CASE AUTH/2091/1/08

GE HEALTHCARE v GUERBET LABORATORIES

Dotarem exhibition panel

GE Healthcare complained about the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' used on an exhibition panel used by Guerbet Laboratories to promote Dotarem (gadoteric acid).

GE Healthcare considered that the claim of 'highest stability' implied a clinical benefit of Dotarem over other products. The relationship between the stability of gadolinium-based contrast media (GdCM) and their propensity to cause nephrogenic systemic fibrosis (NSF) had been widely debated. GE Healthcare was unaware of any evidence of a clinical benefit, safety or otherwise, linked to a higher stability, especially when the claim might be based on *in vitro* measurements in a non-physiological environment. GE Healthcare alleged that the claim was misleading.

The Panel noted that the issue of stability of GdCM and the development of NSF had been examined. The use of some agents was associated with a higher risk of NSF than others. Dotarem was one of the three agents considered the most stable and least likely to cause NSF. The risk of NSF with three other agents (MultiHance, Primovist and Vasovist) remained under investigation. The public assessment report (PAR) for GdCM stated that NSF and the role of GdCM was an emerging science. The Dotarem summary of product characteristics (SPC) included a statement in relation to patients with impaired renal function that there was a possibility that NSF might occur with Dotarem which should only be used in such patients after careful consideration.

The supplementary information to the Code stated that the extrapolation of, *inter alia*, *in-vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. It was also stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel noted that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated.

The Panel considered that the claim at issue 'Dotarem The MR Gadolinium Complex with the highest Stability' implied a clinical benefit as a consequence of its stability over less stable agents which had not been proven. In that regard the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

Upon appeal by Guerbet, the Appeal Board considered that the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' was true. The claim could be substantiated with the available physicochemical data and no contrary data had been provided. The Appeal Board ruled no breach of the Code in this regard.

The Appeal Board considered that even when a claim was true, the context in which it was used was very important. It was an accepted principle under the Code that claims etc related to the clinical situation unless otherwise stated. The claim at issue had been used with clinicians who would be familiar with the ongoing debate regarding stability and NSF. In Appeal Board's view the claim could be interpreted to mean that the 'highest stability' resulted in the 'highest safety'. In that regard the Appeal Board noted the statements from the various regulatory organisations, in particular the PAR which stated 'NSF and the role of gadolinium-based contrast media is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical properties of gadolinium-containing agents *might* (emphasis added) affect the amount of free gadolinium released in patients with renal impairment'. The PAR concluded that the data did not *suggest* that the risk of NSF in patients with advanced renal impairment was the same for all GdCM. The non-ionic linear chelates (Omniscan and optiMARK) were associated with the highest risk because they were *more likely* to release free gadolinium than the cyclical chelates (Gadovist, ProHance and Dotarem) which were the most stable and *likely* to have the lowest risk of NSF.

The Appeal Board noted the submission that the claim at issue had been used for many years without complaint. Stability of GdCM had, however, only relatively recently been postulated to be linked to the development of NSF. In that regard the claim had taken on a new relevance for clinicians and the Appeal Board considered that within the context of the current scientific debate it implied a clinical benefit for Dotarem as a consequence of its stability which had not been proven. The Appeal Board considered that, as used, the claim was misleading and it upheld the Panel's rulings of breaches of the Code.

GE Healthcare Limited complained about the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' on an exhibition panel used by Guerbet Laboratories Ltd to promote Dotarem (gadoteric acid).

COMPLAINT

GE Healthcare considered that the claim of 'highest stability' implied a clinical benefit of Dotarem over other products. GE Healthcare was unaware of any evidence of a clinical benefit, safety or otherwise, linked to a higher stability, especially when the claim might be based on *in vitro* measurements in a non-physiological environment. GE Healthcare alleged that the claim was misleading in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

GE Healthcare considered that Guerbet had used the claim at a clinical meeting to imply a benefit in the clinic and noted that the Code stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance (Clause 7.2). GE Healthcare knew of no clinical data which substantiated this. The findings from laboratory and animal studies on the relative stability of some gadolinium-based contrast media (GdCM) were variable and the methodology frequently lacked validation. In fact, even the definition of stability in this context was unclear as many different definitions were used in the literature.

- Nephrogenic systemic fibrosis (NSF), GdCM and stability: There had been considerable discussion since early 2006 on the chemical stability of the gadolinium (Gd)-chelate used to provide contrast in magnetic resonance imaging (MRI) studies and whether this was a factor in the development of the rare, but potentiality serious, chronic, disabling condition nephrogenic system fibrosis in patients with severe renal impairment. Three types of stability constant had been defined for GdCM: the thermodynamic (Ktherm), conditional (Kcond), and selectivity (Ksel). Ktherm was measured at very high pH values incompatible with life. Kcond was the stability constant at physiologic pH (pH 7.4). Ksel was the stability at pH 7.4 toward exchange of the Gd3+ ion in a chelate for another ion such as H^+, Zn^{2+}, Cu^{2+}, etc. These three stability constants were measured *in vitro*, and in water (or calculated from data measured in water), rather than a physiological solution or blood. They applied to pure chelates only and not to commercial formulations of GdCM because they did not take into account factors such as extra ligand. They were contradictory in their predictions of GdCM stability, and as they did not necessarily reflect the stability of the Gd complex *in vivo*, it was not surprising that they did not correlate well with measures of acute toxicity.

