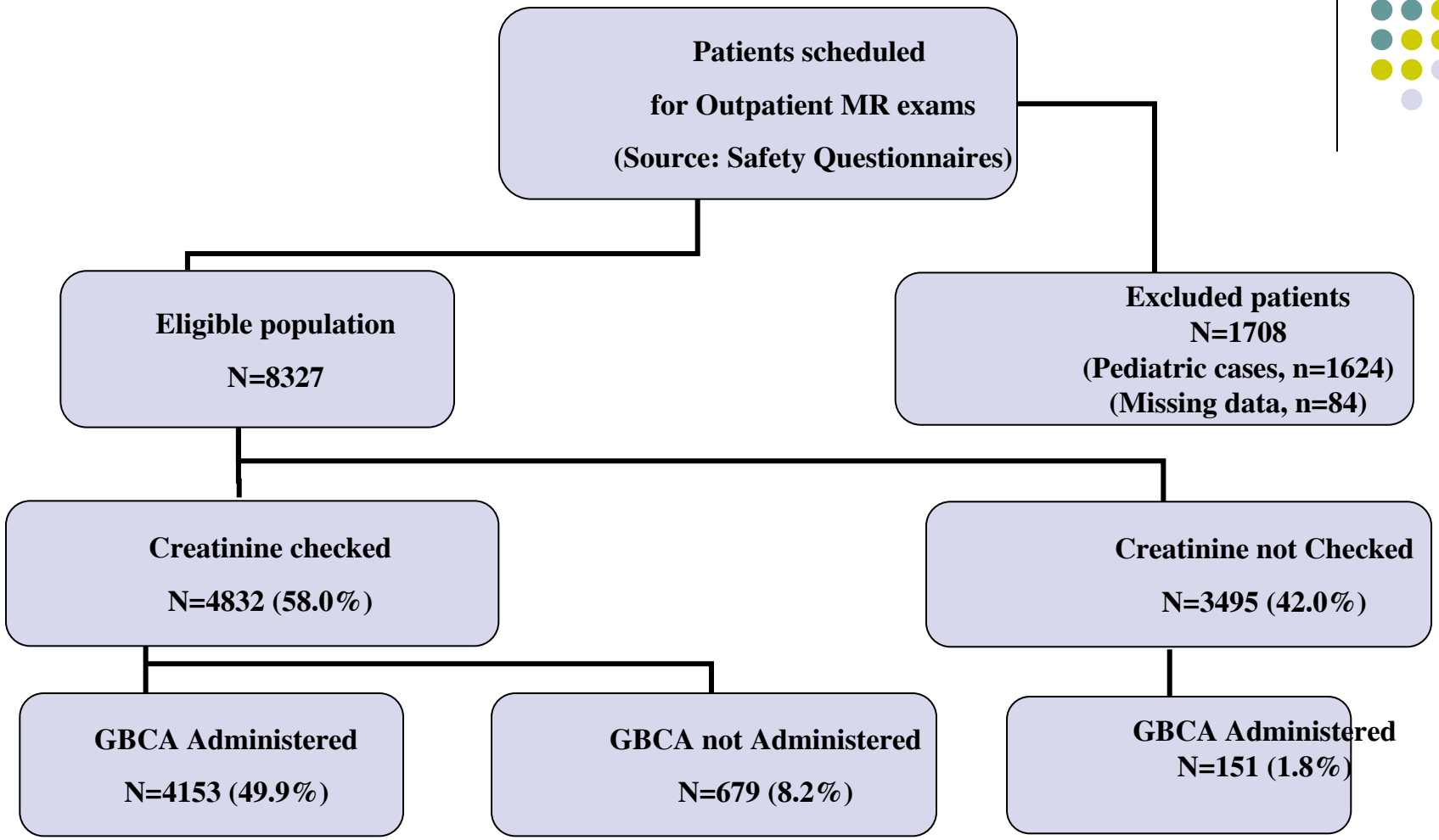
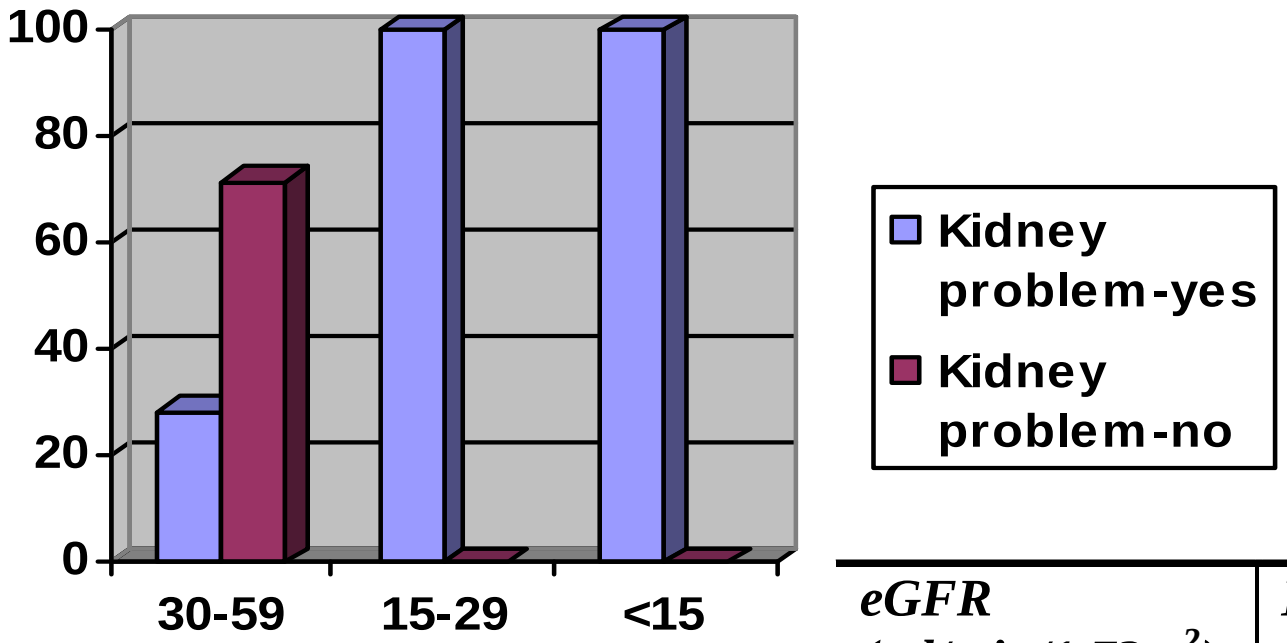




Patel J, Weinreb J and Abu-Alfa A: American Society of Nephrology, Nov 2009, San Diego, Abstract Poster # SA-P2277

CKD Prevalence and Awareness per Stage



eGFR (ml/min/1.73m²)	*N*	%
>60	4718	97.67
30-59	105	2.17
15-29	6	0.12
<15	2	0.04

Patel J, Weinreb J and Abu-Alfa A: American Society of Nephrology, Nov 2009, San Diego, Abstract Poster # SA-P2277

Multivariate Analysis: CKD

Variables	Adjusted OR	CI	p-value
Age ≥ 50	3.67	2.10 - 6.43	0.00
Self-reported Diabetes	1.68	1.05 - 2.69	0.03
Self-reported Hypertension	2.00	1.32 - 3.04	0.00
Self-reported Kidney Problem	11.2	7.07 - 17.7	0.00
Self-reported Single or Transplant kidney	5.00	2.70 - 9.28	0.00

Patel J, Weinreb J and Abu-Alfa A: American Society of Nephrology, Nov 2009, San Diego, Abstract Poster # SA-P2277

Joint Committee of the National Kidney Foundation and American College of Radiology

- A group of 10 physicians representing Radiology, Dermatopathology, adult and pediatric Nephrology, Hepatology and Epidemiology convened a meeting in 2008 to draft a position paper on NSF and GBCA.

- Among the suggested recommendations and work in progress:
  - Use of alternative imaging options before administering GBCA in patients at risk.
  - Screening for reduced GFR in patients at risk for CKD, and identification of AKI patients.
  - If use of GBCA is absolutely necessary for a patient at risk (eg: ESRD, CKD stage 4 or 5, AKI) then detailed patient informed consent should be implemented.
  - In addition, other interventions to potentially reduce the risk of NSF should be considered such as use of the lowest cumulative GBCA dose possible, offering immediate post-administration hemodialysis.
  - The increased risk of post administration dialysis for a patient already established on hemodialysis is minimal. The risks of catheter insertion and infection for patients treated with PD and those with CKD or AKI should be weighed against the potential benefit to reduce the risk of NSF.
  - Provide comparative risk assessment between contrast induced AKI and NSF in patients at risk for both complications.
  - Address risk in special populations: advanced liver disease, pediatric patients.

International Center for NSF Research

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and many thanks to the many patients, their families and referring physicians

4th Annual Scientific Symposium on NSF and GBCA
New York, NY- May 14-15, 2010
Yale University and New York Academy of Sciences
http://cme.yale.edu or http://www.nyas.org/events

