CONTRAST AGENTS – PARAMAGNETIC GADOLINIUM AND MANGANESE CHELATES AND SUPERPARAMAGNETIC IRON-BASED PRODUCTS. THIRD WHO-ITA / ITA-OMS 2010 CONTRIBUTION USING WHO SYSTEM ORGAN CLASS DISORDERS (SOCDs) AND ADVERSE REACTION AND EVENT PREFERRED NAMES (ADRs)

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Summary

WHO-ITA / ITA-OMS are acronyms adopted by the World Health Assembly for the delegation, composed of government ministers, of the sixth founding member, Italy, which subsequently hosted the 5th Annual Meeting of the Representatives of the National Participating Centres. This is where the first international collaborative data collection and electronic exchange network began its activity. The Centre's headquarters are in Uppsala, Sweden, set up with funds from the Swedish government. The data, generously been made available by the international Centre to one of the authors (L.R.) (Cf [5]), who has continuously collaborated with it for more than 40 years, consist of reports of 201,928 adverse drug reactions (ADRs) that were received by the WHO in the framework of its Drug Monitoring Programme, 50,765 from 1968 to 1989 and 151,153 from 1990 to 2010. Their aggregation into 30—later 32—WHO-system organ class disorders & codes (SOCDs), corresponds to the basic adverse reactions and events collated as preferred names and codes in the still only comprehensive world database.

On July 5, 2010 we applied for and obtained the full PR22-2010 dataset of the current classification of ATC V08 diagnostic contrast agents. The SOCDs related to the seven most frequently reported iodinated radiographic products were extracted (103,035 cases, subdivided in two 20-year periods) and processed with a novel software in a pilot study (See [17]). The software has been thereafter improved, modified and finally substituted with a new technique, which has been applied to the study of all diagnostic contrast agents until the present time, analysing the full ADR dataset on all V08CA-NMR paramagnetic imaging contrast agents: 1 - gadobenic acid, 2 - gadobutrol, 3 - gadodiamide, 4 - gadofosveset, 5 -

gadopentetic acid, 6 – gadoteric acid, 7 – gadoteridol, 8 – gadoversetamide, 9 – gadoxetic acid, and 10 – mangafodipir, and on all previously introduced V08CB-NMR superparamagnetic imaging products 1 – ferristene, 2 – ferrixan, 3 – ferumoxides, and 4 – ferumoxil. Most of the 38,523 ADRs were reported in the second 20-year period, with the exception of 305 ADRs for gadopentetic acid, introduced previously, which pertained to the first 20 years. Their total SOCDs and ADRs frequencies were published, and the updated statistics applied, yielding clustering groups and confirmatory plots.

A set of 12 common physico-chemical parameters was also evaluated for all 9 Gd-paramagnetic chelates, in order to obtain a more comprehensive analysis correlating ADR groupings to at least a basic set of analytically identified features, to find a logical relationship between experimental data and the clinical exploratory epidemiological model being developed. Indeed, also for the diagnostic agents used more frequently, the current subdivision into ionic and nonionic, which is related to different osmolalities, and/or macrocyclic or linear characteristics, etc, namely to highly individual and personal criteria, is not wholly convincing, and the most commonly recognized toxicological facts and the potential safety data would benefit from a more objective qualification.

Finally, some new suggestions to improve and connect the Programme to other ongoing studies and global perspectives are presented.

Key words: WHO-Uppsala Gadolinium-, Manganese- and Iron-based NMR diagnostic contrast agents monitoring; correlation based clustering and confirmatory Euclidean plots. Comparisons of WHO-System Organ Class Disorders and/or ADRs (preferred names) collected from the beginning of the WHO-Uppsala Centre for international collaborative monitoring of ATC V08CA gadobenic acid, gadobutrol, gadodiamide, gadofosveset, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide, gadoxetic acid and mangafodipir, and V08CB ferristene, ferrixan (ferucarbotran), ferumoxides and ferumoxsil products.

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"Nobody has answered or will ever answer this question, because it's the absolute truth". Sergej P. Mel'gunov, Red Terror in Russia (1918-1923). 1st Italian ed., Jaca Books October 2010, p 101.

Since 2006, with the publication of the report by Grober & al in April [1] and a press release of the Danish Medicines Agency in May describing a possible association between nephrogenic systemic fibrosis (NSF) and gadolinium-based contrast agents (GBCAs), mounting data have been indicating that GBCAs increase the risk of developing NSF in patients with severe renal insufficiency or renal dysfunction due to hepato-renal syndrome and (in the perioperative period), in liver transplant recipients. Indeed, a 1996 retrospective analysis of the routine laboratory data and clinical course of 15,830 patients who had received intravenous gadolinium dieethylenetriamine pentaacetic acid (DTPA) dimeglumine (gadopentetate dimeglumine, Magnevist R, the first linear ionic gadolinium chelate, approved in the US in 1988) while undergoing 3D contrast-enhanced MRI of the brain and spine, 151 of whom had impaired glomerular filtration [a creatinine value > 2 mg/dL; mean half-life of the product eliminated unaltered by glomerular filtration calculated in normal subjects to be 1.6 h, vs up to 30 h in patients with creatinine clearance < 20 mL/(min x1.73m^2)] was unable to detect any clinical adverse effect in patients with impaired renal function for a period spanning 3 days before to 30 days after administration [2]. This further demonstrates how difficult it can be to find such effects in single studies. In 1990 the same product at the customary dosage had previously been reported to induce no nephrotoxic reaction in 5 patients with renal insufficiency [3], a reliable finding since the study had been registered according to the standard procedure for clinical trials. However, a retrospective review of 6 NSF cases, diagnosed from 1997 to 2007 by skin biopsy 19 days to 2 months after gadodiamide injection (Omniscan R, a linear nonionic medium with 5% excess of free ligand in the formulation), suggested agent dechelation as the cause of NSF. This led to call for changes in clinical practice [4]. These examples, which are certainly not isolated, highlight not only the well-known fact that even the best individual clinical pharmacotoxicology studies unfortunately need to be repeated, but also that disasters due to lack of data on drug safety depend first of all on the flawed design of the clinical trials themselves as well as on an irresponsible failure to adopt alternative designs, which do exist, despite repeated lessons and alarms (Cf [5]), which clearly do not exclude the same problems related to gadolinium-based diagnostic products.

In some more recent studies (Cf [6]), and in the 2008 safety report [7], NSF were described after administration of another linear nonionic chelate, gadoversetamide (OptiMARK R; low thermodynamic stability 16.7, acid dissociation rate $2.2x10^{-2}$ sec^{-1}, half-life 1.73 h, 10% excess free ligand in the preparation); a case of NSF was also reported in the US in relation to the macrocyclic nonionic product gadoteridol (ProHance R; thermodynamic stability 23.8, acid dissociation rate $6.4x10^{-5}sec^{-1}$, half-life 1.57 h, 0.1% excess free ligand [8]). So far (see [6 - 8], and later [18] and [20]), more than 90% of all NSF cases have occurred after exposure to linear nonionic gadodiamide (low thermodynamic stability 16.9, dissociation rate $2.2x10^{-2}sec^{-1}$, half-life 1.30 h), followed by ionic linear gadopentetate dimeglumine (thermodynamic stability 22.3, acid dissociation rate $1.2x10^{-3}sec^{-1}$, half-life 1.50 h, 0.1% excess free ligand), whereas to our knowledge no cases have yet been published or reported in relation to the macrocyclic ionic product gadoterate meglumine (Dotarem R; thermodynamic stability 25.6, acid dissociation rate $8.4x10^{-7}sec^{-1}$, half-life 1.50 h, 0% free ligand), subjected to specific post-marketing registered use (Cf [9]).

Finally, also the last FDA Drug Safety Newsletter of August 13, 2009 [10] insisted on the need to help define risk factor for NSF, while the FDA has not approved GBCAs for use in magnetic resonance angiography, and only five GBCAs have been approved (Gadodiamide - Omniscan R, gadopentetate dimeglumine - Magnevist R, gadoteridol - ProHance R, and gadoversetamide, OptiMARK R mentioned above; gadobenate dimeglumine, MultiHance), while the other two contrast agents ferumoxides, Feridex R, and mangafodipir, Teslascan R, an iron-superparamagnetic, and a manganese paramagnetic-containing injection solution, have been approved by the FDA only for liver imaging. On November 19, 2009 the European Medicines Agency issued recommendations to minimize the risk of NSF related to GBCAs, which were classified into high-, medium-, and low-risk categories [11] based on a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents [12], and a survey of nephrologists' perception and practices on NSF [13], among other contributions. Not only NSF, but other general events and adverse reactions that may be seen or diagnosed, reported and collected in the International Bank will be examined. Similar to GBCAs, iodinated contrast media used in computed tomography scanning can result in the potentially fatal contrast-induced nephropathy (CIN) for which the highest risk patients are those with moderate-to-severe chronic kidney disease (CKD, stage 3-5). Various studies ([14]; see also later [16], [18] and [20]) recall different overlapping, prevalently non-systematic studies. Although large grants are being offered [15], any work that does not adopt new model ideas on associated specific risk factors, more selective methods (Cf [16]), and stringent long-term cohort post-marketing verifications may entail unjustifiable waste of effort and of increasingly more limited resources. Therefore, while "once is never enough", indefinitely repeated studies that are not based on substantially new rationales are nonetheless useless.