  Furthermore, there was no clear correlation between the numbers of reported NSF cases for the various GdCM and their thermodynamic stability. This seemed to question a relationship between NSF and the thermodynamic stability of GdCM, a suggestion which was made repeatedly by Guerbet.

  Although the exhibition panel in question did not overtly tie stability to the risk of NSF, the stability claim was clearly designed with discussion of NSF in mind; there was no other reason to raise the issue. That a number of independent authors had raised the issue of stability as a possible factor in the potential differences in the risk of NSF did not excuse this line of promotion by Guerbet, when there was no clinical evidence to support this theory.

- NSF and the Medicines and Healthcare products Regulatory Agency (MHRA): in intercompany correspondence, Guerbet referred to the updated public assessment report (PAR) regarding NSF and GdCM issued in June 2007 by the MHRA in co-operation with the Committee for Medicinal Products for Human Use (CHMP) Pharmacovigilance Working Party (PhVWP). GE Healthcare was concerned about the PAR, and did not believe that it could or should be used to justify Guerbet's claims. The PAR was not clinical research, but a collection and comment on some of the NSF data. Certain hypotheses regarding the physiochemical stability of Gd chelates and the development of NSF were presented in the PAR as fact or substantiated theories, rather than hypotheses that were still the subject of considerable scientific investigation, because no causative mechanism for NSF had yet been identified.

  Different Gd chelates exhibited different levels of thermodynamic stability *in vitro*, but GE Healthcare knew of no data to demonstrate that this had any clinical consequences given that the amount of free Gd released *in vivo* appeared to be negligible for all compounds. It was not known whether transmetallation (substitution of the Gd ion in the Gd/chelate complex for another heavy metal ion) played a role in the development of NSF. No published studies had found transmetallation of GdCM or metabolism of free Gd after use of GdCM in humans. Some studies did not use commercial formulation and no studies had used analytical methods capable of distinguishing between complexed and free Gd.

  Regarding Kimura *et al* (2005), cited by Guerbet, GE Healthcare noted that any link between zinc elimination and stability or transmetallation, was unproven. The authors stated that excess ligand was also considered to be responsible for the increase in urinary zinc excretion (which was not clinically significant). In fact, relating to gadodiamide, it was far more likely that zinc elimination in the urine was due to excess chelate, as the affinity of zinc for the chelate was in the region of 30,000 times lower than the affinity of Gd for the chelate. Therefore it seemed highly unlikely, and was certainly not proven, that zinc would displace Gd from the Gd-chelate complex when there was an excess of free ligand (as in the commercial formulation of Omniscan GE Healthcare's product).

- Research and an evolving clinical situation: GE Healthcare noted that much of the research conducted to date was in animals or *in vitro*, and the relevance of such studies to humans must be judged very carefully. Furthermore, the human studies must be viewed in light of the entire body of knowledge on GdCM for proper interpretation. To date, it had still not been shown that Gd whether free or chelated, caused NSF. Furthermore, recent case reports of NSF occurring in association with purportedly more stable cyclic GdCM continued to throw doubt upon the physiochemical stability hypothesis.

RESPONSE

Guerbet submitted that kinetic and thermodynamic stability data were acceptable measures of stability assessed by the MHRA and the European Pharmacovigilance Working Group during their recent assessment of agent stability and investigation into the causes of NSF. The detailed PAR published by the MHRA in June 2007 stated 'Cyclic molecules offer better protection and binding to Gd compared with linear molecules. For example, the ionic cyclic chelate gadoterate meglumine has a much longer dissociation half-life and higher thermodynamic stability than the non-ionic chelate gadodiamide'.

Guerbet considered that this report was a definitive collation, review and assessment of all of the current data relating to NSF and the stability of GdCM made by the definitive group of decision makers and experts. The meetings that took place at the EMEA and the subsequent document had been used not only in the UK, but across Europe to influence and change practice relating to choice of GdCM based upon the agents' stability and potential for contribution to cause of NSF. Guerbet was surprised that GE Healthcare did not accept the importance of this report, especially when the clinical evidence upon which it was based had contributed to a review of and significant changes to the safety data contained within the summaries of product characteristics (SPCs) for all Gd agents and in particular GE Healthcare's product Omniscan.

Further the MHRA PAR stated that 'The non-ionic linear chelates (Omniscan and OptiMARK) are associated with the highest risk of NSF because they are more likely to release Gd from the chelate complex in patients with severe renal impairment than are other agents. By contrast, the cyclical chelates (Gadovist, ProHance and Dotarem) are considered the most stable and likely to have the lowest risk of NSF'. The stability data to which the report referred included kinetic and thermodynamic measurements and was purely based on irrefutable physicochemical facts. GE Healthcare's opinion that the stability data could not be extrapolated to the clinical setting contradicted the European Pharmacovigilance Working Group and eminent scientists/clinicians called as experts to this issue.

To further support the claim of 'highest stability' Guerbet submitted that when comparing an ionic agent against a non-ionic agent: 'The simple removal of one anionic donor atom (carboxylate) and replacement by a non-ionic functional group (amide or ester) resulted in a decrease in stability of the resulting Gd complex by about three orders of magnitude' (Brücher and Sherry, 2001). More simply, an agent would be more stable if it was ionic rather than non-ionic.