Colleague

Dialysis Patient

Mother

Wife

Celeste Castillo Lee

Sister

Person with NSF

Advocate

Friend

Daughter

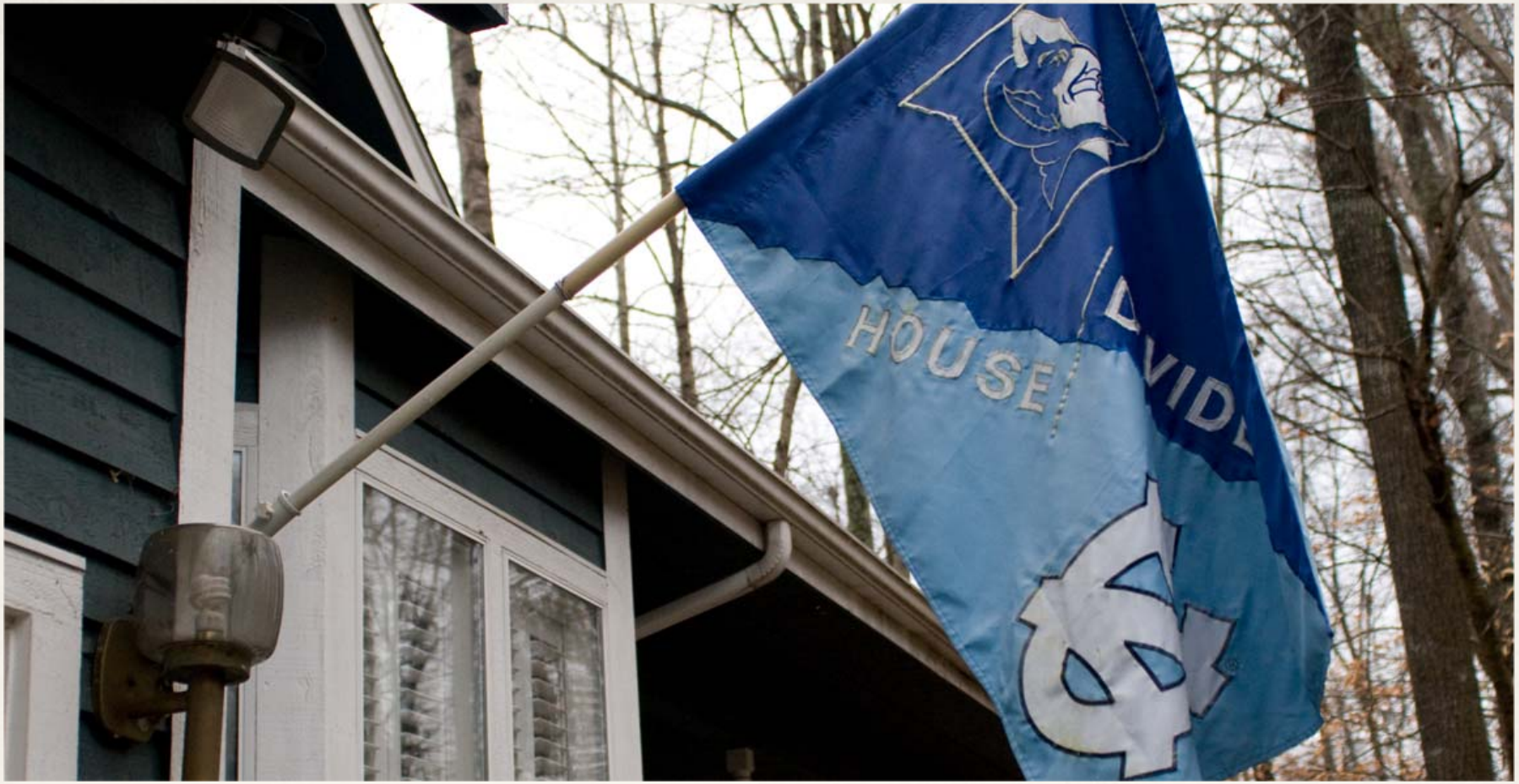
SAFETY CONSIDERATIONS

- Safety considerations related to FDA approved Gadolinium Based Contrast Agents used with MRI scans
- Risk Factors?
- Exposure to GBCA?
- Is the use of GBCA in a high risk patient ever warranted?
- Difference in agents?

I won’t be helping you out with this today

However, I am here to share my story with you --- to humanize the risk of being exposed to gadolinium

My Story.....



NSF is not my only challenge

It is Basketball Season and I live in a house divided!

Let's GO Devil's!!!

T A R H E E L S

THANK YOU

Dotarem®*(gadoterate meglumine)

A brief overview

Dr Pierre Desché, VP, Medical & Regulatory Affairs

Dr Sophie Gaillard, Head of Drug Safety

Food and Drug Administration Advisory Committee, December 8, 2009

* Not marketed in USA

Guerbet
Contrast for Life

About Guerbet and Dotarem®*

- International pharmaceutical group fully dedicated to medical imaging since 1926
- US approved products: Oxilan® (1995) and Hexabrix® (1985)
- Now investigating Dotarem®* (gadoterate meglumine) for US market
  - Dotarem®* is the only macrocyclic and ionic GBCA
  - Classified as “low risk agent for NSF” by EMEA
  - Currently in four Phase III studies in the US
  - Actively recruiting for subjects to expedite studies
  - **NDA filing planned for 2012**

* Not marketed in USA

Guerbet

Dotarem®*

- Marketed internationally since 1989
- Available in 67 countries
  - European market leader (in volume)
  - Asia (incl. Japan under Magnescope® name)
  - Latin America
- 15 million doses injected so far
- Approved indications:
  - CNS, “whole body” MRI and angiography
  - Adults, children and infants
  - Dose = 0.1 mmol/kg (up to 0.3 mmol/kg for special indications)

* Not marketed in USA

Dotarem®*, macrocyclic and ionic, is highly stable

Complexes	Structure	Thermodynamic Stability-log K (1)	Apparent Stability pH 7.4-log K_{cond} (1)	Kinetic Stability pH=7 (2)	Dissociation half-life pH=1 at 25°C (1)
Dotarem®*	Macrocyclic -Ionic	25.6	19.3	High	338 hours
Prohance®	Macrocyclic -Non ionic	23.8	17.1	High	3.9 hours
Gadovist®*	Macrocyclic -Non ionic	21.8	14.7	High	43 hours
Multihance®	Linear-Ionic	22.6	18.4	Medium	< 5 sec
Magnevist®	Linear-Ionic	22.1	17.7	Low	< 5 sec
Omniscan®	Linear-Non ionic	16.9	14.9	Low	< 5 sec
Optimark®	Linear-Non ionic	16.6	15.0	Low	< 5 sec

* Not marketed in USA

(1) Port M., *Biometals*, Feb 2008
(2) Idée JM., *Radiologic Clinics of North America*, Sept 2009

Guerbet

Dotarem®* efficacy and safety

- Demonstrated in 41 European studies (1,943 patients)
- Confirmed in Post Marketing Studies (64,025 patients)
  - Herborn study (1): 24,308 patients
    - Diagnostic quality achieved in 99.6% of cases
    - Excellent or very good image quality in 97.6% of cases
    - 94 patients (0.4%) reported adverse events (most of them related to GBCA)
- Low and stable reporting rate of adverse reactions in post-marketing setting
  - 1.1 for 10,000 patients
  - Mostly feeling of warmth/coldness, pain at injection site, allergic and allergic-like reactions)

* Not marketed in USA

(1) Herborn CU et al, *Inv Rad*, Jan. 2007

Dotarem®* Pharmacovigilance data regarding NSF

- 15 million doses injected
- **NO “single agent” cases**
- 9 “multiple agents” cases
- 1 case still “under investigation”
  - Chronic RI and diabetes
  - Unknown GBCA in 1997 ; 30mL of Dotarem®* on August 29, 2006
  - Clinical signs during summer 2006 / disease onset dated September 5
  - Biopsy in 2008 (transdermal fibrosis, negative CD34 and CD68)
  - Many missing info (renal function, vascular status, surgeries, pro-inflammatory events, indications for MRI)
- 1 case where Dotarem®* was administered after disease onset and before disease worsening

* Not marketed in USA

No NSF cases from FINEST study (1)

- Retrospective study conducted in 2008
- 9 nephrology centres in France
- 308 renally impaired patients had an MRI examination
- 4-month follow up to detect clinical signs suggestive of NSF
- 234 patients (76%) received Dotarem®*
  - 180 patients (77%) with eGFR < 30 mL/min/1.73m²
- No cases of NSF reported

* Not marketed in USA

(1) Choukroun, *Eur. Rad.*, 2008

Guerbet

Rate of reported "single agent" cases of NSF (worldwide data)

	Contrast agent	Number of single agents NSF reports	Number of doses injected (millions)	Single agents NSF Rate
Linear-Non Ionic	Omniscan®	438	50	8.76/million
	Optimark®	7	not avail.	not avail.
Linear-Ionic	Magnevist®	135	90	1.5/million
	MultiHance®	1*	3.5	0.28/million
Macrocyclic-Non Ionic	Gadovist®**	1	not avail.	not avail.
	ProHance®	1	not avail.	not avail.
Macrocyclic-Ionic	Dotarem®**	1? ***	15	0.07/million

* FDA briefing document Table 3

** Not marketed in USA

*** 1 case still "under investigation" (unknown GBCA administered 9 years prior to Dotarem®)

⇒There is a difference between different products

⇒ May be linked to the structure/stability:

- Linear vs. Macrocyclic
- Non ionic vs. ionic

Guerbet

Summary

- Dotarem®* is **the only macrocyclic and ionic GBCA**
- Dotarem®* is widely used outside US
- Has an excellent safety profile for all patients, including (severely) renally impaired patients
- Guerbet's mission is to complete clinical trials in US to support a **priority** FDA review and approval
- Actively recruiting subjects for trials
- More information on Dotarem®* clinical studies available on **clinicaltrials.gov**

* Not marketed in USA

Thank you for your attention

Guerbet

BACK UP SLIDES

December, 8. Washington DC

Guerbet
Contrast for Life

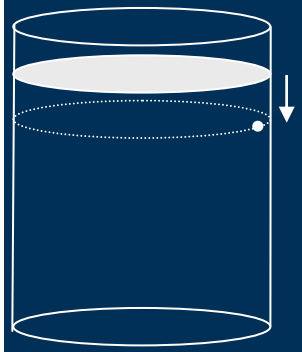
Risk categories

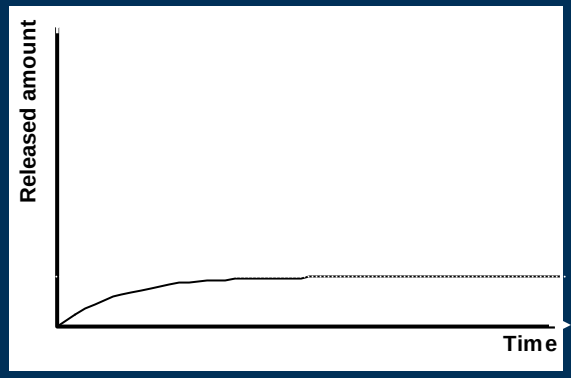
- It appears that risk of NSF is different among different products
- As EMEA recently concluded, 3 categories can be identified:
  - High risk agents
    - Agents with high number of cases and low stability - Linear agents
    - Screening of patients for eGFR should be done before injection
  - Medium risk agents
    - Agents with low number of cases and low to medium stability - Linear agents
    - Screening of patients for eGFR is recommended
  - Low risk agents
    - Agents with low number of cases and high stability - Macrocyclic agents
    - Screening of patients for eGFR is recommended

Understanding NSF

- Guerbet is dedicated to understand NSF and has several ongoing studies:
  - Studies regarding the stability of the various categories of gadolinium chelates in renally impaired rats and the mechanism of NSF (role of risk factors, investigation of reliable biomarkers)
    - Results to be presented at ECR 2010
  - In vitro studies regarding the physico-chemical properties of gadolinium chelates
  - Collaboration with academic centres involved in preclinical studies dealing with the mechanism of NSF

Relation thermodynamic/kinetic stabilities





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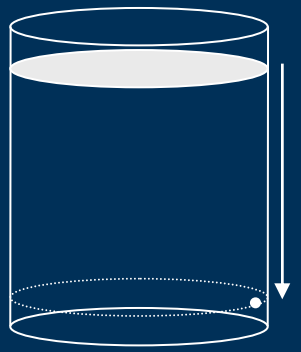

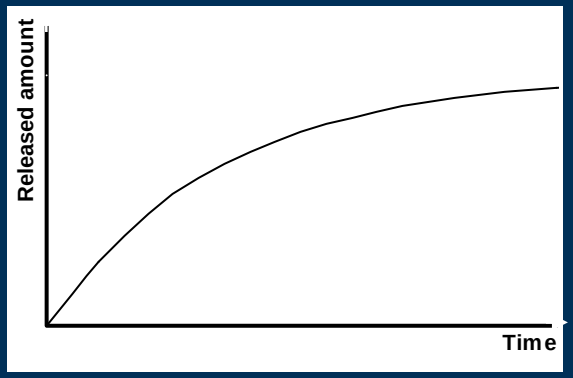

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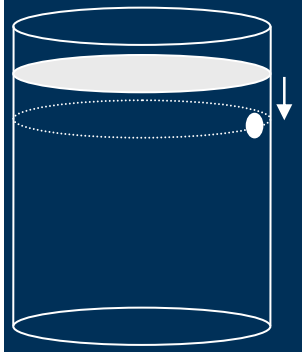