In this context we have recently presented two reviews on the WHO 30 aggregated system-organ class disorders (SOCDs) and the most frequently reported adverse effects and events (ADRs; preferred names) to seven iodinated X-ray contrast agents [17] collected over two 20-year periods. Here we analyse for the first time similar comparative data regarding the ADR reports collected in the WHO-Uppsala database for all ATC MRI-enhancing VO8C-A and B products and try to explore them objectively using a more appropriate clustering procedure. Our next effort will be devoted to assessing other ATC VO8A/A, B, C and D iodinated contrast agents, their more frequent, common and/or selective clinical toxicities, and their burden on national health budgets, with special emphasis on those that allow substitutions.

1. Data presentation and correlation clustering of SOCD frequencies of ATC VO8AC A and B NMR products

1.1. VO8CA paramagnetic products. Tables 1 and 2 of SOCD frequencies

Table 1 (1990-2010). Ten ATC V08ACA NMR paramagnetic contrast agents and their number of reports, total or for each of the 29 WHO SOCD codes. Reports sent on 5.7.2010 by Dr Marie Lindquist, Director, WHO Uppsala Collaborating Centre for 1990-2010, new PR-22-2010 file. SOCD numbers and codes: 1- 0100, Skin and appendages; 2 - 0200, Musculo-skeletal; 3 – 0300, Collagen; 4 – 0410, Central & peripheral nervous system; 6 – 0431, Vision; 7 – 0432, Hearing and vestibular; 8 – 0433, Special senses; 9 – 0500, Psychiatric; 10 – 0600, Gastrointestinal; 11 – 0700, Liver and biliary; 12 – 0800, Metabolic and nutritional; 13 – 0900, Endocrine; 14 – 1,010, Cardiovascular, general; 15 – 1,020, Myo-, endo- pericardial & valve; 16 – 1,030, Heart rate and rhytm; 17 – 1,040, Vascular (extracardiac); 18 – 1,100, Respiratory; 19 – 1,210, Red blood cell; 20 – 1,220, White cell and RES; 21 – 1,230, Platelet, bleeding & clotting; 22 – 1,300, Urinary; 23 –

1,410, Reproductive, male; 24 – 1,420, Reproductive, female; 25 – 1,500, Foetal; 26 – 1,600, Neonatal and infancy; 27 – 1,700, Neoplasms; 28 – 1,810, Body as a whole, general; 29 – 1,820, Application site; 30 – 1,830, Resistance mechanism. SOCD 5 - 0420, autonomic nervous system: zero reports. New SOCD 31 – 2,100, Poison specific terms, and 32 – 2,000, Secondary term had not been used.

		1	2	3	4	5	6	7	8	9	10	
	SOCDs (Code)	**Gadobenic acid**	**Gadobutrol**	**Gadodiamide**	**Gadofosveset**	**Gadopentetic acid**	**Gadoteric acid**	**Gadoteridol**	**Gadoversetamide**	**Gadoxetic acid**	**Mangafodipir**	**Reports (Total number)**
1	**100**	862	189	1,073	5	4,119	1	504	371	20		**7,144**
2	**200**	192	6	330		402		166	216			**1,312**
3	**300**			10		4			2			**16**
4	**410**	530	91	593	10	2,041	2	384	329	8	1	**3,989**
6	**431**	53	10	43	2	323		28	8	1		**468**
7	**432**	1	3	6		26		2				**38**
8	**433**	16	3	39		100		2	2	1		**163**
9	**500**	599	9	735		1,109		585	620	3		**3,660**
10	**600**	792	129	419	6	2,836	3	217	66	12		**4,480**
11	**700**	6	1	25		36		4	5	2		**79**
12	**800**	14	3	39		94		12	21			**183**
13	**900**	1		7		9		1	5			**23**
14	**1,010**	149	43	79	5	597		115	47	2	1	**1,038**
15	**1,020**	10	3	25	2	51		9	23	2		**125**
16	**1,030**	79	21	56	5	416		48	19	4		**648**
17	**1,040**	48	28	72	3	627		24	34	3	2	**841**
18	**1,100**	414	111	264	14	2,713	2	243	73	15	2	**3,851**
19	**1,210**		1	25		18		1	4			**49**
20	**1,220**	3	2	3		26		2	3			**39**
21	**1,230**	12	2	21		49		8	16			**108**
22	**1,300**	57	19	77	1	521		36	18	1		**730**
23	**1,410**	2		2		2		1	2			**9**
24	**1,420**		1	3		5		1				**10**
25	**1,500**	1		2		11		2				**16**
26	**1,600**			1		1		1				**3**
27	**1,700**	51		85		84		46	55			**321**
28	**1,810**	1,399	160	1,270	9	3,035		938	814	20	3	**7,648**
29	**1,820**	40	2	28	1	520		3	13	4		**611**
30	**1,830**	50		102		122		45	70			**389**
	Total	**5,381**	**837**	**5,434**	**63**	**19,897**	**8**	**3,428**	**2,836**	**98**	**9**	**37,991**

Table 2 (1968-1989). ATC V08ACA NMR paramagnetic contrast agents and their number of reports, total or for each of the 29 WHO SOCD codes. Reports sent on 5.7.2010 by Dr Marie Lindquist, Director, WHO Uppsala Collaborating Centre for 1990-2010, new PR-22-2010 file. Number 5, gadopentetic acid, was the only available product (since 1988), and its SOCD numbers and codes are already specified as named in the legend to Table 1.

		5	
	SOCDs(Code)	**Gadopentetic acid**	**Reports (Total number)**
1	**100**	61	61
4	**410**	47	47
6	**431**	6	6
8	**433**	1	1
9	**500**	2	2
10	**600**	51	51
14	**1,010**	9	9
15	**1,020**	1	1
16	**1,030**	6	6
17	**1,040**	13	13
18	**1,100**	38	38
20	**1,220**	3	3
21	**1,230**	1	1
22	**1,300**	9	9
28	**1,810**	26	26
29	**1,820**	31	31
	Total	**305**	**305**

1.2. V08CA paramagnetic products. Correlation clusters and confirmatory plots.

Data for VO8CA products, 1968-2010 (29 x 10)(identical to data for VO8CA 1990-2010 (Table 1), with the sole addition of gadopentetic acid, years 1968-1989, for 16 classes (Table 2)).

We have already attempted to obtain an auto-classification of Iodinate Contrast Agents starting from tables of ADRs frequencies, where the rows represented categories of ADRs, and the columns- Agents.

In a first version, a clustering technique for the columns was used, based on the WILKS's Chi-Square statistic. In this technique, the WILKS's statistic square root gives the diameter of any

subset of columns and in particular, a pair- wise column dissimilarity (a pseudo- distance) function.

The attraction of this approach is that it permits an objective clustering within the frame of a GABRIEL Simultaneous Testing Procedure. However, in spite of its appeal, this technique failed to correctly identify the sets of agents having close ADR profiles. The point which we missed was the fact that WILKS's statistic small values can originate also in configurations other than subtables with close ADR profiles (such as in the cases of tables where one or more of the agents have small ADR values throughout).

The solution was to change the inter-column pseudo-distance. The appropriate choice was to define this pseudo-distance in terms of the "brute correlation" of the two column vectors (brute in the sense that averages are not subtracted), that is of their multidimensional cosine. This choice proved itself successful.

We proceed now with the description of **this alternative technique,** using **an exact inter- column distance function, based on the multidimensional cosine of the column vectors, that is on their "brute" correlation coefficient**.

Our data sets are contingency (rxc) tables $X = \{x_{ij} : i = 1,2,...,r; j = 1,2,...,c\}$, with nonnegative elements. The r rows correspond to ADRs and the c columns, to the drugs. Each combination (i, j) is a cell of the table, with which is associated the cell value x_{ij}, the value of the ADR i for the drug j. Denote by x_{i+} the sum of row i, by x_{+j} the sum of column j and by x_{++} the total sum of elements of X.

If one divides all the elements of column j by the column total x_{+j}, one obtains **the column j profile**, a vector of weights $\frac{x_{ij}}{x_{+j}}$ summing up to 1. Two columns have **the same profile** if and only if they have **proportional elements**, i.e. the elements of one column can be obtained from those of the other column by multiplying by the same nonzero factor. A table in which **all column profiles coincide**, has a multiplicative structure expressed by the relations

$$x_{ij} = \frac{x_{i+}x_{+j}}{x_{++}} : i = 1,2,...,r; j = 1,2,...,c .$$

Or, in other words, all column profiles coincide with the **marginal column profile**

$$\{\frac{x_{i+}}{x_{++}} : i = 1,2,...,r\} .$$

One introduces in the Euclidean Space R^r to which the column vectors belong, a **dissimilarity measure** d defined on pairs of vectors of this space, measuring the departure of the pair from the situation of having the same profile, i.e. from being proportional. If $a = (a_1,...,a_r)'$ and $b = (b_1,...,b_r)'$ are **two vectors of** R^r, then we define **their dissimilarity** $d(a,b)$ as:

$$d(a,b)=\sqrt{\frac{1-\cos(a,b)}{2}} \quad ,$$

where $\cos(a,b)$, the multidimensional cosine of a,b, is given by:

$$\cos(a,b)=\frac{a'b}{\sqrt{(a'a)(b'b)}}=\frac{\sum_{i=1}^{r}a_i b_i}{\sqrt{\sum_{i=1}^{r}a_i^2}\sqrt{\sum_{i=1}^{r}b_i^2}}\,.$$

The measure $d(a,b)$ in general, takes values between 0 (for a,b proportional with a positive factor of proportionality, and their respective profiles identical) and 1 (for a,b proportional with a negative factor of proportionality). In our case, a,b are column vectors with non-negative coordinates, and $d(a,b)$ varies from 0 to $\frac{1}{\sqrt{2}}$ (for a,b orthogonal).