In addition and as an overview, Guerbet noted that Morcos (2007) stated:

> 'Currently, there are seven extracellular Gd-CA available for clinical use (Table 1). They are all chelates containing Gd ion (Gd+++). The configuration of the molecules is either linear or cyclic. They are available as ionic or non ionic preparations. Understanding the synthesis of metal chelates is somewhat difficult especially for those of us who have no deep knowledge in chemistry. However, the author of the article attempted to present some of the chemical principles involved in the production of Gd chelate in a simplified manner and hopefully without important compromise of scientific accuracy. The gadolinium ion has nine coordination sites (coordination sites represent the number of atoms or ligands directly bonded to the metal centre such as Gd++. A ligand is a molecule or atom that is bonded directly to a metal centre. The bonding between the metal centre (Gd+++) and the ligands is through valent bonds in which shared electron pairs donated to the metal ion by the ligand). In the ionic linear molecule such as Gd-DTPA, Gd+++ is coordinated with 5 carboxyl groups and 3 amino nitrogen atoms. The remaining vacant site is coordinated with a water molecule which is important in enhancing the signal by the contrast agent in T1 weighted MR imaging (Figure1). In the non ionic linear molecule such as gadodiamide and gadoversetamide the number of carboxyl groups are reduced to three as the other two carboxyl groups have been replaced by non ionic methyl amide (Figure 2). Although both amide carbonyl atoms are directly coordinated to Gd+++ the binding is weaker in comparison to that of carboxyl groups. This will result in weakening the grip of the chelate on the Gd+++ and decreasing the stability of the molecule. The other feature which influences the binding between the Gd+++ and the chelate is the configuration of the molecule; the cyclic molecule offers a better protection and binding to Gd+++ in comparison to the linear structure.'

This meant that an ionic macrocylic gadolinium agent would have the highest stability. As Dotarem was the only ionic macrocyclic gadolinium agent available for MRI it was therefore the agent with the highest stability. GE Healthcare knew this and in fact the team that worked on Omniscan published 'The benefits of high kinetic and thermodynamic stability offered by structurally preorganized and rigid metal

chelates such as DOTA macrocycles for use as magnetic resonance imaging contrast agents are well established' (Varadarajan *et al* 1994).

Guerbet stated that the exhibition panel in question made no clinical claims for Dotarem; in fact it did not promote any licensed indication and purely stated a physiological fact.

Guerbet was not surprised by GE Healthcare's assumption that Guerbet implied extrapolation to the clinical setting. This statement was made from the practices of GE Healthcare. It was interesting that this assumption arose from a company that depicted a sign leading to a renal unit/ITU to promote one of its own products; this appeared to be far more evocative advertisement than any that Guerbet had produced.

There was no evidence to support the assumption that Guerbet promoted in a similar way to GE Healthcare or that the exhibition panel suggested anything other than the physiological stability of the molecule. Guerbet noted that it had presented the stability of the Dotarem molecule in various promotional pieces at international events for many years and this was the first formal complaint about the issue of stability.

PANEL RULING

The Panel noted that the issue of stability of GdCM and the development of NSF had been examined. The use of some agents was associated with a higher risk of NSF than others. Dotarem was one of the three agents considered the most stable and least likely to cause NSF. The risk of NSF with three other agents (MultiHance, Primovist and Vasovist) remained under investigation. The PAR for GdCM stated that NSF and the role of GdCM was an emerging science. The Dotarem SPC included a statement in relation to patients with impaired renal function that there was a possibility that NSF might occur with Dotarem which should only be used in such patients after careful consideration.

The supplementary information to Clause 7.2 stated that the extrapolation of, *inter alia*, *in-vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. It was also stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel noted that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated.

The Panel considered that the claim at issue 'Dotarem The MR Gadolinium Complex with the highest Stability' implied a clinical benefit as a consequence of its stability over less stable agents which had not been proven. In that regard the claim was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

APPEAL BY GUERBET

Guerbet appealed the Panel's rulings for the following reasons:

1 The claim 'highest stability' had not been made in connection with the current debate on NSF – evidenced by the fact that Guerbet was using the claim 8 years before NSF was first reported and almost 10 years before a link between NSF and Gd based agents was proposed.

Guerbet submitted that NSF was first reported in 1997. A causal connection between NSF and use of Gd based agents was first proposed in 2006. Guerbet had been using the claim that Dotarem was the most stable Gd based agent since its launch in France in 1989 (promotional items from 1992, 1995, 2000, 2005, and 2006 were provided). The high stability of Dotarem was an important, material property of the agent independent of the current debate on NSF. It had been known for many years that free Gd was poorly tolerated in the body. It was therefore desirable under the precautionary principle to seek to maximise the stability of gadolinium based agents to reduce the release of free gadolinium.

Guerbet submitted that given its consistent use of the term pre-dated awareness of NSF, it was self evident that the claim 'highest stability' was not intended to suggest that use of Dotarem was less likely to result in NSF. As a competitor of Guerbet, GE Healthcare must have been aware of the long standing use of this claim. But it was not until 2007 when independently of any statement by Guerbet the Commission on Human Medicines (CHM) and the EMEA both suggested a possible link between the stability of gadolinium based agents and NSF, that GE Healthcare complained.