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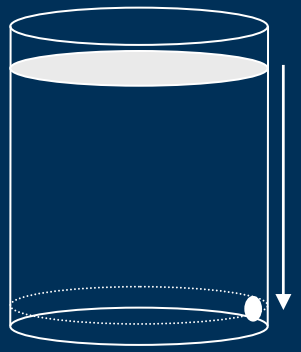

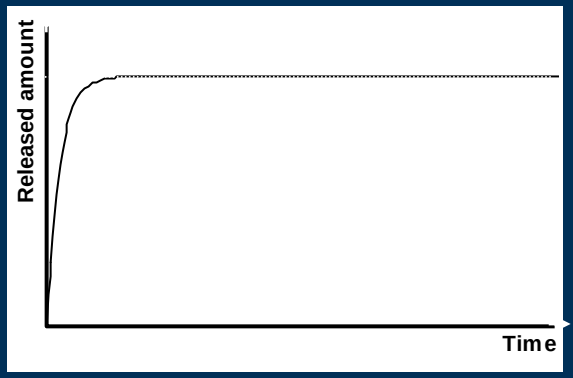

D

Guerbet

Dotarem® has a unique structure

The only macrocyclic and ionic GBCA

	Ionic	Non ionic
Macrocyclic	Dotarem®*	Prohance® Gadovist®*
Linear	Magnevist® Multihance® Primovist® Eovist® Ablavar®	Omniscan® Optimark®

* Not marketed in USA

Joint
Cardiovascular and Renal Drugs
and
Drug Safety and Risk Management
Advisory Committee Meeting

December 8, 2009

Emanuel Kanal, MD, FACR, FISMRM, AANG
Professor of Radiology and Neuroradiology
Director, Magnetic Resonance Services
University of Pittsburgh Medical Center
Department of Radiology

1. Cumulative Dose Issues

1. Cumulative Dose Issues

- NSF incidence (and severity?) seems to scale with total, possibly lifetime, cumulative administered dose(s)

- Increasing gadolinium concentrations have been reported in serial tissue biopsies of NSF patients

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

1. Cumulative Dose Issues

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Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

1. Cumulative Dose Issues

Recommend:

That practitioners record, monitor, and review total GBCA doses already administered to patients with significant renal disease prior to further GBCA administration to these patients.

2. Neonates, Infants

2. Neonates, Infants

- No known patients <6 years old
- Thousands of neonate/infant CE-MR have been studied for, eg, congenital heart disease, with no NSF Dx in this age group
- NSF is clearly not a "GFR-only" issue, or MANY more low GFR patients - and neonates - would contract NSF
- Risks of alternate tests involving ionizing radiation are especially high/concerning in this age group

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

2. Neonates, Infants

Recommend:

Against any special wording/warning for this age group, despite prior European recommendations in this regard

3. Hepatic Disease

3. Hepatic Disease

- No known cases of NSF in patients without significant renal disease, regardless of hepatic disease status; this has become a significant source of confusion for MR practitioners

- Although severe hepatic disease may be associated with labile renal function, overall AKI incidence does not appear to be frequently associated with hepatic disease*

*Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod, A. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol, 2007;18(4):1292-1298.

Incidence and Outcomes in Acute Kidney Injury: A Comprehensive Population-Based Study

Tariq Ali,* Izhar Khan,† William Simpson,‡ Gordon Prescott,§ John Townend,§ William Smith,§ and Alison MacLeod*

*Departments of *Medicine & Therapeutics and §Public Health, University of Aberdeen; Departments of †Nephrology and ‡Biochemistry, Grampian Health Board, Aberdeen, United Kingdom*

Epidemiological studies of acute kidney injury (AKI) and acute-on-chronic renal failure (ACRF) are surprisingly sparse and confounded by differences in definition. Reported incidences vary, with few studies being population-based. Given this and our aging population, the incidence of AKI may be much higher than currently thought. We tested the hypothesis that the incidence is higher by including all patients with AKI (in a geographical population base of 523,390) regardless of whether they required renal replacement therapy irrespective of the hospital setting in which they were treated. We also tested the hypothesis that the Risk, Injury, Failure, Loss, and End-Stage Kidney (RIFLE) classification predicts outcomes. We identified all patients with serum creatinine concentrations >150 mol/L (male) or >130 mol/L (female) over a 6-mo period in 2003. Clinical outcomes were obtained from each patient's case records. The incidences of AKI and ACRF were 1811 and 336 per million population, respectively. Median age was 76 yr for AKI and 80.5 yr for ACRF. Sepsis was a precipitating factor in 47% of patients. The RIFLE classification was useful for predicting full recovery of renal function ($P < 0.001$), renal replacement therapy requirement ($P < 0.001$), length of hospital stay [excluding those who died during admission ($P < 0.001$)], and in-hospital mortality (P 0.035). RIFLE did not predict mortality at 90 d or 6 mo. Thus the incidence of AKI is much higher than previously thought, with implications for service planning and providing information to colleagues about methods to prevent deterioration of renal function. The RIFLE classification is useful for identifying patients at greatest risk of adverse short-term outcomes.

J Am Soc Nephrol 18: 1292–1298, 2007. doi: 10.1681/ASN.2006070756

Discussion

This is the first study to define the incidence of AKI and ACRF in a defined geographic population base, regardless of whether RRT was required and irrespective of where treatment took place. The combined annual incidence of AKI and ACRF was 2147 pmp, very much higher than all previous published estimates. The RIFLE classification predicted the probability of

Table 3. Comorbid conditions[a]

Condition	Total (%)[b]	AKI (%)	ACRF (%)	*P*
IHD	31.5	29.5	42	0.028
Hypertension	27.8	27.2	30.7	0.591
Malignancy	22.5	21.7	25	0.591
CVD	17.1	17.3	15.9	0.870
Diabetes	15.7	15	19.3	0.385
Cardiac failure	13.2	12.9	14.8	0.754
None	15.7	16.0	13.6	0.683
PVD	7.7	6.8	12.5	0.100
COPD	7.7	7.8	6.8	0.919
Liver disease	2.8	3.0	2.3	1.000
CT disease	2.3	2.5	1.1	0.703
Comorbid sum[c]				0.173[d]
0	15.7	16.0	13.6	
1	42.2	43.2	36.4	
2	24.2	24.3	23.9	
3	18.0	16.5	26.1	

[a]COPD, chronic obstructive airway disease; CT, connective tissue; CVD, cerebrovascular disease; IHD, ischemic heart disease; PVD, peripheral vascular disease.

[b]ARF ACRF.

[c]Number of comorbid conditions in a patient.

[d] [2] for all groups 4.982, df 3, *P* 0.173.

3. Hepatic disease

Recommend:

Against any special wording/warning for this disease group, despite prior recommendations in this regard

4. Specific GFR/CKD Levels

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

4. Specific GFR/CKD Levels

- Track Record:
  1. June 8, 2006 PHA: Dialysis or **GFR<=15** (cc/ml/1.73m2)
  2. December 22, 2006 PHA: **GFR < 60**
  3. May 23, 2007 PHA: **GFR < 30**

- The vast majority of NSF patients are stage 5 CKD or AKI at time of GBCA administration, with some stage 4 CKD, even rare biopsy confirmed stage 3 CKD cases now known (1,2)

1. Kaori Shibui, Hiroshi Kataoka, Naoyo Sato, Yoshihko Watanabe, Mamiko Kohara, Takahiro Mochizuki. A case of NSF attributable to contrast MRI repeated in a patient with stage 3 CKD at a renal function of eGFR > 30 ml/min/1.73 m2. Japanese Journal of Nephrology, 2009;51(6):676. Proceeding of the 39th Eastern Regional Meeting of the Japanese Society of Nephrology, October 2-3, 2009, Tokyo
2. FDA Medwatch database as per verbal communication, Eric Cantor ,MD, GE Healthcare, September 16, 2009

4. Specific GFR/CKD Levels

- The "moving target" GFR level is very confusing to MR practitioners. Worse, it connotes absolute safety above the stated threshold.

- Unrelated to NSF, nephrologists are now considering subdividing CKD into stages 3a and 3b, recognizing the marked range of renal function in 30<=GFR<60 (stage 3).

- Between 1:5 and 1:8 of all reported cases were in AKI at time of administration (1-3)

1. Verbal communucation, Dr. Ali Abu-Alfa,, March 4, 2008
2. Prince MR, Zhang H, Morris M, MacGregor JL, Grossman ME, Silberzweig J, DeLapaz RL, Lee HJ,Magro CM, Valeri AM. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology, 2008;248(3)807-816
3. Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA. Nephrogenic Systemic Fibrosis: Incidence, associations, and effect of risk factor assessment-Report of 33 cases. Radiology, 2009;250(2):371-377

4. Specific GFR/CKD Levels

Recommend:

1. Remove any reference to a specific GFR "threshold"; replace with "...significant renal disease". Provide facts/incidence distribution, permit physicians to exercise their judgement on a case-by-case basis.

4. Specific GFR/CKD Levels

Recommend:

2. Increase emphasis on incidence in AKI patients!

5. High dose agents' contradictory labeling wording

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

- Gadolinium-based contrast agents (GBCAs) increase risk of NSF in patients with:
  - acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or
  - acute renal insufficiency of any severity due to hepato-renal syndrome or in perioperative liver transplantation period.
- In these patients, avoid use of GBCAs unless diagnostic information is essential and not available with non-contrast enhanced MRI.
- NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs.
- Screen all patients for renal dysfunction by history and/or laboratory tests.
- When administering a GBCA, do not exceed recommended dose and allow sufficient time for elimination before readministration (5.2).

GE Healthcare

OMNISCAN™ (gadodiamide) Injection

ONC-2Q-OSLO
Revised June 2007

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use OMNISCAN safely and effectively. See full prescribing information for OMNISCAN.

OMNISCAN™ (gadodiamide) Injection for Intravenous Use

Initial U.S. Approval: 1993

2 DOSAGE AND ADMINISTRATION

2.1 CNS (Central Nervous System)

Adults: The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. An additional 0.4 mL/kg (0.2 mmol/kg) can be given within 20 minutes of the first dose [*see Dosage and Administration (2.3)*].

F1/3.5524.44

Bracco Diagnostics

Revised May 2007

ProHance®

(Gadoteridol) Injection, 279.3 mg/mL

DOSAGE AND ADMINISTRATION

Central Nervous System

ADULTS: The recommended dose of ProHance (Gadoteridol) Injection is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min). In patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose.

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

5. High dose agents' contradictory labeling wording

Recommend:

1. Reword labeling

2. Reconsider high dose approval for any/all linear agents

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

5. High dose agents' contradictory labeling wording

Recommend:

Assume that these agents were being introduced for the first time now, with what we know today: Which would you approve for high dose administration - and which would you not?

6. Minimal Dosing Required

6. Minimal Dosing Required

- Innumerable references confirm that the lower the administered dose, as well as the lower the total cumulative administered doses, the lower the likelihood of contracting NSF.