Most of the dissimilarity measures in use are not true distances. But t**he dissimilarity measure** $d(a,b)$ **is a true distance.** One can prove that it satisfies the triangle property: for any vectors a,b,c, one has

$d(a,b)\le d(a,c)+d(c,b)$.

We will call $d(a,b)$ simply **the distance between** a **and** b**.**

The **Diameter of a subtable** formed of columns is defined as the largest distance between two columns of the subtable. At one end, we have the diameter of the set X itself; on the other end, the diameters of the subtables formed of just two columns. In the latter case, the diameter is simply the distance between these two columns. In fact, even subtables of one single column may be considered, regarding such a subtable as containing two identical columns. Its diameter must obviously be taken as equal to zero. The diameter as a function defined over the subtables of columns, is **monotonic with respect to the relation of subtables inclusion:** if S_1 and S_2 are subtables of columns such that $S_1 \subseteq S_2$, and $diam(S_1)$ and $diam(S_2)$ are their respective diameters, then $diam\,(S_1)\le diam\,(S_2)$.

Let $\delta>0$ be a **gauge** arbitrarily chosen. A subset S of columns is δ**-homogeneous** if $diam(S)\le\delta$. Of course, the smaller is δ, the closer is S to a subset of columns having the same profile. This can be **visualized by a common plot of the column profile values versus the row indices** $1,2,...,r$. The closer the column profile curves are, the more useful will be for us the set S. **A better variant of this common plot is obtained by taking as abscissas instead of the row index** i**, the mean (arithmetic or geometric) or the median of the** i^{th} **profile values of the involved columns.** It is to be desired that **the curves corresponding to columns shall be rather close to the bisector of the first quadrant.**

Given a gauge δ>0, our aim will be to **group the columns** (drugs in our case) **into clusters.** A cluster is a **maximal δ-homogeneous set of columns.** Being maximal, means being such that any larger subset including it will be non-homogeneous.

Assuming that we know how to split the columns into clusters for any given δ>0, we will try by playing with δ, to achieve a compromise between two opposite aims: to have **clusters as large as possible** on the one hand, and clusters **of as small a diameter as possible**, on the other hand.

Once this is done, the clusters will represent suggestions made by the statistician to the specialist, who will try to **find out the connection, if any, between the drugs (columns) which enter into the composition of each cluster.** It is clear that in this subsequent research, **only clusters containing at least two columns** (drugs) **are of interest.**

Our technique will consist mainly from constructing a **binary tree clustering based on a technique for optimally splitting a set into two subsets.**

We use a program written by us, following the elegant metaphoric explanation (which amounts to a pseudo-algorithm) given by **Leonard Kaufman and Peter J. Rousseeuw** in their book "**Finding Groups in Data,** An Introduction to Cluster Analysis", 1990, John Wiley [27], Chapter 6, Divisive Analysis, pp. 253-279.

In our implementation, the result of the algorithm is a table of the subsets obtained in the successive splitting into two, ordered on decreasing diameter. This table permits to tackle the problem formulated above.

As additional checking means, we use

a) **A graphical procedure whose result is an Euclidean Map** where the columns of the table are represented by markers, **the Euclidean distances between markers approximating the inter-column distances.** One starts from the matrix of column pair-wise dissimilarities (proper distances in our case), and by means of the Torgerson-Gower **Multi-Dimensional Scaling**, one obtains a "**reification**", that is a set of points in an Euclidean space, whose pair-wise Euclidean distances approximate the pair-wise (dissimilarity) distances. The coordinates are ordered in decreasing importance, and the first two are used in the Euclidean Map which permits to see the cluster structure of the columns to an extent which **will confirm the clustering already obtained.**

This is true, provided the GOF (Goodness of Fit) given by the fist two dimensions is high enough. Otherwise, some of the pair-wise dissimilarities may be poorly approximated.

b) The plots described above, which permit to get an idea of **the extent to which the clusters are homogeneous.**

We will understand better the clustering procedure by following it on an example.

As example we take the **Paramagnetic Contrast Media Data, given as a 29x10 table of ADRs frequencies**. The columns stand for drugs as follows:

1. Gadobenic ac 5381 reports

2. Gadobutrol 837 "

3. Gadodiamide 5434 "

4. Gadofosveset 63 "

5. Gadopentetic ac 20202 "

6. Gadoteric ac 8 "

7. Gadoteridol 3428 "

8. Gadoversetamide 2836 "

9. Gadoxetic ac 98 "

10. Mangafodipir 9 "

The rows stand for 29 categories of SOCD-ADRs.

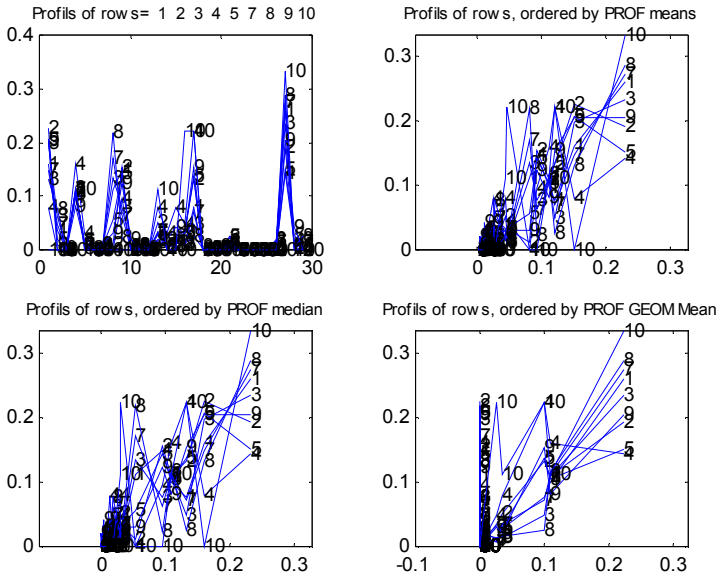
The result of the successive splitting in two algorithm described is the following **Table 3**. The ones show the columns included in the subset. The subset Nr.0 contains all the columns, hence is uninteresting. The last 10 subsets are singletons, of diameter zero. They are also uninteresting. We take up the subsets from Nr.1 to Nr.7.

Table 3.

Diameter	**Column**										**Subset**
(Gauge)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
.60116	1	1	1	1	1	1	1	1	1	1	**0**
.4752	1	1	1	1	1		1	1	1	1	**1**
.39324	1	1	1		1		1	1	1		**2**
.3359				1						1	**3**
.22853	1		1				1	1			**4**
.11137		1			1				1		**5**
.10593			1				1				**6**

.09087		1			1						**7**
0	1										
0		1									
0			1								
0				1							
0					1						
0						1					
0							1				
0								1			
0									1		
0										1	

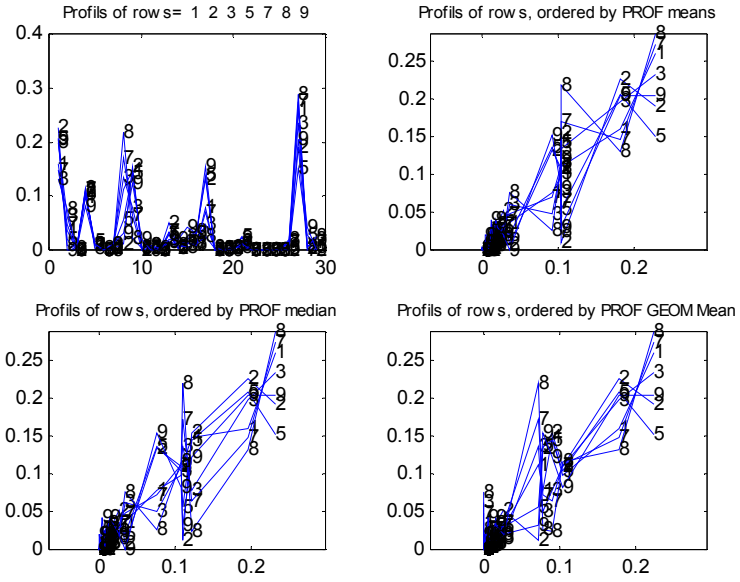
The **subset Nr. 1**, of diameter .4752, is maximal: any other subset is included in it. That means that this subset, specifically of columns 1,2,3,4,5, 7,8,9,10 can be viewed as giving a splitting of the table into two clusters, the second being the singleton 6. The following plot, shows that this cluster is of poor quality:



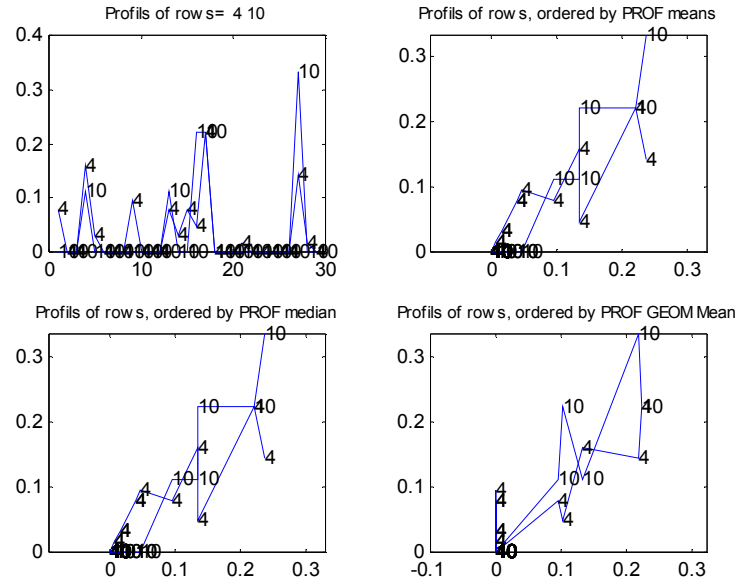
The **subset Nr. 2**, of diameter .39334, of columns 1,2,3,5,7,8,9 can be taken as cluster, and this eliminates the subsets Nrs. 4, 5, 6, 7 which are all included in it. The next not included, is the

subset Nr. 3, of diameter .3359 and of columns 4 and 10. Subset Nr. 2, subset Nr. 3, and the singleton 6, give a splitting of the columns into three clusters.