2 The claim 'highest stability' was factually correct and scientifically substantiated.

Guerbet noted that Clause 7.2 required that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.

Guerbet submitted that it was true that Dotarem had the highest kinetic and thermodynamic stability of any MR gadolinium complex. This stability resulted from its ionised macrocyclic structure, which was unique. The greater stability of Dotarem was recognised by the MHRA, which stated in the PAR that 'the cyclical chelates … (including) Dotarem …are considered to be the most stable' issued in cooperation with the European

Pharmacovigilance Working Party ('PhVWP') of the Committee for Medicinal Products for Human Use (CHMP). This conclusion was based on a review of all existing material, including the articles cited by GE Healthcare in support of its arguments. The material included *in vitro*, *in vivo* and human studies.

Guerbet submitted that the MHRA was even more unequivocal in its question and answer document released in February 2007, which stated that 'Dotarem has a molecular charge and a cyclical structure, and is least likely to release free Gd into the body'. In the nearly 20 years since Dotarem was first introduced in Europe, no competitor except for GE Healthcare had objected to the 'highest stability' claim. GE Healthcare only objected to this claim when the MHRA and the European Pharmacovigilance Working Group linked stability with the risk of NSF.

Guerbet provided a detailed review of the scientific literature on the favourable stability of Dotarem. The claim made by GE Healthcare that the data on relative stability was variable and lacking in validation was simply unfounded.

3 Guerbet's advertising did not state that Dotarem's stability characteristics had clinical implications.

Guerbet's advertising did not state that Dotarem's high stability had any clinical significance. Guerbet made no claim about the relative clinical performance of gadolinium products either expressly or by implication. It did not even mention NSF (which was unsurprising since, as set out above, Guerbet was using this claim long before the first case of NSF was identified or any link between NSF and stability was posited). It merely educated health professionals about the product's stability.

Guerbet submitted that a clinician reading the exhibition panel would appreciate that a comment on 'stability' would be based on preclinical data. It might be that those professionals who were aware of MHRA's and the PhVWP's recommendations would appreciate the potential significance of those characteristics, but if that was the case they would already be aware of the MHRA's and PhVWP's conclusion that Dotarem appeared to have a lower risk of NSF. The clinician could not make a link to NSF without being aware of the independent literature on NSF and the guidance of the regulator. They would also be aware of any continuing debate from the literature. Any extrapolation made to the clinical setting would be a matter for the clinician's own judgment based on the scientific literature and the guidance given by the regulatory authorities.

4 While Guerbet did not make this claim, the regulator had concluded that there might be a link between stability and incidence of NSF.

Guerbet submitted that in February 2007, after reviewing all available evidence, the EMEA concluded that there might be a link between stability and NSF. The PAR of February 2007 stated that 'there were differences in the stability of the gadolinium complex of the different substances that may impact on their propensity to trigger NSF'.

Guerbet submitted that in February 2007, the MHRA sent a circular to health professionals on gadolinium containing MRI contrast agents and NSF which stated:

> **'Mechanism**
> The mechanism by which some gadolinium-containing contrast agents are more likely to trigger NSF than other agents is not understood fully, but is thought to be related to their different physicochemical properties that affect the extent to which they release free gadolinium ions. Deposition of free gadolinium ions in tissues and organs might stimulate NSF through induction of fibrosis…'

Guerbet submitted that the MHRA also issued a questions and answers document in February 2007, which went into more detail on the relationship between the stability of different structures and the risk of NSF. It stated

> 'Gadolinium-containing contrast agents have different properties that affect their behaviour in the body. Contrast agents such as Omniscan and OptiMARK that carry no molecular charge and are arranged in a linear structure with excess chelate seem to be more likely to release free gadolinium ions (Gd3+) into the body. Those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist), and those that carry no molecular charge and have a cyclical structure (eg, Gadovist and ProHance), seem to be less likely to release free Gd3+ into the body. **Dotarem has a molecular charge and a cyclical structure, and is least likely to release free Gd3+ into the body…'** (emphasis added by Guerbet).

'… Current evidence suggests that the risk of developing NSF may be related to the structure of the gadolinium-containing contrast agent …. Most cases of NSF have been associated with agents Omniscan and OptiMARK, which have similar structures. A small number of cases have been associated with Magnevist, and, to date, no cases of NSF have been associated with some gadolinium-containing contrast agents. This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary' and

'… The UK Commission on Human Medicines (CHM) and one of its expert advisory groups reviewed the issue of NSF and gadolinium-based contrast agents in January, 2007. CHM proposed a step-wise approach to restricting the use of gadolinium-based contrast agents in patients with kidney disease, in liver-transplant patients, and in neonates. They advised that Omniscan (and OptiMARK) should not be given to these patients, and that Magnevist, MultiHance, Vasovist,

Primovist, Gadovist, ProHance should not be given to these patients unless regarded clinically essential. For Dotarem, a warning for its use in at-risk patients was also proposed.