- EVERY societal and regional guideline includes the common sense recommendation to decrease administered dose to this population to as low as diagnostically required

Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting

6. Minimal Dosing Required

Recommend:

Despite it being "off label" to do so, STRONGLY advocate administration of the lowest dose diagnostically required in patients with significant renal impairment.*

* NOTE: If you WOULD recommend this conservative behavior - it would no longer be "off label"!

Medwatch

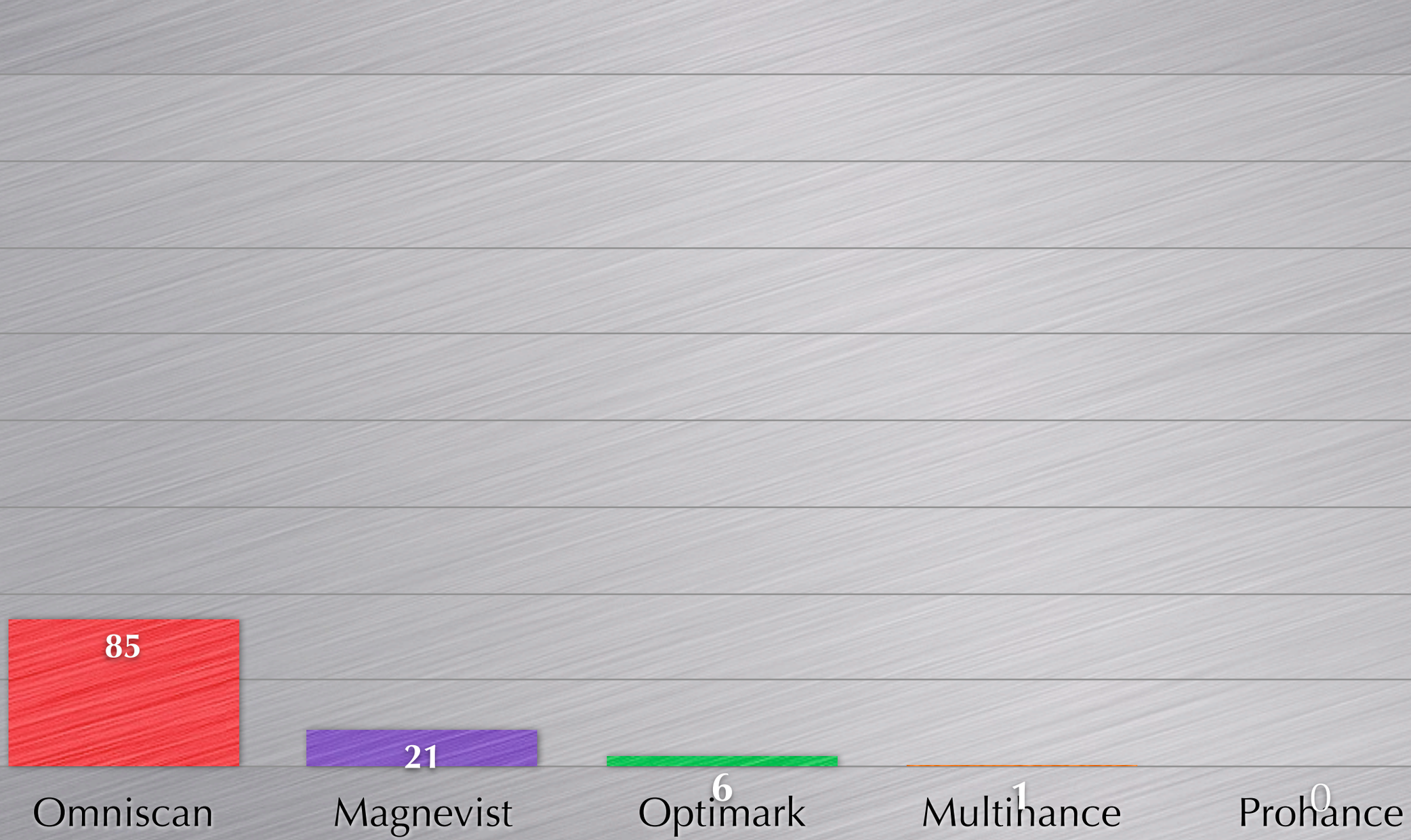
NSF Medwatch Reports
10/26/06

Medwatch Reported Cases To Date (including confounded cases)

Oral communication, Dr. George Mils, FDA Office of Surveillance and Epidemiology (Drug Safety group), 10/26/06.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports
1/18/07

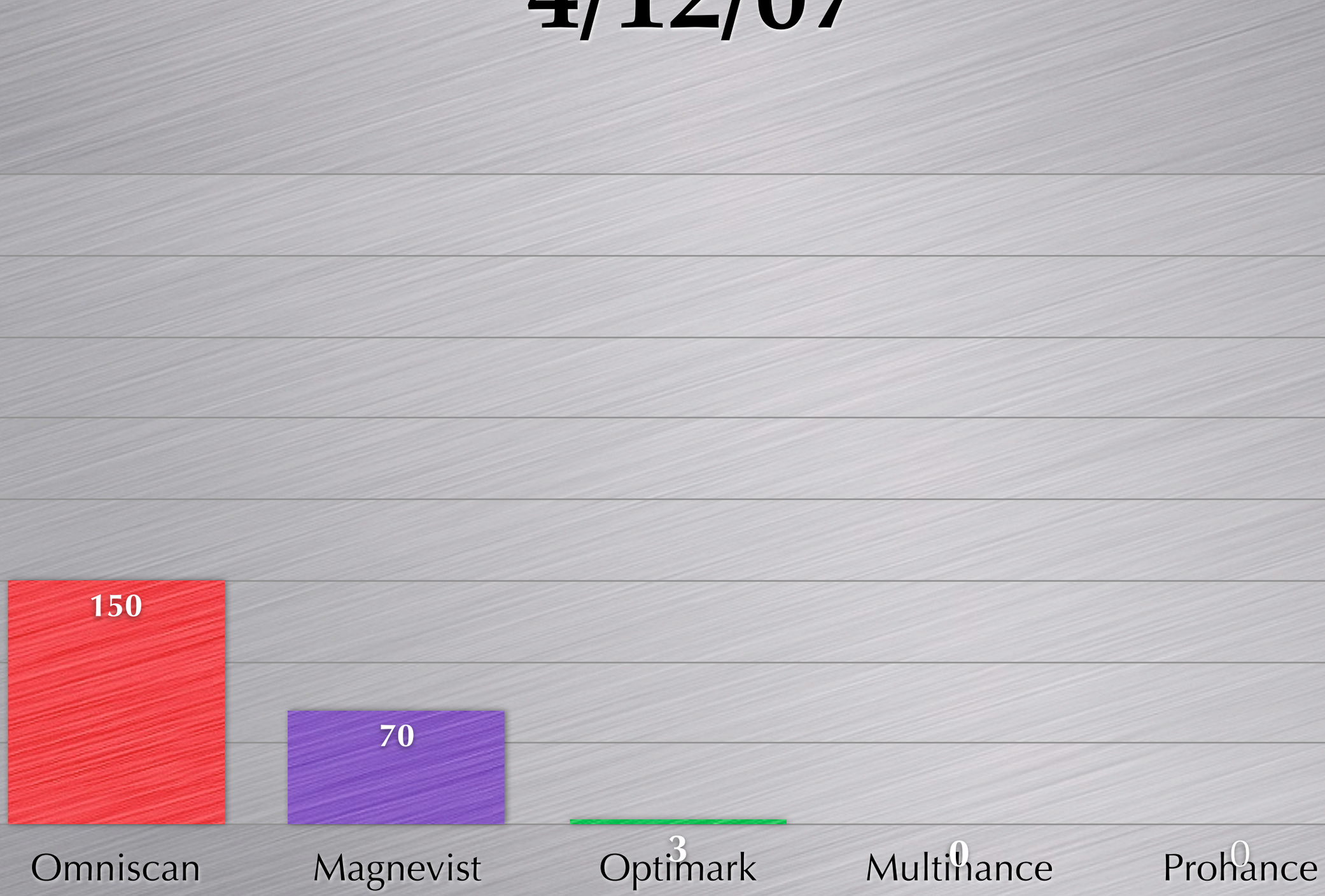


Medwatch Reported Cases To Date (including confounded cases)

Written communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 1/18/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports
4/12/07

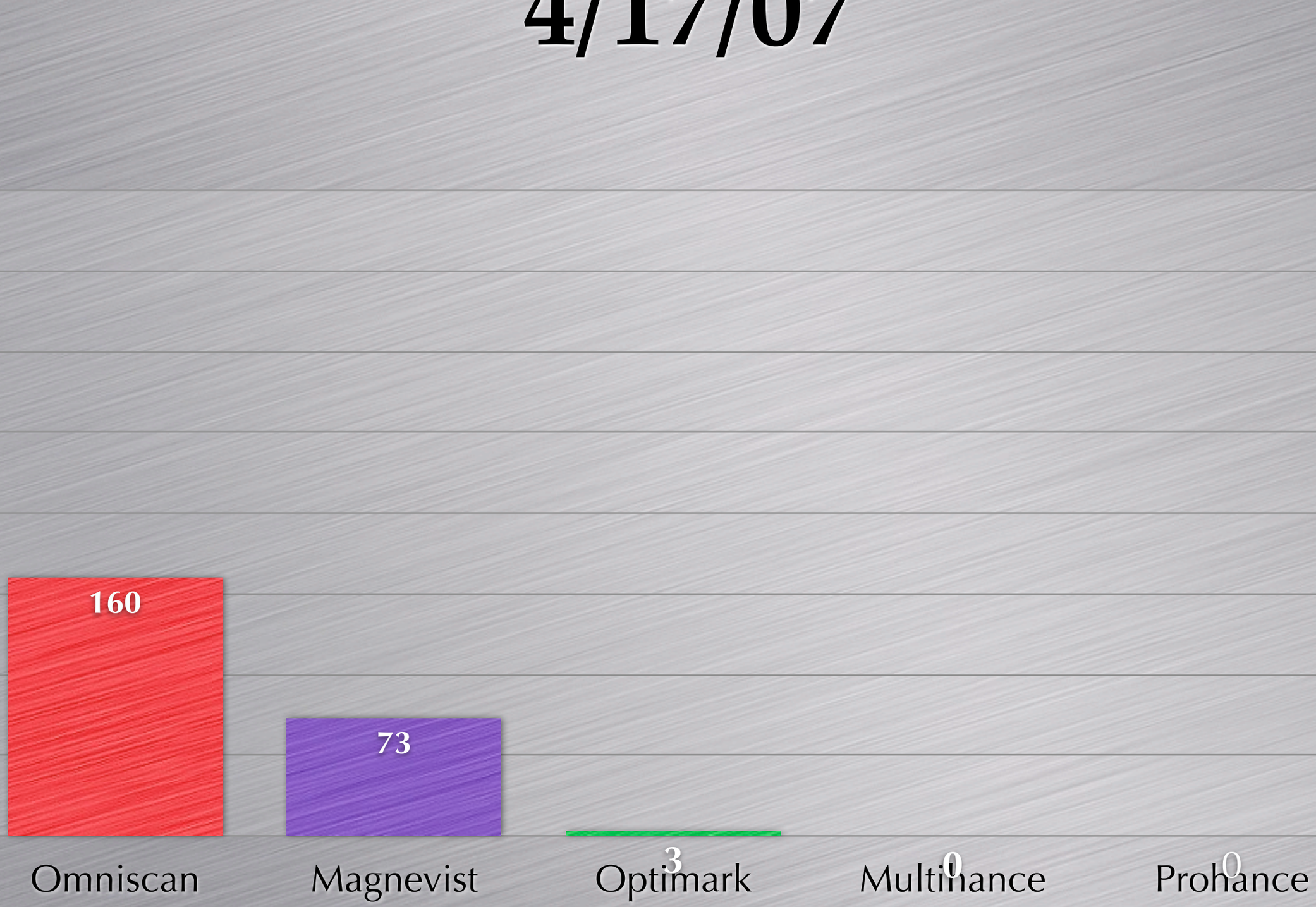


Medwatch Reported Cases To Date (including confounded cases)