The plot for subset Nr. 2, shows it to be a rather poor quality cluster:



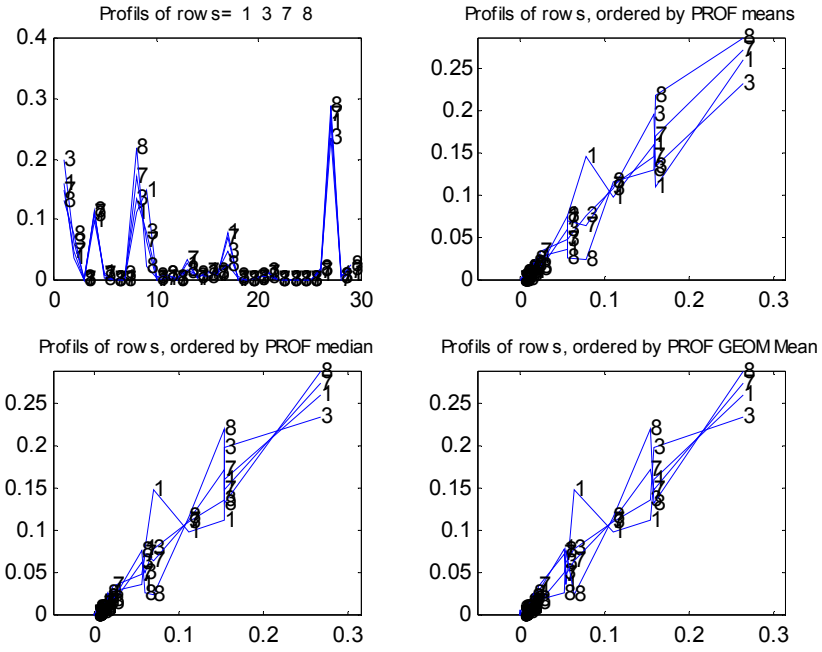
and the plot for subset Nr. 3,



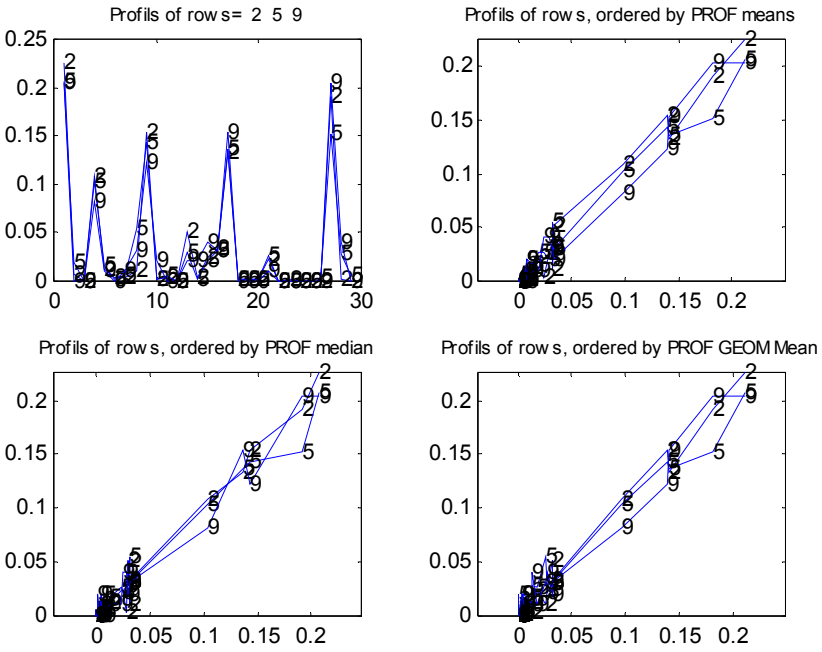
is still worse. This cluster system is unsatisfying.

The next candidate to be considered is the **subset Nr. 4**, of diameter .22853 and of columns 1, 3, 7, 8. This choice excludes subset Nr. 6, but admits **subset Nr. 5,** of diameter .11137 and of columns

2,5,9. This choice further eliminates subset Nr. 7. We have thus obtained the splitting of the columns into **cluster 1** = 1, 3, 7, 8, **cluster 2** = 2, 5, 9 and the **three singletons** 4,6 and 10. The Plot

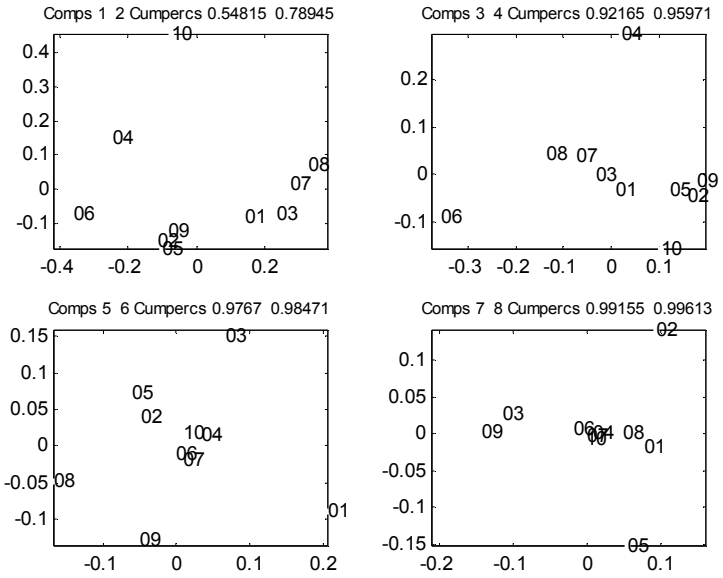


shows cluster 1 as rather acceptable, and the plot



shows cluster 2 to be rather good. We may stop here and **recommend to the specialist scientist to concentrate his attention on subset 1, 3, 7, 8 and on subset 2, 5, 9.**

The confirmatory plots, of which in most cases the plot of the first two coordinatesn is already sufficient for confirmation, are here



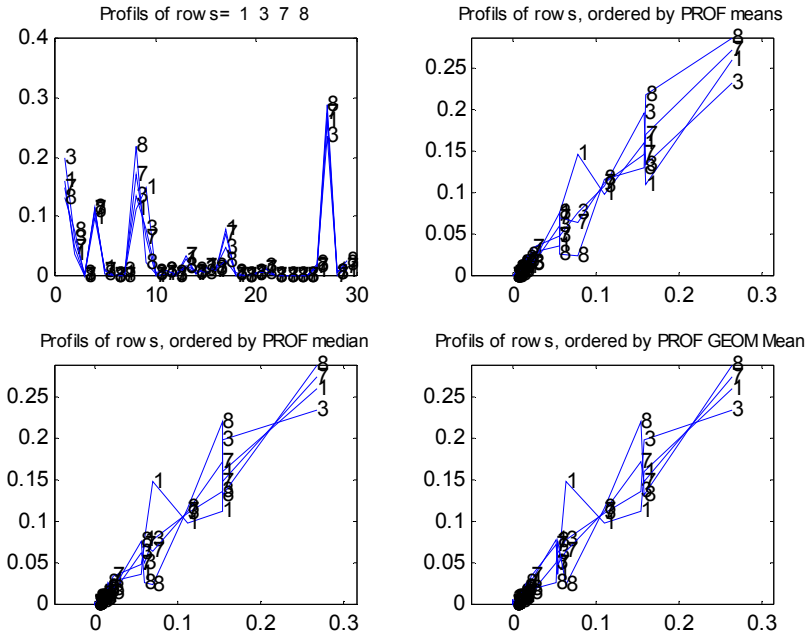
The two clusters 1, 3, 7, 8 and 2, 5, 9 appear clearly (on the lower part of the plot of components 1, 2) and so do the singletons 6, 4 and 10.

Note finally, that the singletons 4, 6, and 10 have the smallest number of reports, and cannot thus be taken seriously. The same holds for the product-column 9, which has a small number of reports too.