Guerbet submitted that in June 2007, the MHRA in conjunction with the PhVWP issued a revised PAR to take account of new evidence. This conclusion as to stability did not change. The report stated that:

> 'A review of the available data does not suggest that the risk of NSF in patients with advanced renal impairment is the same for all gadolinium-based contrast agents. Distinct physicochemical properties affect their stabilities and thus the release of free gadolinium ions, and pharmacokinetic properties influence how long the contrast agent remains in the body…'

Guerbet submitted that the non-ionic linear chelates (Omniscan and OptiMARK) were associated with the highest risk of NSF because they were more likely to release Gd from the chelate complex in patients with severe renal impairment than were other agents. By contrast, the cyclical chelates (Gadovist, ProHance, and Dotarem) were considered the most stable and likely to have the lowest risk of NSF.

Guerbet submitted that in August 2007, the MHRA issued a Drug Safety Update which stated:

> 'The exact mechanism by which a gadolinium-containing contrast agent can cause NSF is not known. However, under some conditions gadolinium ions (Gd3+) are released from chelate complexes through a process of transmetallation with endogenous ions in the body and can accumulate in the skin and other tissues. Gadolinium-containing MRI contrast agents have different levels of NSF risk based on their physicochemical and pharmacokinetic properties (see table). Risk of NSF is considered to be highest with Omniscan and OptiMARK, which have a linear chemical structure with excess chelate, carry no molecular charge, and seem more likely to release free Gd3+ into the body. Those that are cyclical in structure (eg, ProHance, Gadovist, and Dotarem) are least likely to release free Gd3+ into the body. Between these two groups are those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist).'

Guerbet submitted that the European Society of Urogenital Radiology had also issued guidance to its members which stated:

> ***'CHOICE OF GADOLINIUM AGENT***
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> There are differences in the incidence of NSF with the different Gd-CM, which appear to be related to differences in physico-chemical properties and stability. Macrocyclic gadolinium chelates, which are preorganized rigid rings of almost optimal size to cage the gadolinium ion which have high stability.'

Guerbet submitted that the guidance commented on the structure and risks of the different agents available. The MHRA referred health professionals to this guidance.

Guerbet submitted that in conclusion, the consensus of the European medical community and medical regulators on a review of all the available evidence was that there was a possible link between NSF and stability, and that Dotarem was in the class of agents (macrocyclic gadolinium chelates) with the highest stability. Within this class, Dotarem was the only agent with a molecular charge. The MHRA described Dotarem as the most stable because of its molecular charge and cyclical structure. This information had been made widely available by the MHRA on its website and through circulation to health professionals.

5 There was a strong public interest in advertising the comparative stability of Dotarem. This public interest had been recognised by the MHRA, the European Pharmacovigilance Working Group, and experts in the field.

Guerbet submitted that the PAR stated that on the basis of current evidence, the use of GdCM in at-risk patients should be restricted based on their physicochemical and pharmacokinetic properties. Further, the CHM and the PhVWP recommended that relevant health professionals (ie, radiologists, nephrologists, and all physicians who might request MRI radiological investigations in patients with severe renal impairment such as geriatricians and cardiologists) should be given this new information promptly.

The PAR stated that 'It is imperative that radiologists, nephrologists and other healthcare professionals receive guidance on how to avoid [NSF]'. It concluded 'The cyclical chelates [including Dotarem] are considered to have the most stable structure and are likely to be associated with the lowest risk of NSF'.

Guerbet submitted that having regard to the objectives of the Code, that the pharmaceutical industry should behave in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high quality care – it was not clear how the use of a claim which was factually accurate, and related to a property considered by the regulator to be important, could be misleading. Indeed, such a communication was in the public interest, as demonstrated by the PhVWP's and the MHRA's efforts to communicate the relative stability characteristics of gadolinium based agents, and the possible relevance of those characteristics, to the medical sector. Indeed, it was preposterous to claim that clinicians had been misled by Guerbet when the regulator itself was widely promoting the importance of stability and the relevance of difference in stability.

6 The Code should not be used as a vehicle to

suppress information which was of public interest and which might assist the promotion of public health.

As set out above, the pharmaceutical industry should behave in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high quality care. GE Healthcare sold Omniscan (gadodiamide), a competing GdCM which had been associated with NSF. As GE Healthcare itself recognised, NSF was more strongly linked with some products than with others. An open letter to health professionals issued in September 2007 by GE Healthcare, Bayer Health, Bracco and Mallinckrodt, stated that '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'** (emphasis added by Guerbet).

Guerbet submitted that the MHRA and the PhVWP had concluded that on the available evidence, it appeared that the link between NSF and Omniscan might be related to its stability characteristics.

Against this background, it was clear that GE Healthcare might be commercially motivated to suppress statements about Dotarem's favourable stability. However, it was inappropriate to use the complaints procedure to achieve this aim.

In summary Guerbet submitted that it had claimed that Dotarem had the highest stability for nearly 20 years; the claim was true and had been accepted by regulators (the PhVWP in European level and the MHRA in the UK) after a review of all of the available evidence. Guerbet did not claim that Dotarem's stability characteristics had any clinical significance. However, a link between Dotarem's superior stability characteristics and safety had been made by UK and European regulators. Again, this conclusion had been reached on the basis of a review of all of the available evidence and not as a result of any claim by Guerbet. This link had been widely promoted by UK and European regulators, in view of the public interest considerations. Guerbet submitted that clinicians who knew about this link from regulatory communications or from the literature might appreciate on the basis of the current state of the evidence that Dotarem's stability characteristics were potentially relevant to the risk of NSF. However, they would appreciate the ongoing debate as to the cause of NSF and would be able to use their clinical judgment. It was illogical and contrary to the purposes of the Code to require Guerbet to stop promoting a feature of its products which the regulator itself considered might be instrumental in lowering the risk of a fatal condition.