Oral communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 4/12/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports
4/17/07



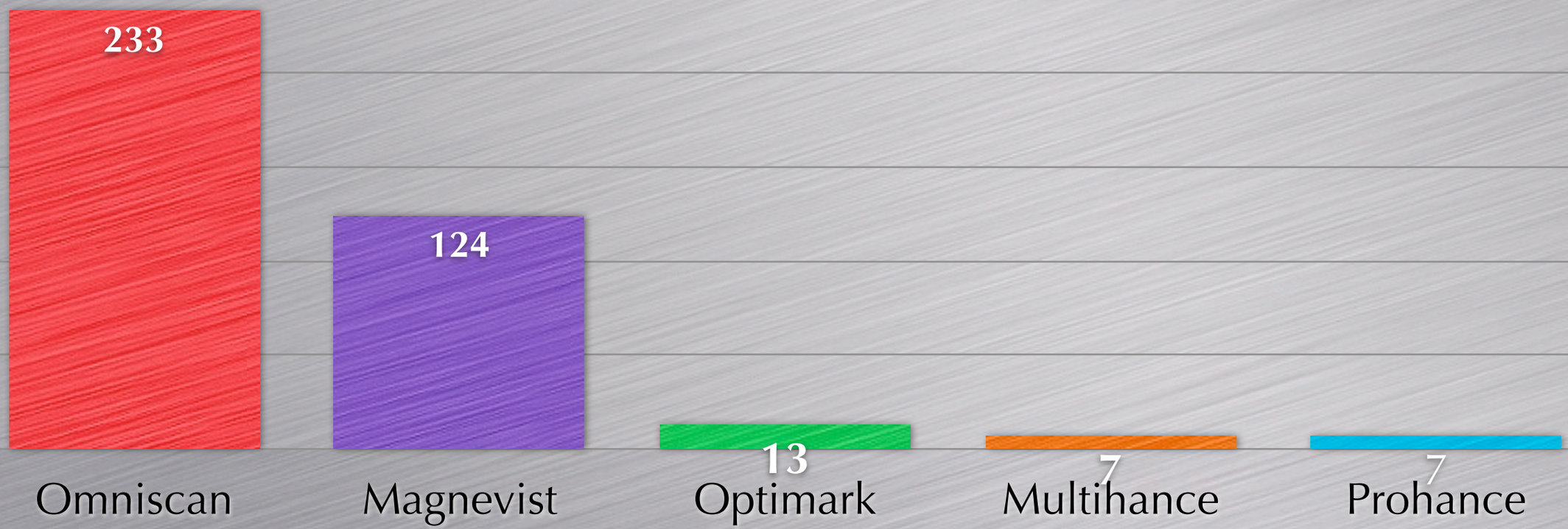
Medwatch Reported Cases To Date (including confounded cases)

Oral communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 4/17/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports

8/8/07



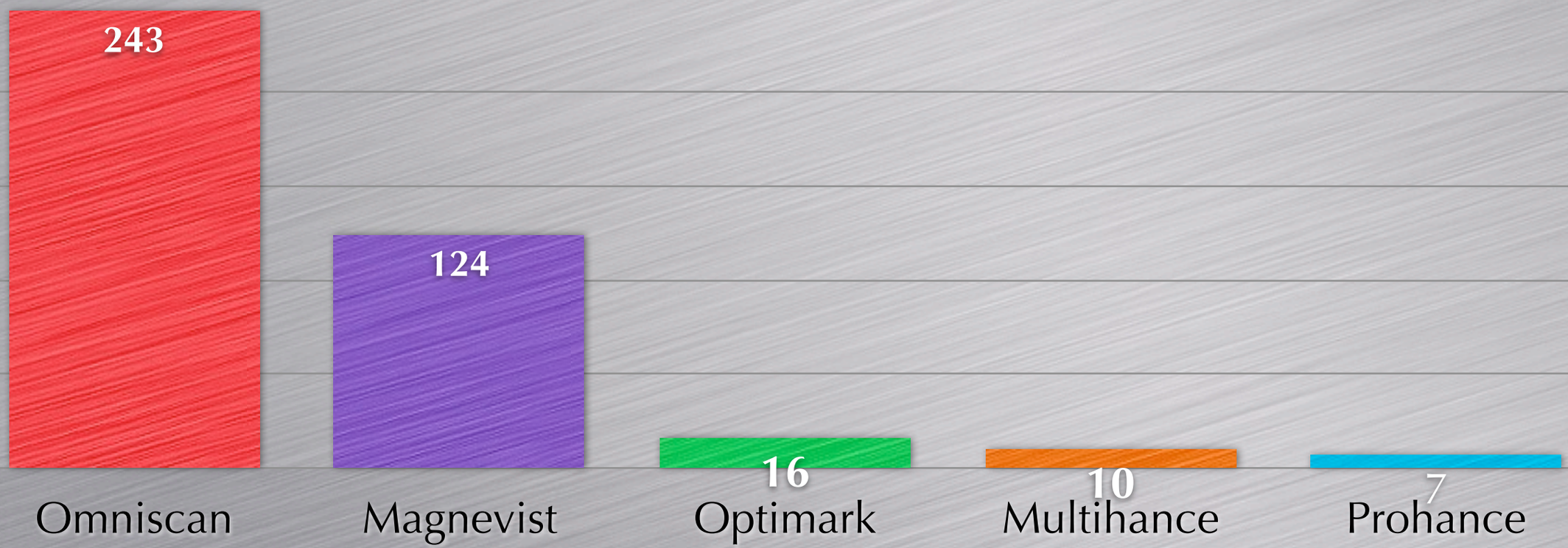
Medwatch Reported Cases To Date (including confounded cases)

Written communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 8/8/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports

9/7/07



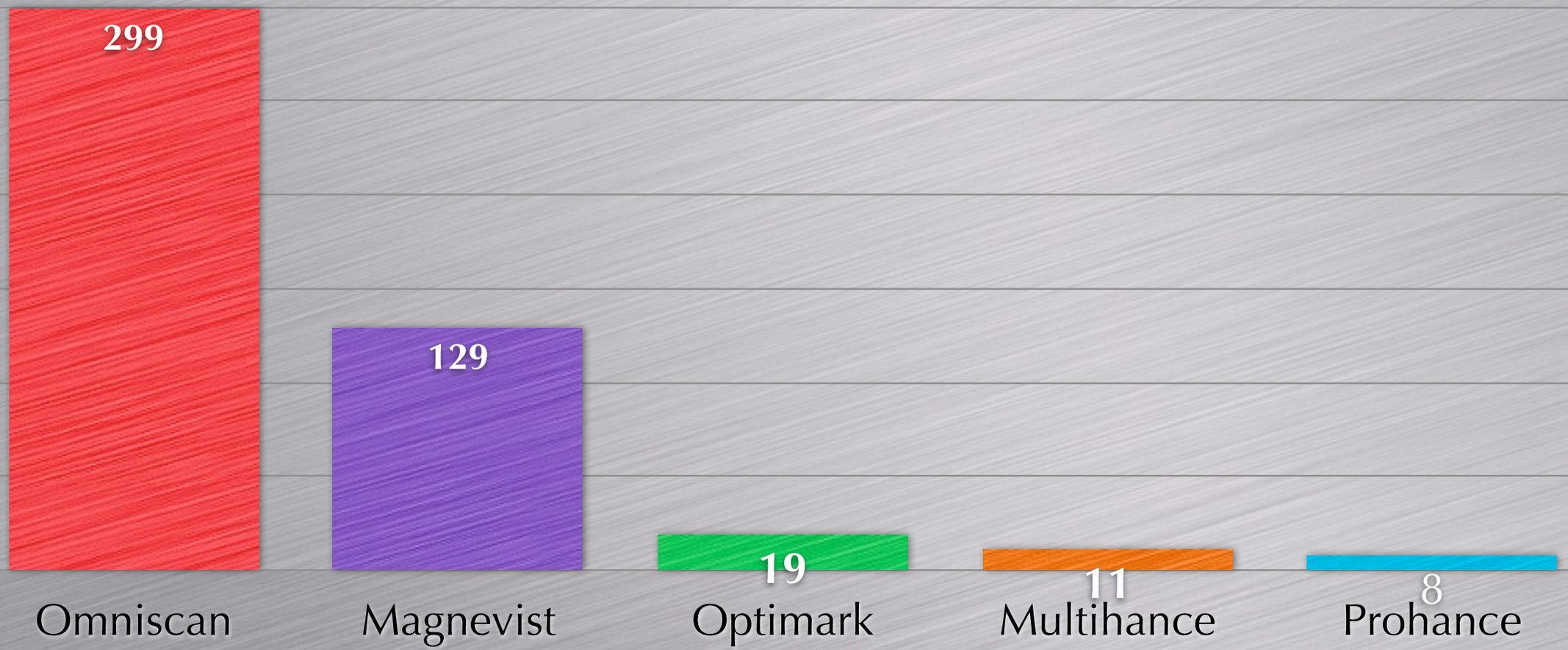
Medwatch Reported Cases To Date (including confounded cases)

Written communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 9/7/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports

10/31/07

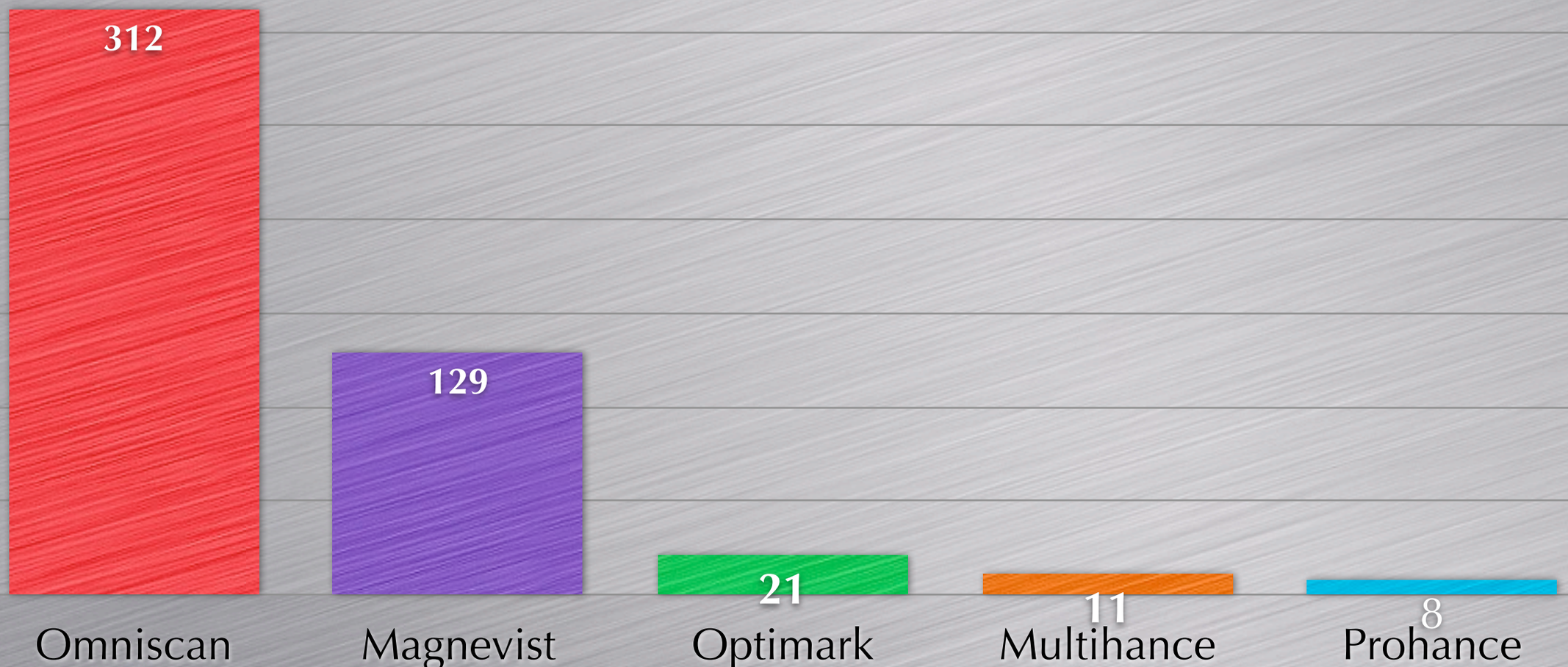


Medwatch Reported Cases To Date (including confounded cases)

Written communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 10/31/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports
11/23/07

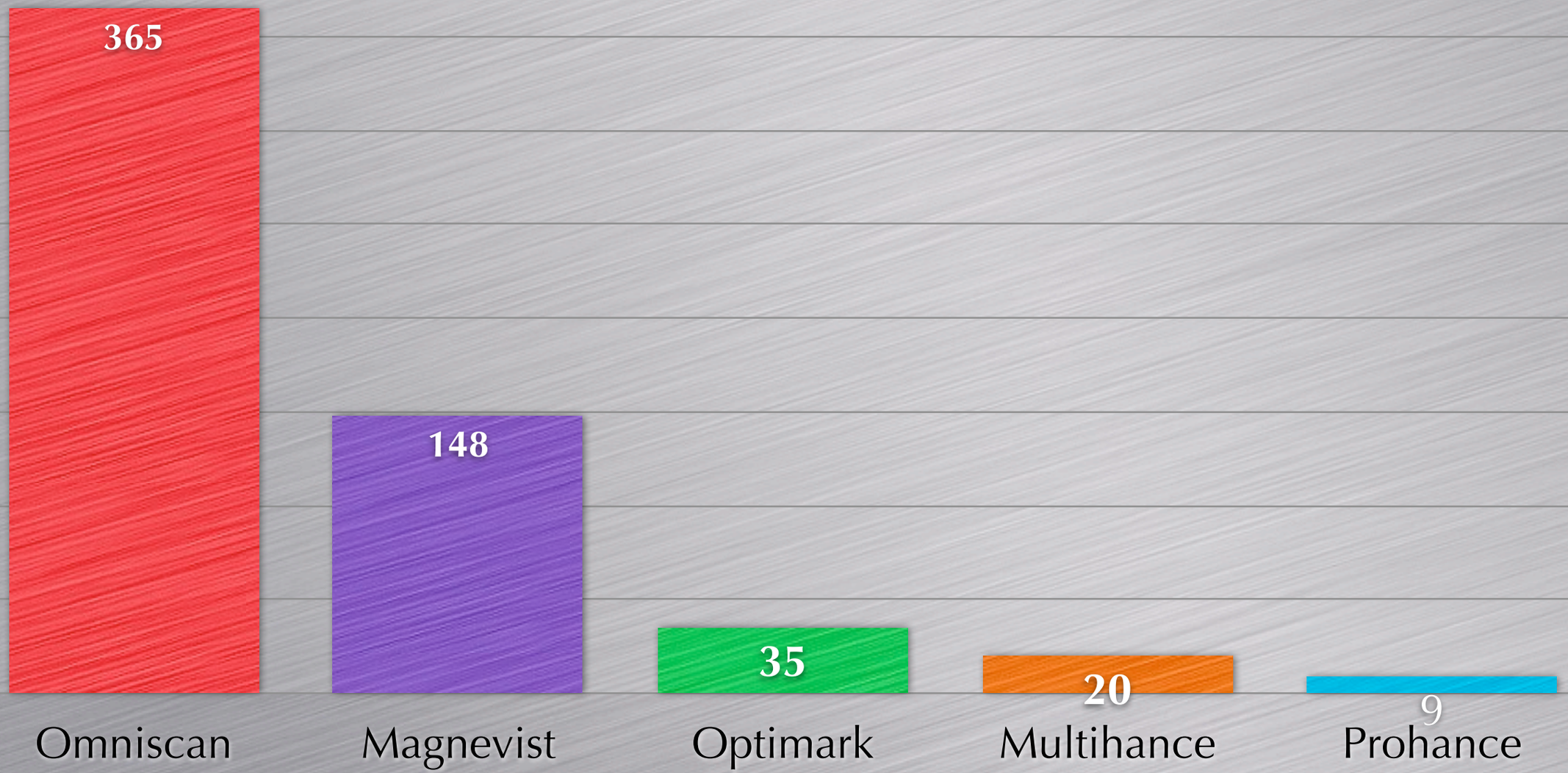


Medwatch Reported Cases To Date (including confounded cases)

Written communication, Dr. Melanie Blank, FDA Office of Surveillance and Epidemiology (Drug Safety group), 11/26/07.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports 1/30/08

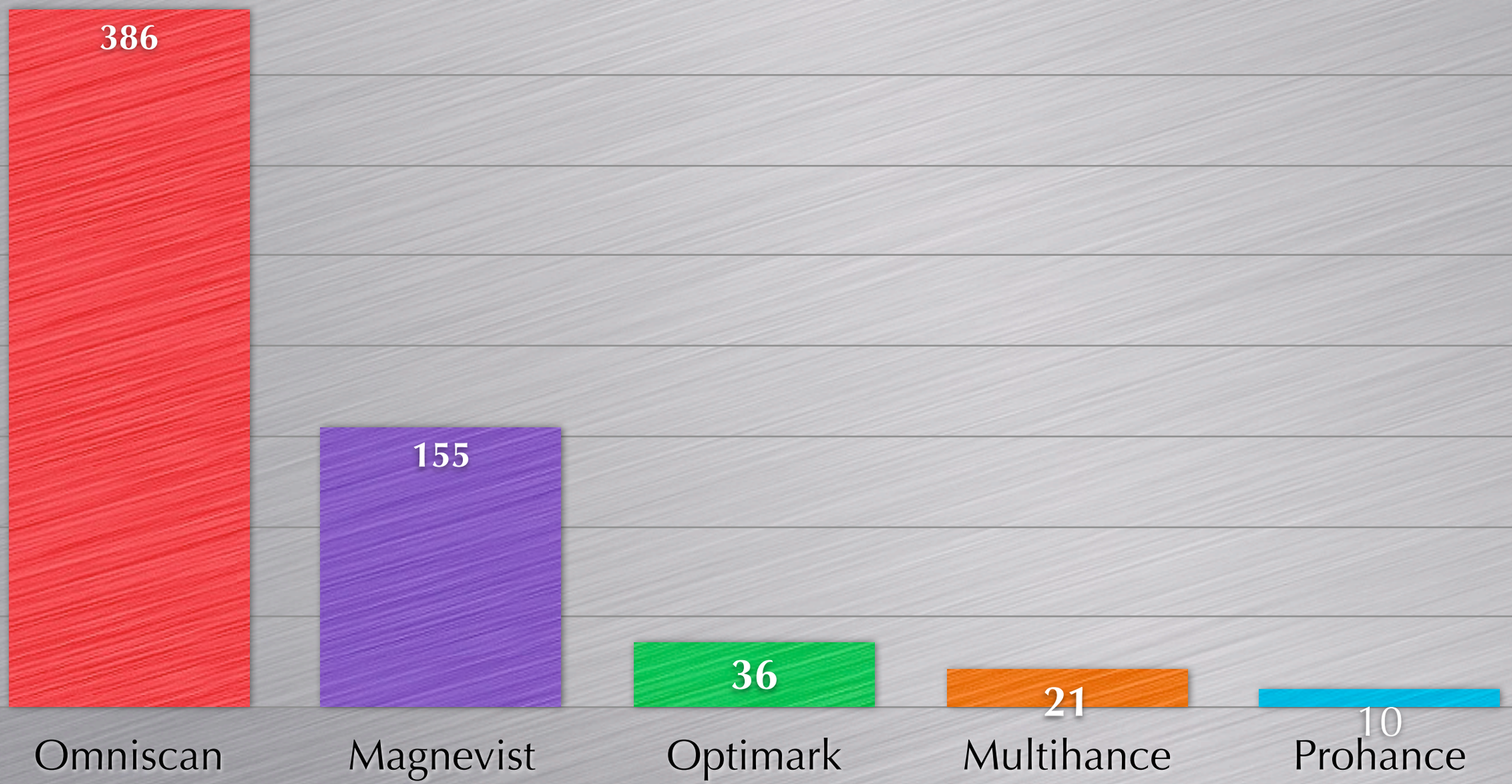


Medwatch Reported Cases To Date (including confounded cases)

Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 1/30/08.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports 2/25/08