We may mention here, without the detailed explanation given above, that if the Data Set is reduced leaving aside the products with small total reports, that is n 4-Gadofosveset (ADRs n 63; 0.16%), n 6-Gadoteric acid (ADRs n 8; 0.02%), n 9-Gadoxetic acid (ADRs n 98; 0,25%) and n 10-Mangafodipir (ADRs n 9; 0.02%), one obtains by the same technique applied with GAUGE = .23, the same cluster 1: 1 3 7 8, and cluster 2: 2 5. The relevant plots are here:

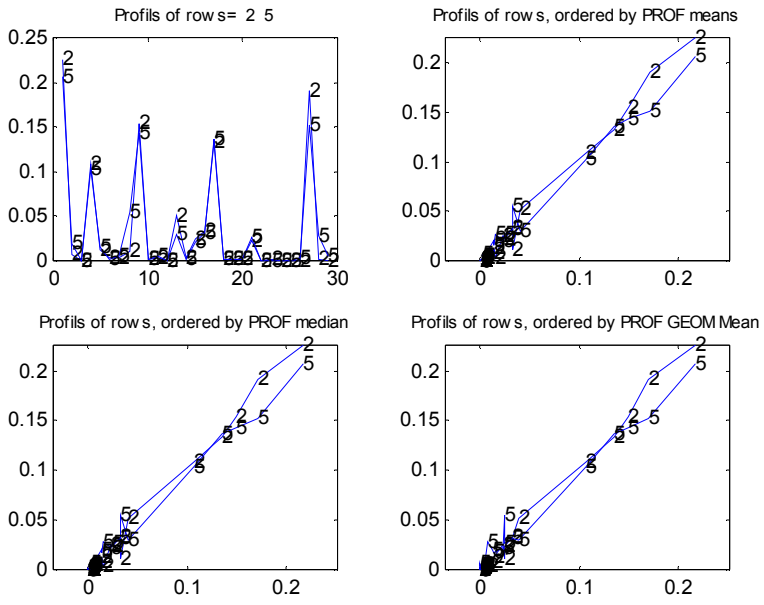
Cluster 1: 1 3 7 8

==========

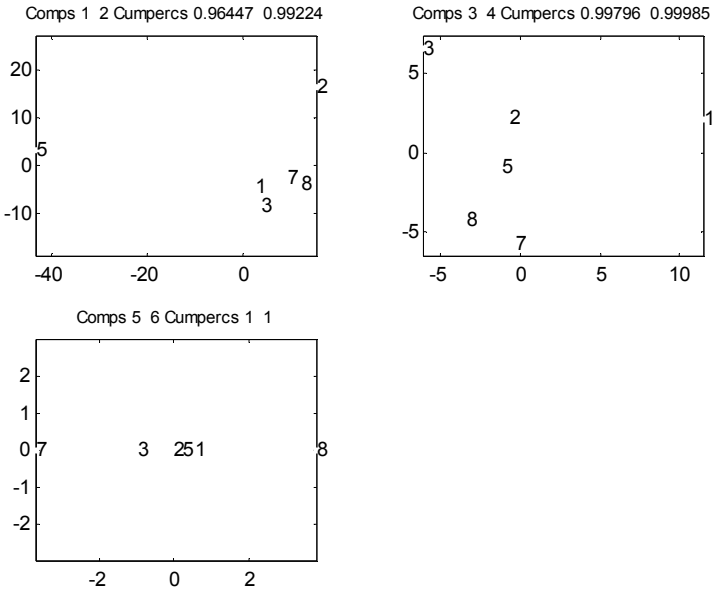

Profils of rows= 1 3 7 8
Profils of rows, ordered by PROF means
Profils of rows, ordered by PROF median
Profils of rows, ordered by PROF GEOM Mean

==========

Cluster 2: 2 5


Profils of rows= 2 5
Profils of rows, ordered by PROF means
Profils of rows, ordered by PROF median
Profils of rows, ordered by PROF GEOM Mean

Confirmatory plots:



In conclusion, in the case of both the above 29x10 dataset (for the full series of 10 paramagnetic agents and 29 WHO-accepted SOCD-ADRs classes), and the reduced 29x6 data set (for 6 most reported Gd-chelates) the algorithm extracts the same two clusters. Namely, one cluster including gadobenic acid, gadodiamide, gadoteridol and gadoversetamide and a second cluster including gadobutrol and the mostly reported gadopentetic acid (with the possible addition of more sparsly reported gadoxetic acid).

1.3 V08CB superparamagnetic products. Table 4. Data of SOCD frequencies

Table 4 (1990-2010). ATC V08CB NMR superparamagnetic contrast agents and numbers of reports, total or for each WHO SOCD code. Reports sent on 5.7.2010 by Dr Marie Lindquist, Director, WHO Uppsala Collaborating Centre as per 1968-2010 years new PR-22-2010 file. SOCD specifications as in the legend to Table 1.

	SOCDs (Code)	Ferristene	Ferrixan	Ferumoxides	Ferumoxsil	Reports (Total number)
1	**100**	1	13		14	**28**
2	**200**		1			**1**
4	**410**		14	1	7	**22**
9	**500**		2		4	**6**

10	**600**	1	10	3	9	**23**
11	**700**				1	**1**
12	**800**		1		1	**2**
14	**1,010**		16	5	7	**28**
15	**1,020**		1			**1**
16	**1,030**		2	1	5	**8**
17	**1,040**		1		7	**8**
18	**1,100**		9	1	11	**21**
21	**1,230**				1	**1**
22	**1,300**		2		4	**6**
28	**1,810**	1	17	8	42	**68**
29	**1,820**			1	1	**2**
30	**1,830**		1			**1**
	Total	**3**	**90**	**20**	**114**	**227**

1.5. V08CB superparamagnetic products. Statistical evaluations based on their standardized SOCDs

DATA 17 x 4, 1990-2010 (2 V08CB)

The four substances data do not clearly indicate any clustering. Of course this holds for the present time, when too few ADRs have been recorded. Collection of additional data should change the situation.

2. ATC-VO8C A and B NMR products. ADR data frequencies and their evaluation by modelling and autoclassification

2.1. V08CA- paramagnetic diagnostic imaging agents. ADR data

In the **Appendix Nr. 1.** the ADR frequencies of all products monitored according to the PR22-2010 file are reported. For each product we list (in bold, in brackets) the total number of ADRs, the frequencies in rising order as aggregated in the WHO-standardized SOCDs, numbered in increasing order, their codes and total numbers per class (in bold, in brackets), totalling 38,296 ADRs reported in the first 40 years. These SOCD-ADRs data can be reduced from 2364, the maximal ordinal number of the involved ADRs to only the 700 appearing, as shown in the **Appendix Nr. 2.**

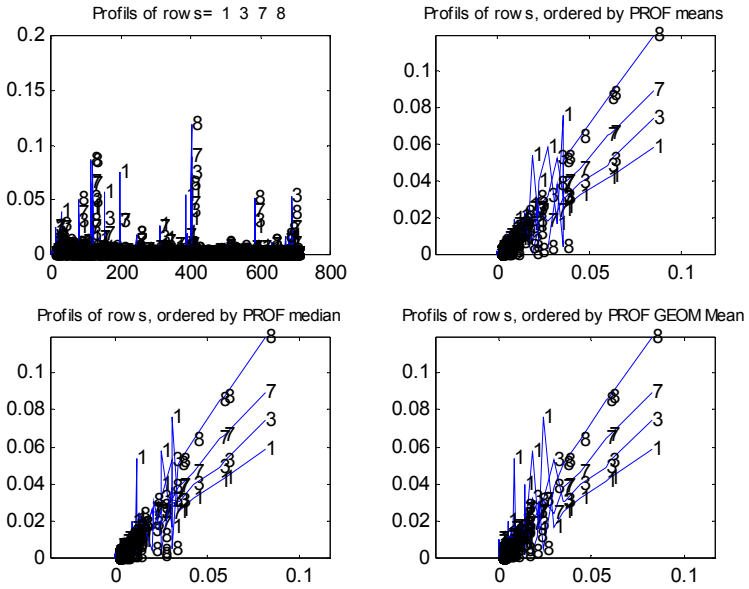
We will deal here first with the data set of the 700 represented ADR-rows x the 10 product-columns, and next for the matrix of the reduced 3% (eliminating in their order all the rows which together, do not contribute more the 3% of the total of the data) 259 data-rows x same 10 columns. In both cases, we will also apply the clustering technique to the 6 most reported products by retaining the columns 1, 2, 3, 5, 7 and 8, and leaving out the columns 4, 6, 9 and 10, as performed on the SOCD-ADRs classes of the Section 1.2. above. The numeration of the drug was kept

always the same. We will give only the results, the full treatment having been already illustrated as the example given in the same Section 1.2.