COMMENTS FROM GE HEALTHCARE

GE Healthcare stated that Guerbet's appeal had failed to assuage its concerns regarding the use of preclinical and *in vitro* data to imply a clinical benefit. This was particularly the case given that the relationship between these *in vitro* measurements and the clinical syndrome of NSF remained to be established. GE Healthcare concurred with the Panel's ruling which concluded that Guerbet's activities in this regard were misleading and in breach of Clauses 7.2, 7.3 and 7.4. Specifically, the Panel highlighted that the extrapolation of, *inter alia*, *in vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance and that where a clinical or scientific issue had not been resolved, particular care must be taken to ensure that the issue was treated in a balanced manner.

GE Healthcare submitted that Guerbet had approached its appeal primarily from two contradictory positions. The first was that its claims for having the highest stability were not intended to imply a clinical benefit and the second that having the highest stability did result in a clinical benefit with regards to NSF.

1 The fact that the claim that Dotarem had the highest stability for nearly 20 years

GE Healthcare alleged that the stability of all gadolinium agents was well established, many with data from two decades of research and clinical use. All the available GdCM were extremely stable in their commercial formulations. Despite gadolinium being toxic in its free form, clinical experience from more than 120 million doses of the supposedly less stable linear formulations of these compounds had demonstrated that GdCM had an excellent safety record (Murphy *et al* 1999).

GE Healthcare noted that whilst this promotional activity had not been complained about in the past, this did not mean that the activity was justified. Clause 14.5 reasonably required that promotional items were re-certified at intervals of no more than two years. This reflected the constant evolution of both regulations and scientific/clinical knowledge. Over the past two years, NSF had developed to become a topical safety issue which formed much of the debate around GdCM.

To date, the role of stability in the aetiology of NSF remained unproven and contentious (Penfield *et al* 2008). This was, in part because stability claims were based upon *in vitro* assays performed at non-physiological conditions. There were no *in vivo* measures of stability. Nor were there any *in vitro*, *in vivo* or clinical demonstrations that stability was related to NSF's aetiology. The supplementary information to Clause 7.2 stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance. In the light of this, GE Healthcare was concerned about the opportunistic and increased activities by Guerbet to promote stability as a differentiator.

There were a number of questions that remained unanswered and cast doubt on the hypothesis that the stability or transmetallation of GdCM played a role in NSF: Firstly, if cyclic GdCM were effectively inert and did not transmetallate, what explained recent reports of NSF occurring in association with these purportedly more stable agents (Penfield *et al*)? Secondly, if the linear agents exhibited instability or transmetallation *in vivo* and this was responsible for the association with NSF then why was there no evidence of NSF patients exhibiting any of the other signs of gadolinium toxicity that might be expected such as impaired liver function? Finally, if the linear GdCM were potentially unstable in renally impaired patients, and if this was the cause of NSF, then why did more than 95% of end stage renal disease patients who received linear GdCM not develop NSF (Penfield *et al*)?

Thus, the association between the stability of GdCM and their propensity to cause NSF remained unclear. The supplementary information to Clause 7.2 stated that where a scientific opinion had not been resolved, particular care must be taken to ensure that the issue was treated in a balanced manner. Since its initial description, NSF had been reported in association with both linear and cyclic GdCM, regardless of stability (Penfield *et al*). Hence, the continuing promotion of Dotarem as a safe option on account of its stability represented an imbalanced and misleading view.

The exhibition panel in question promoted Dotarem as 'The MR Gadolinium Complex with the highest Stability'. Although it did not overtly claim a clinical significance in relation to stability, Guerbet's use of the superlative 'highest' in its claim clearly showed that it was trying to differentiate Dotarem from other products in this class. This differentiation could only be to encourage health professionals to choose Dotarem over the other products and it was counter-intuitive to suggest that no clinical benefit was implied.

GE Healthcare fully supported the Panel's view that it was an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated. The promotional material did not state that the claims regarding stability should be viewed other than from a clinical perspective which further supported the belief that the material was misleading. In fact, as noted below, recent promotional material for Dotarem made clinical inferences by carrying headings such as 'Maximised stability for minimal biological impact in patients'.

2 Guerbet suggested that its claim that Dotarem had the highest stability was true and had been accepted by regulators.

GE Healthcare alleged there had been considerable discussion since early 2006 on the chemical stability of the gadolinium (Gd)-chelate, and whether this was a factor in the development of NSF in patients with severe renal impairment. Three questions were pertinent to Guerbet's claim that Dotarem was 'The MR Gadolinium Complex with the highest Stability'. Firstly, of the various methods employed to measure stability, which was of the greatest accuracy? Secondly, what were the actual comparative stabilities in the clinically relevant setting? Thirdly, were these of relevance to the commercial formulations of GdCM? GE Healthcare addressed all three questions in detail and concluded that Guerbet's allusion to the fact that its claim was accepted by the regulators bordered upon an over-statement. The guidance from these regulators (and published literature) was phrased in terminology which made it clear that the aetiology of NSF was not understood. These also made it clear that the impact of stability upon an agent's propensity to trigger NSF was not certain.