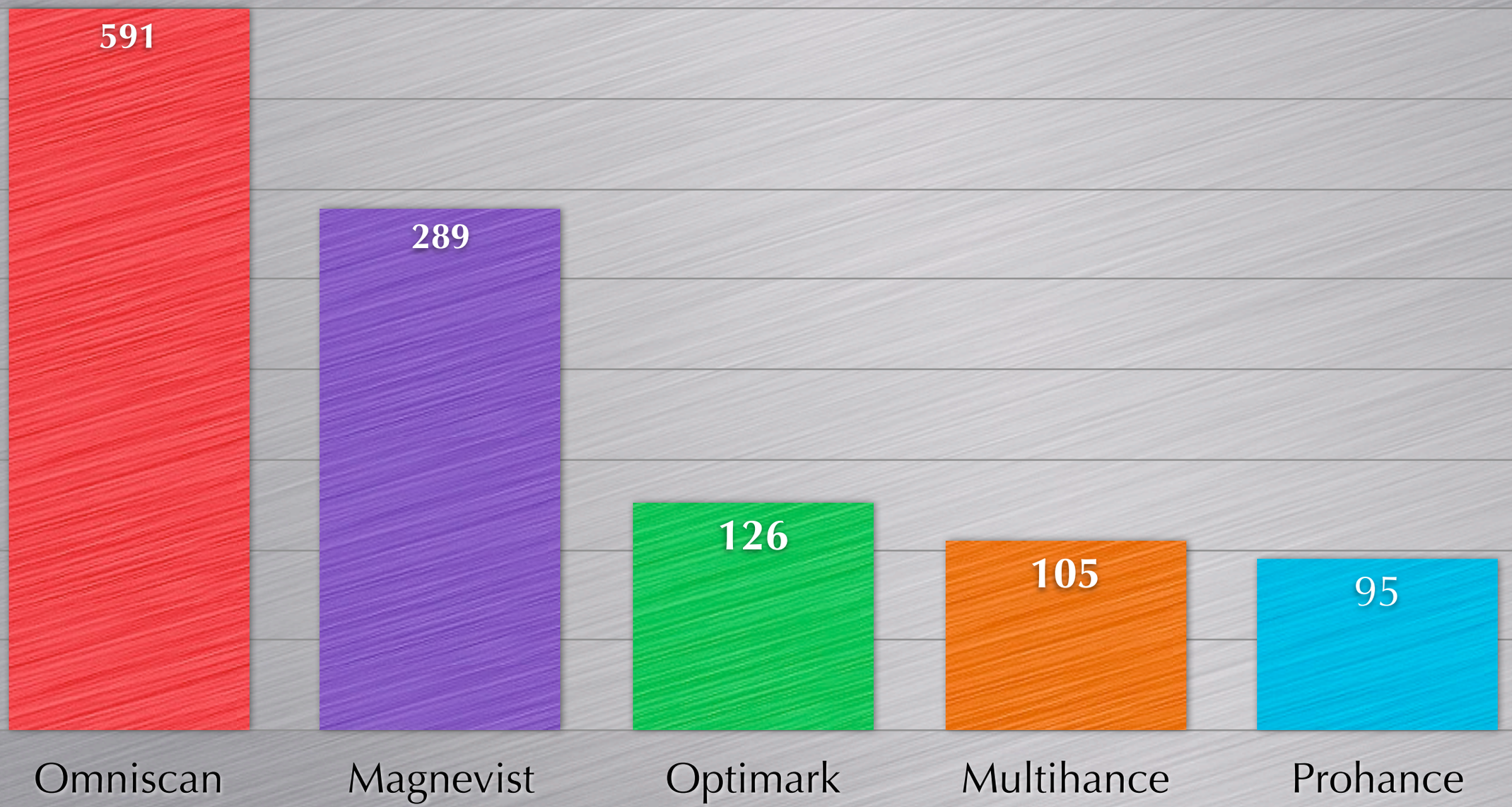


Medwatch Reported Cases To Date (including confounded cases)

Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 2/20/08.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports 7/1/08



Medwatch Reported Cases To Date (including confounded cases)

Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 7/1/08.

Kanal FDA Presentation 12/8/09

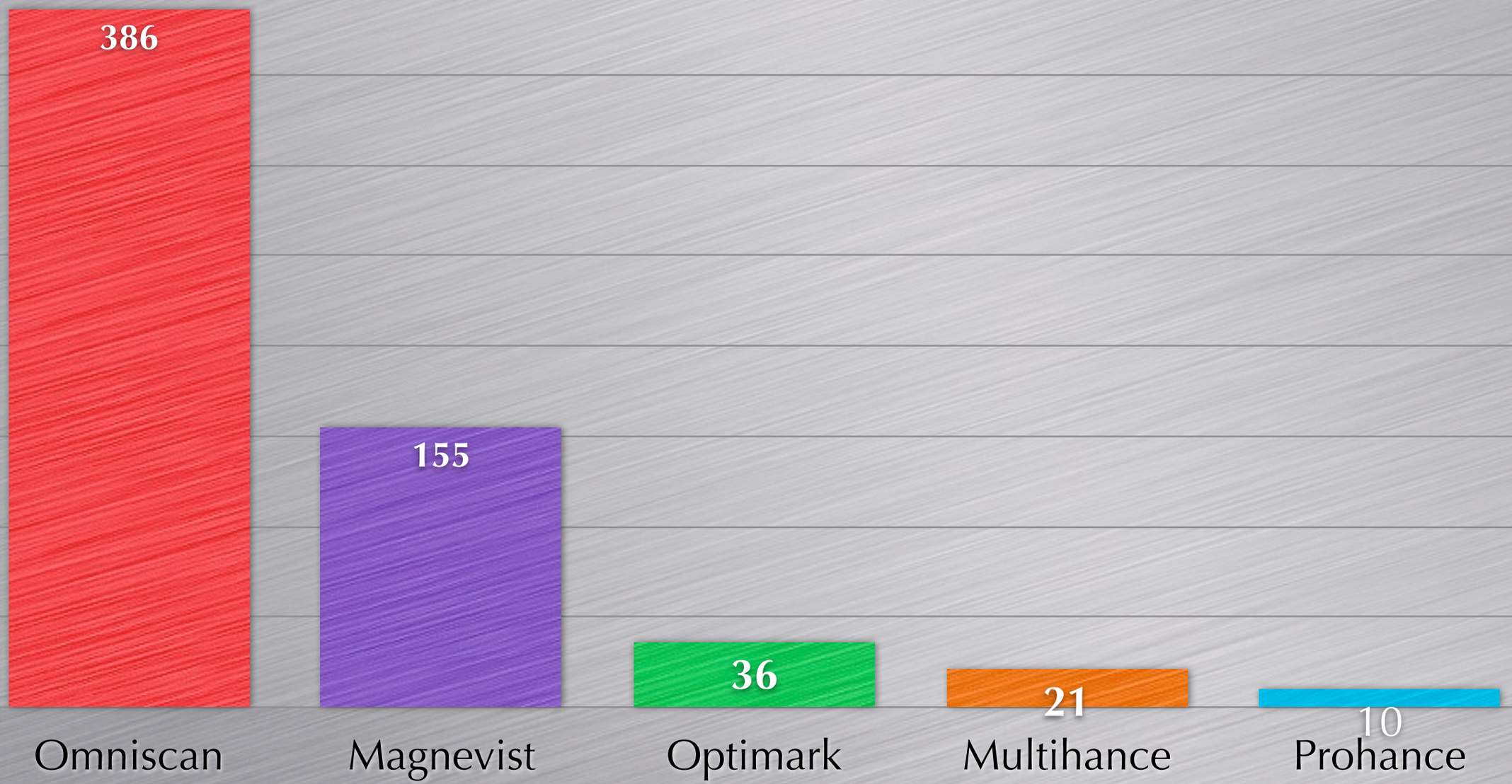
NSF Medwatch Reports

In Spring, 2008, one of the pharmaceutical firms reported to the FDA ~85 cases of NSF for which the agent was unknown as 85 new case reports for *each agent*.

All subsequent Medwatch relative agent data were rendered inaccurate by this single move.

Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 7/1/08.

NSF Medwatch Reports 2/25/08



Medwatch Reported Cases To Date (including confounded cases)

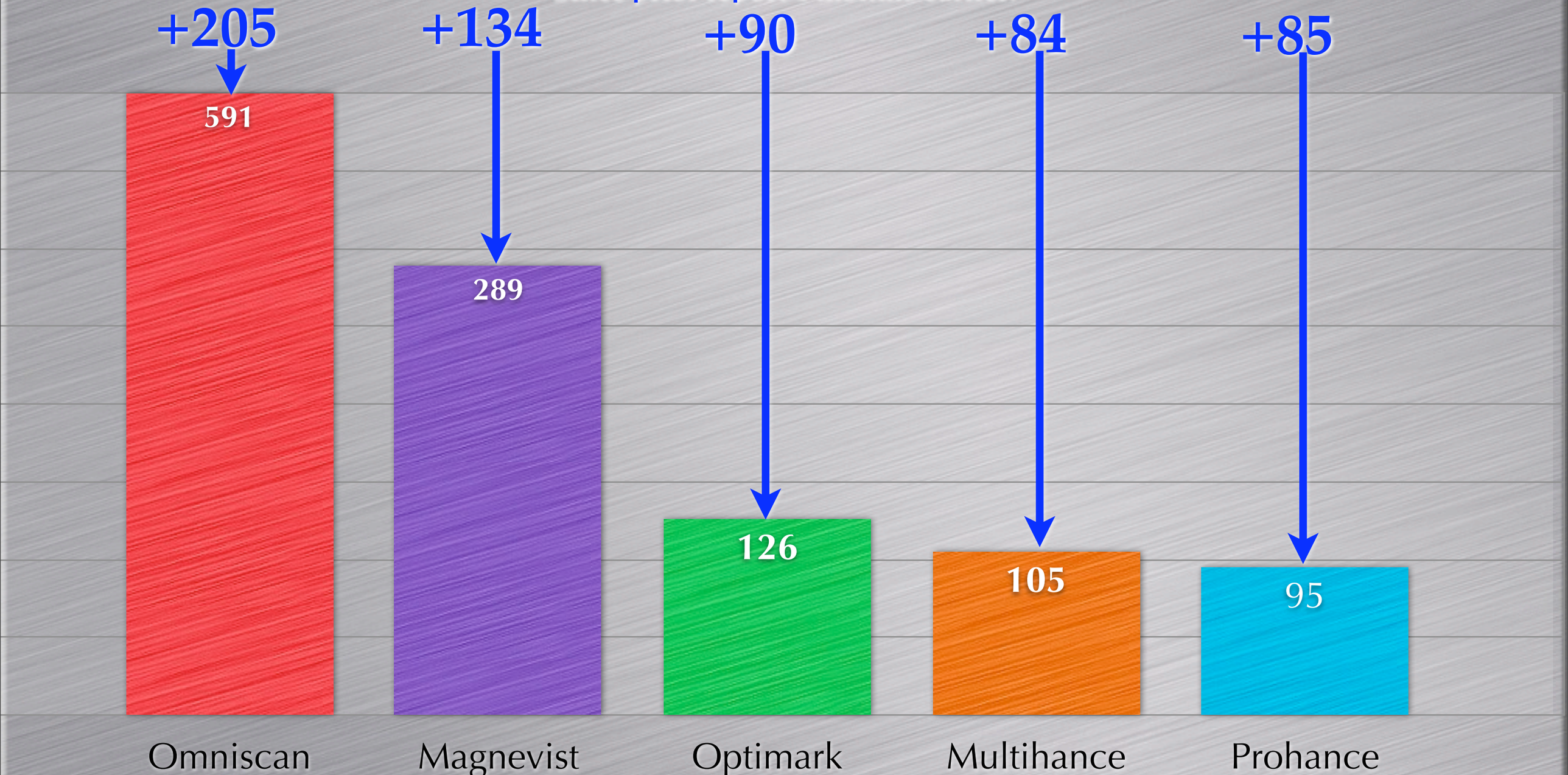
Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 2/20/08.