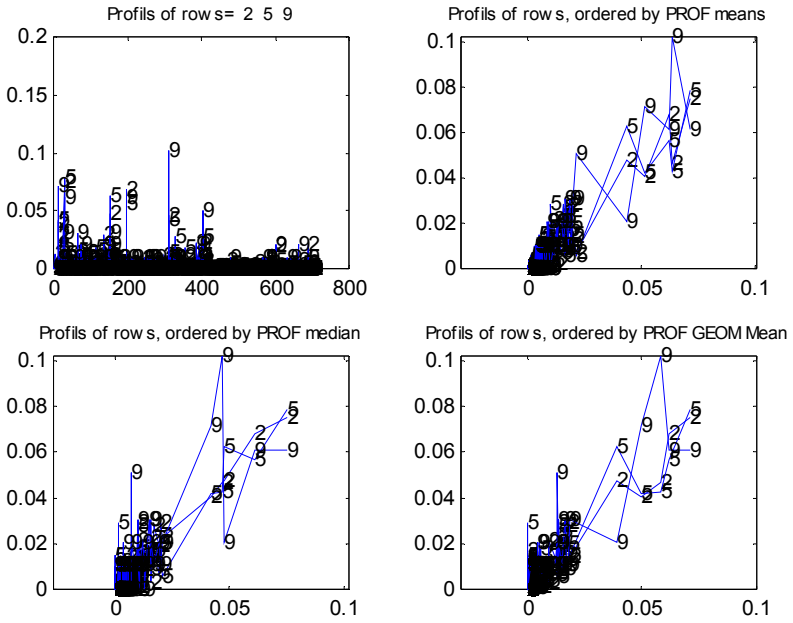
DATA SET 700x 10

GAUGE = .42

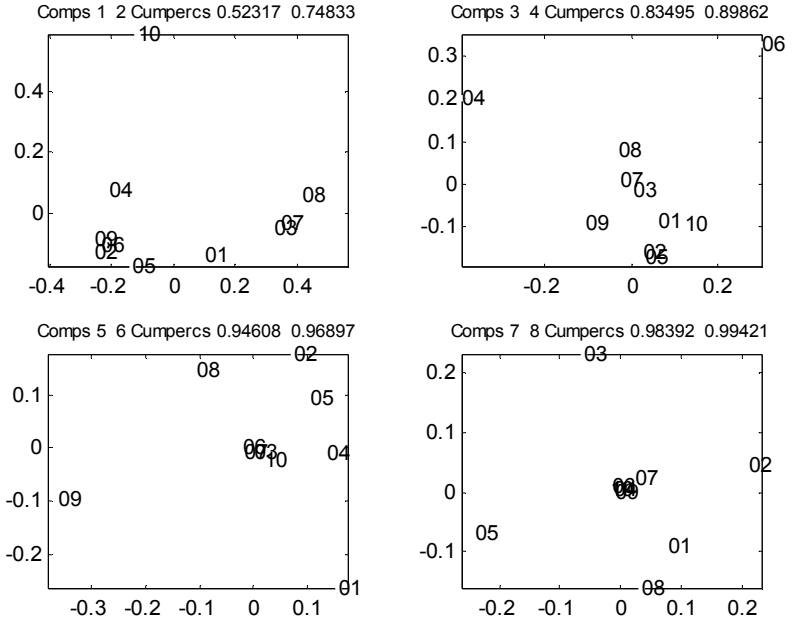
Cluster 1: 1 3 7 8



Cluster 2: 2 5 9 (that means drugs 2, 5, 9; please do not confound with the number of rows in the 3% reduced matrix, which happens by chance to be also 259!)



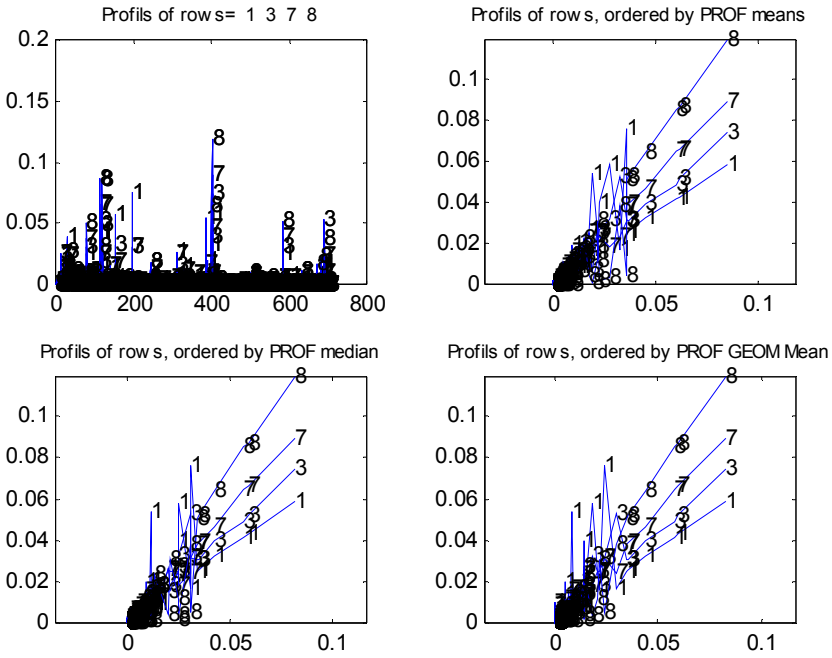
Confirmatory PLOTS. The first plot, for Components 1 2, is sufficient.



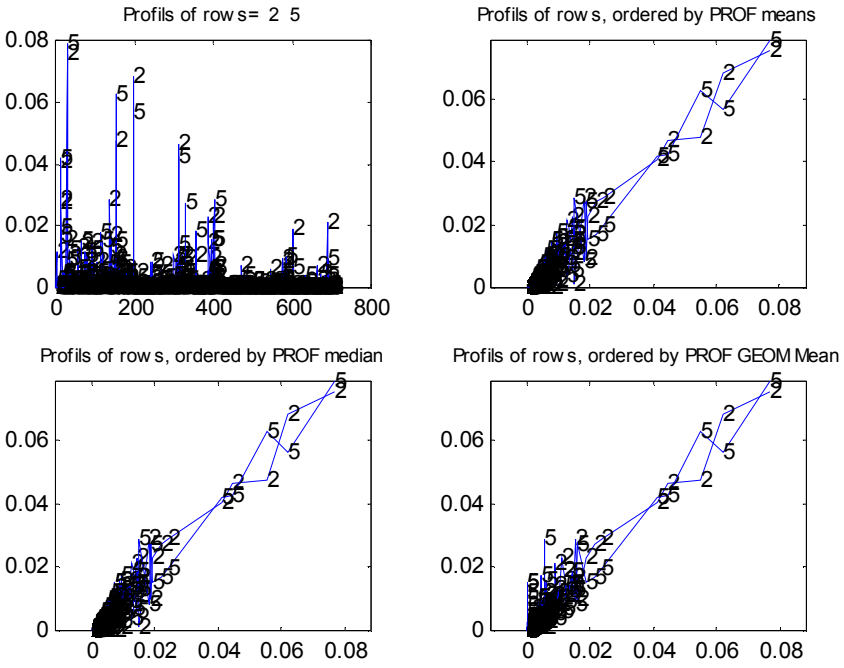
DATA SET 700 x 6

GAUGE = .42

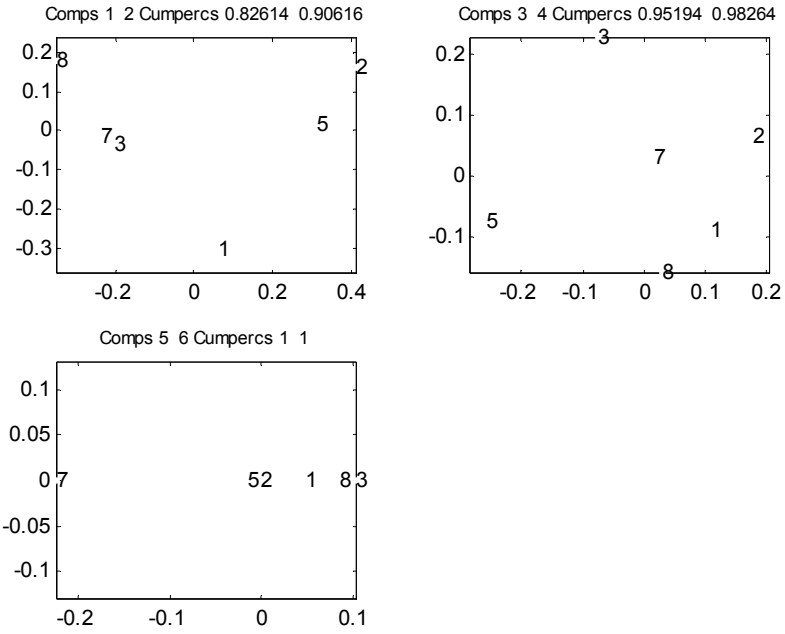
Cluster 1: **1 3 7 8**



Cluster 2: 2 5



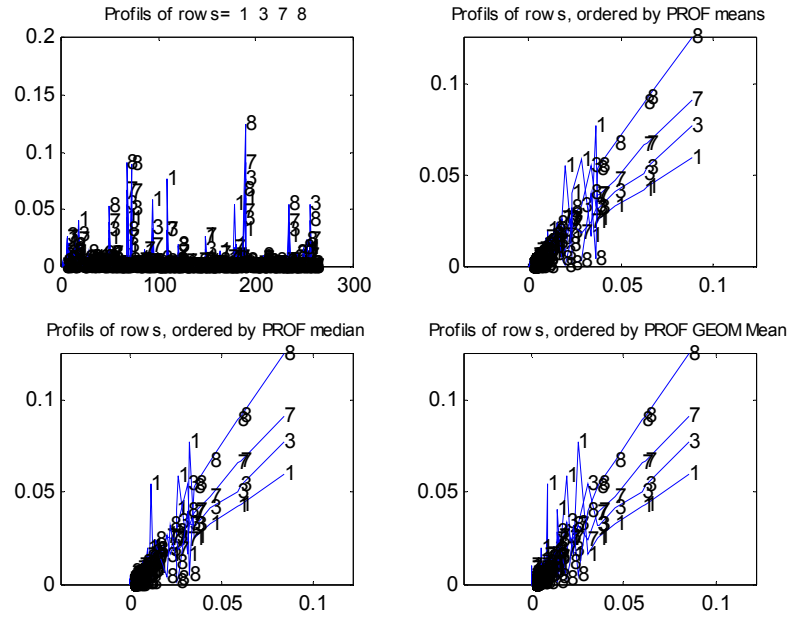
Confirmatory PLOTS:



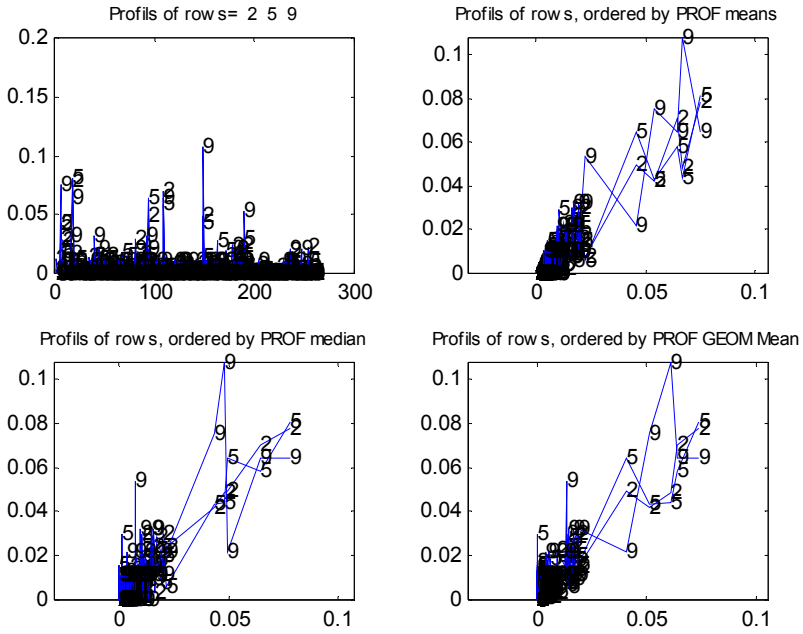
DATA SET 259x 10

GAUGE = .42

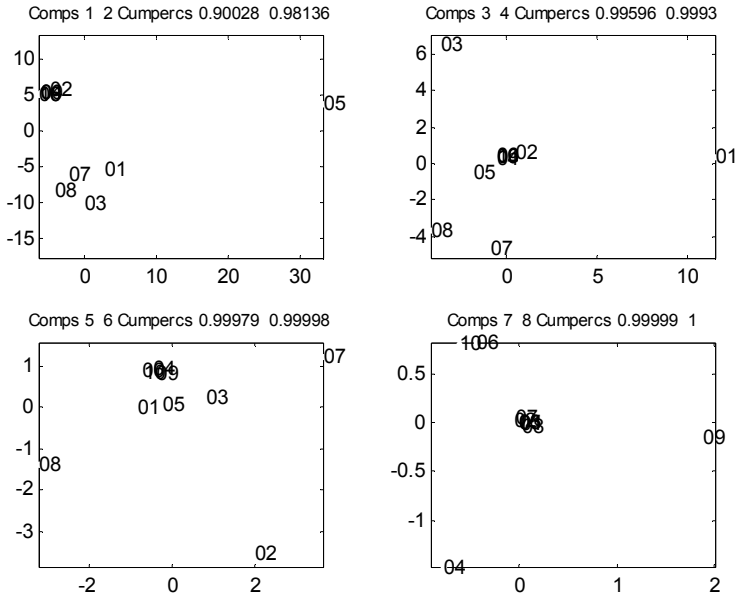
Cluster 1: 1 3 7 8



Cluster 2: 2 5 9



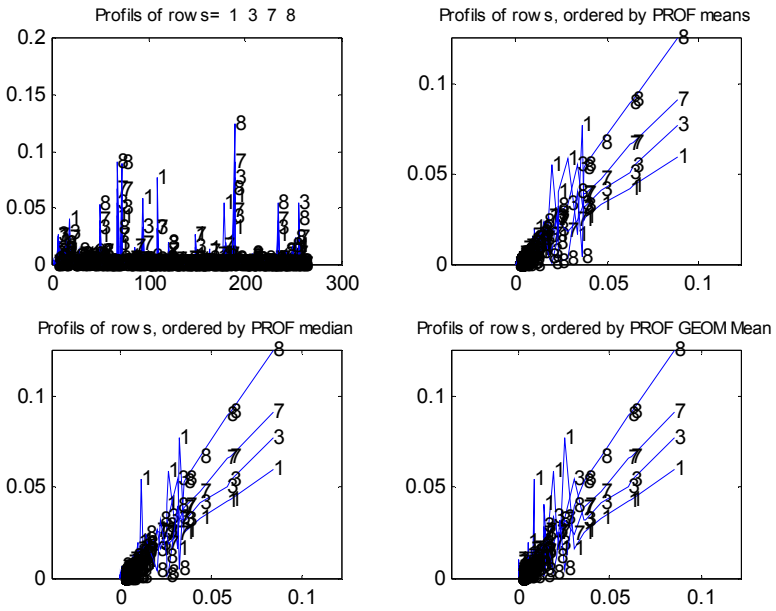
Confirmatory Plots:



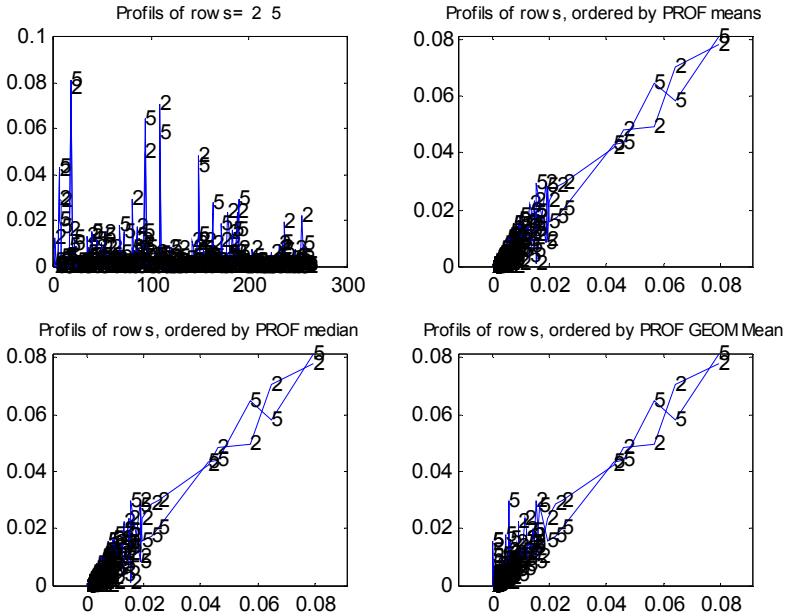
DATA SET 259x 6

GAUGE = .42

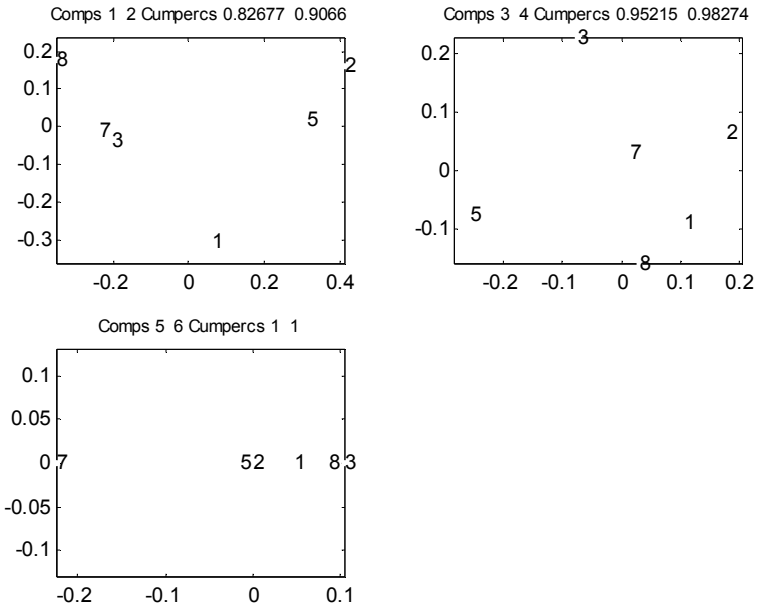
Cluster 1 = 1 3 7 8



Cluster 2 = 2 5



Confirmatory Plots



Conclusion. In this section 2.1, we applied the correlation clustering routine to the whole set 700x10 (all the 700 ADRs, all 10 drugs) and to the partial set 700x6 (all the 700 ADRs, 6 most reported drugs). The operation was repeated in both cases, on sets 259x10 and 259x6, obtained after reducing the corresponding data by 3% by taking away the ADRs having a too small contribution.

It results that the newly adopted correlation based clustering routine, yields in all 4 cases, for very similar gauges, the same two clusters 1, 3, 7, 8 and 2, 5(, 9) of drugs. This result differs from the subdivisions suggested by the parameters commonly adopted for their previous characterization. We will return on this point in the next Discussion Section.

2.2. VO8CB-superparamagnetic diagnostic imaging agents

Tables of the individual ADRs were not subjected to statistical evaluation due to their present small number of SOCD-ADRs. Their data have been already reported in Table 4, Section 1.3.