3 Guerbet purported not to claim that Dotarem's stability characteristics had any clinical significance.

GE Healthcare noted that this was contrary to the basic understanding that all promotional materials had a clinical purpose and thus relevance. Guerbet would not have used the claim at a clinical meeting if the intention was not to imply a benefit in the clinical situation. The Code stated that care must be taken to ensure that data from *in vitro* and animal studies were not extrapolated to the clinical situation unless there were data to show that they were of direct relevance and significance (Clause 7.2). GE Healthcare was not aware of any preclinical or clinical data which substantiated this. Where laboratory and animal data on the relative stability of some GdCM had been examined, the findings were variable and the methodology frequently lacked validation.

GE Healthcare alleged that the exhibition panel in question did not make it clear that the claim of 'highest stability' was based on laboratory data. Guerbet's statement that clinicians reading the panel would appreciate that a comment on stability would be based on preclinical data was, as with its implied claim, without any evidence to support it. As stated above, the Panel noted that it was 'an accepted principle under the Code that all claims related to the clinical situation unless otherwise stated'. Guerbet's material provided no such statement to deflect a recipient of such material from assuming that it was clinically supported.

Guerbet's suggestion that its claim had no intended clinical relevance was also contradicted by the company's other promotional activities eg Guerbet's symposium at the European Congress of Radiology (ECR) in Vienna (March 7 – 10), was entitled 'From kinetic stability to patient benefits'. Within this symposium, as well as being the main area of discussion in the chairman's opening remarks, two of the three presentations covered NSF. In addition, Guerbet's promotional material for Dotarem at the ECR was headed 'Maximised stability for minimal biological impact in patients', which clearly implied clinical benefit (which had not been substantiated).

This symposium represented only the latest of a series of similar activities by Guerbet. Amongst its promotional materials was a CD entitled 'Nephrogenic Systemic Fibrosis and Gadolinium contrast agents'. In this CD, was a presentation entitled 'Possible mechanisms for the induction of NSF and stability of gadolinium complexes'.

GE Healthcare stated that although none of the above actually provided any evidence that stability was related to the risk of developing NSF, this clearly demonstrated that Guerbet's strategy was to lead health professionals to believe that Dotarem was a safer product than other GdCM on the basis of a claim to highest stability.

4 Guerbet had claimed that a link between Dotarem's superior stability characteristics and safety has been made by UK and European regulators.

Much of the rest of Guerbet's appeal seemed to hinge upon the updated PAR regarding NSF and Gadolinium containing MRI contrast media issued on 26 June 2007 by the MHRA in cooperation with the CHMP PhVWP and the guidelines also published in 2007 by the European Society of Urogenital Radiology (ESUR) safety committee.

GE Healthcare had a number of concerns regarding both the PAR and ESUR guidelines. Firstly, neither the PAR, nor the ESUR guidelines were clinical research, but rather a collection of, and comment on some of the data on NSF existing at that time. The discussion within these publications regarding the physiochemical stability of Gd chelates and the development of NSF were hypotheses that were still the subject of considerable scientific investigation, because no causative mechanism for NSF had been identified to date. Secondly, it should be noted that since their publication, increasing data suggested that NSF was a risk associated with the use of any gadolinium agent, irrespective of stability. Finally, it ought to be noted that both these organisations had relied upon the advice of some of the same expert clinicians. Thus, it could not be suggested that Guerbet's claims were supported by a diverse expert field. The FDA's guidance underlined the uncertainty within the field and was clear that NSF was a risk associated with GdCM (FDA website). The FDA made no distinction between agents irrespective of structure or claimed stability. This position had been supported by the manufacturers of those products available in the US as evidenced by communications sent to health professionals in that country.

GE Healthcare submitted that the majority of the advice published by the ESUR and PhVWP, differentiating between the various GdCM was based on a perceived difference in the incidence of spontaneous reports for the various products. Spontaneous reporting could be misleading and it was important to consider not only relative market share but also how this exposure had looked over the past few years and the time over which the cases of NSF had been reported. It was also important to consider the exposure of the various products to those patients at greatest risk and the doses used of these products.

1 How long had a product been available?
2 Has the product been available in those markets from which most cases were reported?
3 Was the product licensed for either angiography or whole body imaging (the procedures that tended to be linked to both patients with renal insufficiency and higher doses)?
4 Did the product, in any of the major markets, have a pre-existing contraindication in patients with severe renal insufficiency (thereby limiting any historical exposure to patients at greatest risk)?

For example, GE Healthcare stated that Dotarem had never been sold in the USA, the market from which the majority of reports had arisen, and during the time that reports had been received, it had been contraindicated in patients with severe renal impairment (those at risk of NSF) in Germany, the largest single market in Europe. Estimation of true incidence would require the number of NSF cases associated with a given contrast medium, n, divided by the number of patients at risk for NSF who were exposed to the contrast medium, N. Neither figure was known for any GdCM.