Kanal FDA Presentation 12/8/09

NSF Medwatch Reports

7/1/08

Since prior report 4 months earlier:



Medwatch Reported Cases To Date (including confounded cases)

Written communication, Janos Bacsanyi,, FDA Office of Surveillance and Epidemiology (Drug Safety group), 7/1/08.

Kanal FDA Presentation 12/8/09

7. Product ID Database Access

7. Product ID Database Access

- Untold millions of dollars have been expended in generating and organizing what today is arguably the world's most comprehensive decade-long NSF database regarding who got how much of what agent and when, the presence or absence of biopsy confirmation of NSF diagnosis, etc. etc. etc.

- For the protection of our patients as well as for investigating this disease, it is imperative that this detailed database be released to the FDA and to radiologists, NSF-researchers, and scientists

7. Product ID Database Access

Recommend:

FDA: Request access to this database from the parties involved in the multidistrict litigation who jointly created it.

MR pharmaceutical firms: For the sake of all our patients, release access to this scientific database to all clinicians and researchers

Thank you

Tuesday, December 8, 2009

Martin Prince MD, PhD

Professor of Radiology

Cornell and Columbia Universities, USA

Author of 4 articles on NSF

Chairman, NSF working group

Disclosures

1. Patent Agreements: Epix, Bayer, Bracco, GE, Siemens, Philips, Mallinckrodt, Medrad, Nemoto, Topspins, Hitachi, Lantheus

2. These are my personal comments.

Papular morphology

Dimpling

Prince Articles on NSF

- Incidence of NSF at Two Large Medical Centers.

  Radiology, 2008; 248: 807-816.

- Features of NSF on radiology examinations.

  AJR 2009;193:61-9.

- Risk Factors for NSF: A Literature Review.

  JMRI 2009; 30: 1298-308.

- NSF and Its Impact on Abdominal Imaging.

  RadioGraphics 2009; 29:1565-1574.

NSF Warnings have Unintended Consequences

- Patients switched to
  - less accurate tests
  - unproven tests
  - tests with other risks: X-ray or nephrotoxicity
- Patients treated empirically without diagnosis
- NSF risk trumps other risks

Excessive NSF focus can reduce patient safety

Ramskov & Thomsen, Acta Radiol 2009;50:965-7

Biopsy confirmed NSF in peer reviewed publications (80 papers – 292 cases)

- 64 papers had data on the relationship of GBCA and NSF involving 243 patients.
  - History of Gd exposure 220
  - Gd looked for but not found 23

- Gd not discussed (16 papers) 49

Total = 292

JMRI December 2009;30:1298-308

Gadolinium dose

Standard Dose (0.1mmol/kg):	23
High Dose (≥0.15mmol/kg):	164
Dose not specified:	56
Total	243

Multiple doses:	63
with at least 1 high dose:	55
only standard dose noted:	7
dose not noted	1

Typical NSF Presentations
(collected from 292 reported cases)

- Dialysis: 208/292 → 71%
  - not specified 17
  - Hemodialysis 150
  - Peritoneal dialysis 37
  - CVVH 4
- Renal transplant: 57/292 → 20%
- failing renal transplant: 34 → 12%

Clinical Features of NSF

Male:	136
Female:	116
Gender not specified:	30
Contractions:	93
Limited range of motion:	15
Death reported:	47
Death hastened by NSF:	2

US FDA Medwatch Database 2004 to 2008

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformationInformation/Surveilance/AdverseDrugEffects/ucm082193.htm

US events only

NSF excluded

Excluding NSF	Gadobenate dimeglumine	Gadoteridol	Gd:DTPA	Gadodiami
Total AE	923	86	1276	46
Death	8	4	23	3
Market share from IMF Inc.	.052	.057	.501	.285
Deaths per million doses	3.6	1.6	1.1	.2

Summary

- NSF Warnings can have unintended consequences
- Do not forget risks of
  - X-rays
  - Iodinated Contrast
  - Empiric therapy without diagnosis
  - New Gd protocols w/o efficacy data
  - Hypersensitivity reactions

National Traffic Safety Administration 2008

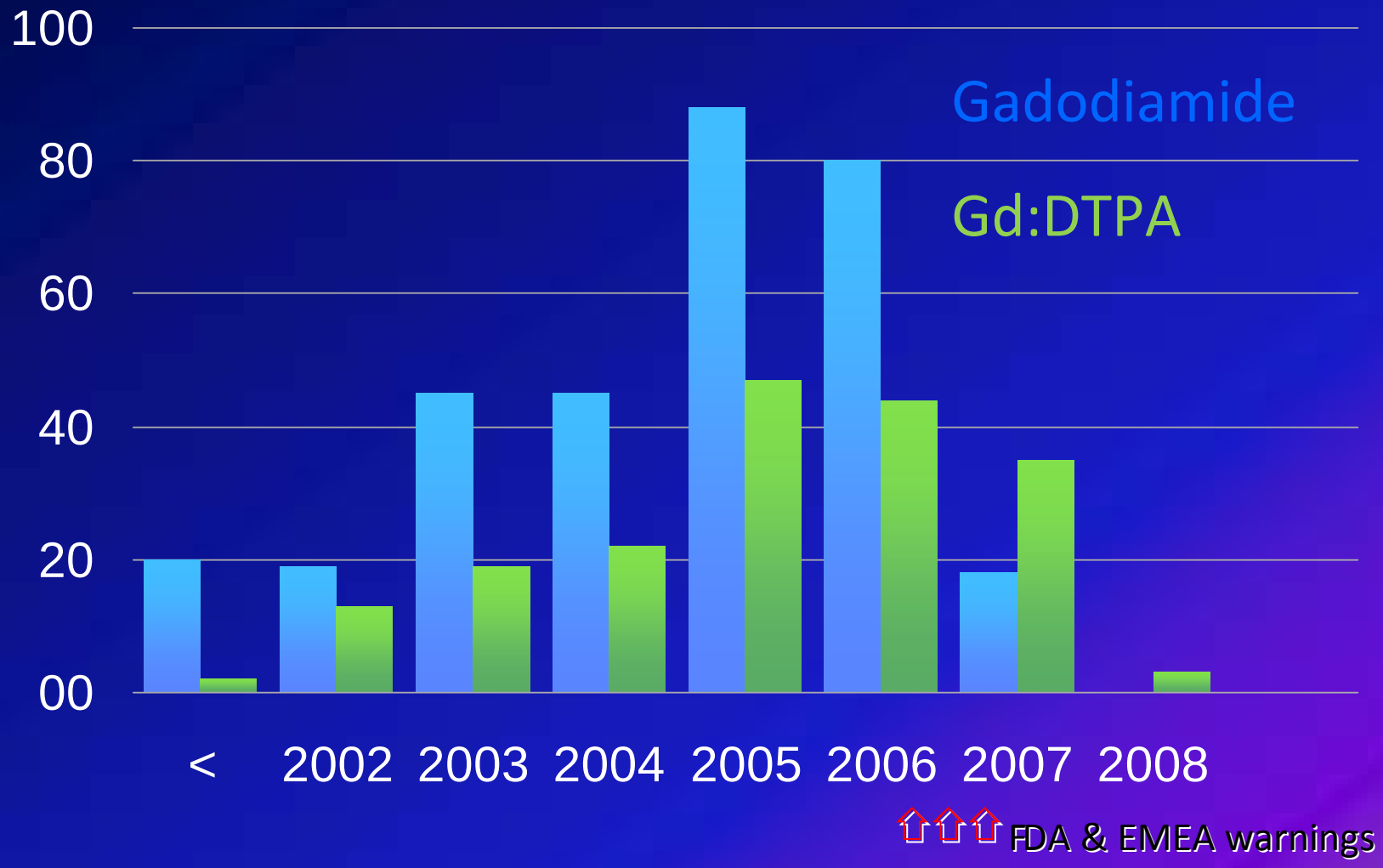
1 in 1 million chance of death

For every 78 miles driven in US

No cases < 6 years old in spite of extensive Gd use in Congenital Heart Disease

- Neonates have immature kidneys, low GFR
- European warnings in children probably inappropriate → switching from MR→Xray

Cases of NSF by Date of Onset*



November 27, 2009

Cardiovascular and Renal Drugs Advisory Committee
Drug Safety and Risk Management Advisory Committee
Food and Drug Administration
5600 Fisher Lane
Rockville, MD 20857 USA
Tel: 301-827-7001
Fax: 301-827-6778
Email: elaine.ferguson@fda.hhs.gov

Re: Written input regarding NSF and gadolinium based contrast agents (GBCA) to be considered at the December 8, 2009 joint meeting on Gadolinium and NSF.

To whom it may concern;

We are a community of dedicated physicians and scientists seeking to provide optimal imaging services that are in the best interests of our patients. Our patients have been enormously impacted by changes in practice patterns and costs associated with efforts to understand and prevent nephrogenic systemic fibrosis (NSF).

It is encouraging to report the universal observation that rapid worldwide implementation of changes in the type and dose of GBCA used in renal failure patients, together with the prompt scheduling of a hemodialysis session in appropriate patients following GBCA administration, have resulted in a virtual elimination of new cases of NSF.

Although all physicians are heartened by the success of the drive to eradicate NSF, many are concerned that changes in practice patterns may undermine patient care by driving algorithms toward inferior diagnostic tests. Alternative tests to contrast enhanced MRI may be less accurate and have different risks (e.g. catheterization, radiation, nephrotoxicity…)such that patients, on balance may be worse off (Ramskov & Thomsen, Acta Radiol 2009;50:965-7). Based upon current knowledge, risk of NSF in patients with liver disease appears to have been overstated and should not be a concern in the absence of renal disease. Furthermore, although European warnings specifically mention small children as being at increased risk of NSF, no confirmed cases have been reported to date in infants in spite of their known reduced renal function and the frequent use of GBCA for imaging congenital heart disease. Small children and infants are harmed substantially more than adults when a test involving ionizing radiation is substituted for contrast enhanced MRI.

The awareness, and at times fear, regarding the medico-legal issues related to NSF have often resulted in patients being exposed to riskier diagnostic procedures/tests simply because the test has less NSF-related risk, without balanced consideration of the benefit-to-risk of one test relative to the other. In the overall interest of our patients, it is important that any warnings/regulations continue to acknowledge that there are clinical situations in which GBCA benefit to the patient will greatly outweigh the dangers of NSF

at any level of renal function and that case by case decisions should be left to the considered judgment of each patient's physician.

To the extent that some agents with a favorable safety profile in certain patient classes are available outside U.S. but not available in the U.S., there is enthusiasm to encourage the FDA to find a way to facilitate bringing these compounds to the U.S. market while still following the FDA's rigorous safety and efficacy requirements.

Finally, we encourage the FDA to lend its support toward an RFA for NIH funded research to help resolve remaining questions surrounding the mechanisms by which NSF occurs as wells for methods of prevention and treatment.

Respectfully,
International Society of Magnetic Resonance in Medicine