GE Healthcare stated that possible differences in the general safety profiles between GdCM were difficult to assess given the low overall incidence and the vagaries of reporting. In a large, retrospective study (Murphy *et al*), adverse events were reported infrequently, and could vary greatly – by up to 9,000 fold agent-to-agent. No statistical differences between the agents studied were found indicating that there was no difference in overall toxicity of the compounds. However, of the three agents principally noted, Omniscan had the fewest allergic and non-allergic reactions.

As stated in supplementary information to Clause 7.2, if Guerbet insisted upon using these opinions of regulatory bodies in its promotional activities, care should be taken to ensure that emerging opinions of an unresolved issue were presented in a balanced manner. Given the current discrepancy between the guidance of the FDA and PhVWP, and the discord between the statements of the guidelines when they were published and current data, the position of UK and European regulators could or should not be used to justify the claims made by Guerbet.

5 Guerbet claimed that the link had been widely promoted by UK and European regulators.

The above statement was used by Guerbet in defence of its promotional activities. This was not a legitimate defence. It was entirely appropriate for

regulatory authorities to issue assessment reports and safety updates. In general, references to regulatory authorities should not be used promotionally. Similarly, pharmaceutical companies had ultimate responsibility for their promotional activities.

6 Guerbet assumed that clinicians …will appreciate the ongoing debate as to the cause of NSF and would be able to use their clinical judgement

GE Healthcare alleged that as with many of the claims discussed in relation to this complaint, this was unsubstantiated. Additionally, the assumption of what clinicians would or would not believe did not remove Guerbet's responsibility for its promotional materials and activities.

7 Guerbet stated that it was contrary to the purposes of the Code to require it to stop promoting a feature of its products which the regulator considered might be instrumental in lowering the risk of NSF

GE Healthcare agreed with Guerbet that the Code was not a vehicle to suppress information. The basis of this complaint was, as stated by the Panel, that these promotional activities were in breach of Clauses 7.2, 7.3 and 7.4. This had come about because of Guerbet's use of preliminary and contradictory *in vitro* or animal data to suggest superior clinical benefit with Dotarem beyond other GdCM. As Guerbet stated in its appeal, the regulatory authorities reported only an association between GdCM and NSF and stability was a factor which had been suggested but not proven to be instrumental in lowering the risk of NSF. Indeed, NSF cases had since been described in association with cyclic agents (including Dotarem).

In conclusion, GE Healthcare alleged that theories regarding stability were largely based on thermodynamic stability which did not reflect physiological conditions. There was no clear correlation between the numbers of reported NSF cases for the various GdCM and their thermodynamic stability. This questioned the relationship between NSF and the thermodynamic stability of GdCM, a suggestion which was made repeatedly by Guerbet.

GE Healthcare alleged that these theories attempted to explain the differences in reported numbers early in the history of the reported association between gadolinium and NSF. They could be argued to not have the same credibility now that reported numbers had changed with a decreasing proportion of cases being associated with Omniscan and reports of cases associated with the supposedly more stable macrocyclic GdCM. The claim of 'highest stability', presented within clinical forums, could lead the reader to conclude that this led to a clinical benefit of the product over other products. GE Healthcare concurred with the Panel that this was misleading and in breach of Clauses 7.2, 7.3 and 7.4.

Furthermore, although this complaint arose from the use of panels at a local meeting, materials based upon a similar theme but overtly linked to a claimed clinical benefit were in general use, suggesting that Guerbet's underlying motivation was indeed to link stability claims with a clinical benefit which was currently unsubstantiated.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Dotarem The MR Gadolinium Complex with the highest Stability' was true. The claim could be substantiated with the available physicochemical data and no contrary data had been provided. The Appeal Board ruled no breach of Clause 7.4. The appeal on this point was successful.

The Appeal Board considered that even when a claim was true, the context in which it was used was very important. It was an accepted principle under the Code that claims etc related to the clinical situation unless otherwise stated. The claim at issue had been used with clinicians who would be familiar with the ongoing debate regarding stability and NSF. In Appeal Board's view the claim could be interpreted to mean that the 'highest stability' resulted in the 'highest safety'. In that regard the Appeal Board noted the statements from the various regulatory organisations, in particular the PAR which stated 'NSF and the role of gadolinium-based contrast media is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical properties of gadolinium-containing agents *might* (emphasis added) affect the amount of free gadolinium released in patients with renal impairment'. The PAR concluded that the data did not *suggest* that the risk of NSF in patients with advanced renal impairment was the same for all GdCM. The non-ionic linear chelates (Omniscan and optiMARK) were associated with the highest risk because they were *more likely* to release free gadolinium than the cyclical chelates (Gadovist, ProHance and Dotarem) which were the most stable and *likely* to have the lowest risk of NSF.

The Appeal Board noted the submission that the claim at issue had been used for many years without complaint. Stability of GdCM had, however, only relatively recently been postulated to be linked to the development of NSF. In that regard the claim had taken on a new relevance for clinicians and the Appeal Board considered that within the context of the current scientific debate it implied a clinical benefit for Dotarem as a consequence of its stability which had not been proven. The Appeal Board considered that, as used, the claim was misleading and it upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal on these points was unsuccessful.

Complaint received **29 January 2008**

Case completed **16 May 2008**