Discussion

The metal Gd^{3+} has 4f "buried", 7 unpaired parallel spin electrons, with a magnetic moment of 7.94 BM, a property that is mantained in complexes, causing water protons around the contrast agent to relax quickly (relaxitivity parameter of each GBCA) thus enhancing the quality of the MRI scans. The products are considered stable enough, but the lanthanoid can be set free after an as yet not clearly defined time and unfavourable conditions in tissues, so that its toxicity can no longer be disregarded when *in vivo* increase of iron mobilization (See Viswamitra & Shah (2007)[14]), and Zn^{2+}, Cu^{2+}, and Ca^{2+} transmetallation become substantial. This is supported by

acute toxicity experimental trials, where despite a 50-fold range of LD50 values for different Gd-complexes, all become lethally toxic when the same quantity of Gd^{3+} is released [16](See also Koop & al (1997) [16] for an example of enzymatic involvement; enzyme inhibition, Ca-blocking voltage channels and glutamate receptor and synaptic interferences of lanthanoids are long-standing issues). Ionic vs nonionic types, linear structures vs macrocyclic ring cores, osmolality, density/viscosity, and other physico-chemical properties (Cf [18]), aggregability and (serum) temperature dependency have been associated with immunogenic and chemotoxicity events and adverse effects, perhaps similarly differing to those of the various classes of some iodinated X-ray contrast agents. Nevertheless, the behaviours appear nonlinearly complex, and principal component multivariate analyses at the concentrations used *in vivo* are not conclusively elucidated. Transmetallation kinetics (Puttagunta & al, and Idée & al (1996)[18]) showed major differences among currently used MR-CBCAs, their equilibrium thermodynamic and selectivity ligand competition constants calculated *in vitro* (and in serum), that therefore do not explain the relative (pre-)equilibrium compartmentalization turnovers. Frenzel & al (2008)[18], measured the release of Gd^{3+} at the initial rate and after 15 days' incubation in human serum *in vitro* at 37°C, pH 7.4, and found that in the presence of additional 10 mmol/L phosphate precipitation – i.e. in a condition mimicking kidney insufficiency -, the initial Gd^{3+} concentration in native serum increased by 100% for nonionic and 12-30% for ionic linear GBCAs, but not for macrocyclic GBCAs, while only the Gd^{3+} concentrations of nonionic linear GBCAs remained increased (75%) at 15 days. It remains to be confirmed whether the macrocyclic chelates with high thermodynamic stability, if reinforced by ionicity, will minimize the amount of free Gd^{3+} released *in vivo* (Cf Port & al (2008)[18]. Nevertheless, our experience of the highly unpredictable instability even of the well-known, best purified protein or hydrocarbon polymers suggests the utmost caution in applying any statistical method to explain kinetics vs (thermo)dynamics in multiple, interacting native, living broths [19], which entails that our presentation in Table 6 may be somewhat incidental. Transient protein conformations, which have only recently been detected and characterized (i.e. [20]), promise to be of greater potential use than extended traditionally full QSARS studies (See References [47-61] in [21]).

Table 6. PHYSICO-CHEMICAL AND KINETIC "CONSTANTS" . Columns: 1) Meglumine Gadobenate, Gd-BOPTA (MultiHance R); 2) Gadobutrol, Gd-BT-DO3A (Gadovist R); 3) Gadodiamide, Gd-DTPA-BMA (Omniscan R); 4) Trisodium Gadofosveset, MS 325 (Vasovist R); 5) Meglumine Gadopentetate, Gd-DTPA (Magnevist R); 6) Meglumine Gadoterate, Gd-DOTA (Dotarem R); 7) Gadoteridol, Gd-HP-DO3A (ProHance R); 8) Gadoversetamide, Gd-DTPA-BMEA (OptiMARK R); 9) Disodium Gadoxetate, Gd-EOB-DTPA (Primovist R). Gadofosveset and Gadoxetate strongly bind reversibly to serum proteins, taken and excreted by liver; other mostly eliminated by glomerular filtration. Rows: 1) Molecular weight; 2) Dissociated particles per molecule; 3) – log P BuOH/H_20; 4) Standard dose ev, mmol/kg; 5) Osmolality mOsm/kg H_2O at 37°C; 6) Viscosity mPa.s at 37°C; 7) Log $K_{thermod}$; 8) Log $K_{conditional}$ at pH 7.4, 37°C; 9) Dissociation rate in 0.1 M HCl (sec^{-1}); 10) Half-life (h, in normal volunteers); 11) Excess free ligand (percentage of the molar concentration of Gd-chelate); 12) Osmotic load (mOsm/l) : {[dose(mmol/kg)x70] / $V_{distribution}$ (l)}x number of dissociated ions. Values calculated on the assumption that the agents distribute homogenously in the interstitial space (10.5 l for a patient

weighing 70 kg). Asterisks indicate averaged values from Frenzel & al (2008), Mark & al (2008)[18], and The London Pharmaceutical Press' Martyndale Pharmacopoeia online edition (2010).

	1	2	3	4	5	6	7	8	9
1	1,058.2	604.3	582.6*	975.9	938.5	753.9	558.7	661.8	725.0
2	3	1	1	4	3	2	1	1	3
3	2.33	2.00	2.13	2.11	3.16	2.87	1.98	x	2.11
4	0.1	0.1	0.1	0.03	0.1	0.1	0.1	0.1	0.025
5	1,970	1,603	789.5*	825	1,950*	1,350	630	1,110	688
6	5.3	4.96	1.4	1.95*	2.9	2.0	1.3	2.0	1.19
7	22.6	21.8	16.9	22.1	22.3	25.6	23.8	16.7	23.5
8	18.4	14.9*	14.9	18.9	18.5	19.3	17.2	15.0	18.7
9	x	2.8×10^{-6}	2.0×10^{-2}	x	1.2×10^{-3}	8.4×10^{-7}	6.4×10^{-5}	2.2×10^{-2}	X
10	1.59*	1.5	1.3	2.5	1.5	1.5	1.57	1.73	0.95
11	0.0	0.1	5.0	0.1	0.1	0.0	0.1	10.0	0.5
12	2.00	0.67	0.67	0.80	2.00	1.33	0.67	0.67	0.50

We intend to attempt in the future to obtain a model representing a unified description of these physico-chemical and kinetic "constants".

An intriguing related problem, and one not involving only to the widely different cost of any new (rational) product choices, is the one first discussed by Elmståhl, whereby there is no contraindication to the adoption of relatively old iodinated contrast agents: indeed, the dogma that Gd-based media are less nephrotoxic than iodine agents is being discussed as a misconception (Cf Nyman & al (2007) [22]. The Katzberg and Newhouse (2010) Editorial, following the Rao and Newhouse (2006) line, such as the contributions of Solomon (2005) and others ([6], [22]) seriously calls for a general comparison of all SOCDs & ADRs collected and analysed, also with a view to identifying potentially more cost-effective agent(s) to replace both iodinated and Gd-based diagnostic procedures. This can be the subject of our next contribution, extended to all intravenous contrast media in use, following the first innovative presentation of Sharma's 2008 review [23].

Finally, it may be convenient to make here some new observations on the need for improving the Uppsala collaborative programme developed by the WHO:

a) there are no data from the various Countries regarding the size of treated patient populations or their conditions, including emerging ones, and/or mean data, as previously noted [17], even though this requires standardizable verification of compliances: only then could our studies be considered as involving the general exposed population of participating Countries, not their specific physiopathology groups or any treated person;

b) there is little information on the date of product introduction into clinical research, or at least the mean duration of such use, as well as the dates when the individual products (and/or their variants, equivalent salts, etc) were approved for clinical use in each Country. This prevents separation and comparison of trends, for instance between the two 20-year periods we addresses, which was previously feasible. Hence the need for agreeing on and repeating well-established statistical procedures, proposed here, as in our first example, and for studying their exploratory kinetics;

c) it would be useful to introduce verification and updating of new pathological conditions, maybe simultaneous to the publication of WHO Technical Reports (e.g. CIN and NSF, which are not yet reported in the presented data and cited Tables. For these new syndromes and chronic pathological entities, properly finalized analytical programmes are already in progress);

d) a long overdue issue is the resolution, or at least the addressing, of the problems relating to reporting immediacy, "suspicion, early alarm", and the necessary analytical verifications (at the central, peripheral, regional, and/or national level or, in case of failed, inappropriate or delayed implementation, at the local level) using pre-established and up-to-date criteria, to be submitted for approval by the annual meetings of the representatives of participating Countries, and involving appropriately followed up, explicitly open, patient cohorts of volunteers;

e) explicit reference to other existing data banks for a range of information including exploratory, representative, ordinative, administrative and scientific (confirmed) analytical data should also be made (i.e., the recently presented new connections regarding outstanding global nutrition problems and health systems (Cf [24]) that variously contribute to environment and disease risks (Cf [25]);

f) an *ad hoc* (voluntary) drug recall programme should be implemented, at least for alarming or new suspected reactions and/or for those syndromes that emerge from previous ADRs (Cf [10], in Bradu & Rossini [17], p 748).

In commenting on the scientific and social philosophy of our unique, collaborative, global WHO programme, we have previously referred to the need for a systematic review process in healthcare (Cf [5], and [11] in [17]). Here, we also take the opportunity to stress the need for participating in, and extend, the so-called open mHealth Architecture [26], based on collaborative, no-barrier, spontaneous, voluntary work, which has the potential to advance clinical care and pharmacotoxicological drug research on a scale and resolution that has never been possible before.

Appendix Nr 1. V08CA paramagnetic diagnostic imaging agents. ADRs data of PR-22-2010 file of the n 10 products monitored.

For each product the total number of ADRs (in bold, in brackets) are listed, then the frequencies in rising order as aggregated in the WHO-standardized SOCDs, numbered in increasing order, their codes and total numbers per class (in bold, in brackets). The total number of the ADRs reported in the first 40 years is 38,296.

1-Gadobenic acid (n 5,381): 1-100 (n 862): (Hyperkeratosis (0966): 1; Skin reaction localized (1,650): 1; Papilloma (1,486): 1; Dermatitis (0007): 1; Skin depigmentation (0035): 1; Scleroderma (0971): 2; Skin atrophy (0034): 2; Rash pustular (0032): 2; Pigmentation abnormal (0973): 2; Skin necrosis (0060): 3; Urticaria acute (0045): 3; Skin nodule (0061): 5; Skin ulceration (0041): 5; Skin cold clammy (0932): 7; Bullous eruption (0871): 9; Dermatitis exfoliative (0008): 11; Skin exfoliation (1,199): 12; Skin dry (1,123): 14; Angioedema (0003): 24; Skin disorder (0037): 24; Rash macula-papular (0030); 27; Induration (1,891): 30; Skin discolouration (0036): 35; Sweating increased (0043): 41; Rash (0027): 50; Fibrosis skin (2,314): 88; Rash erythematous (0028): 112; Pruritus (0024): 135; Urticaria (0044): 214); **2-200 (n 192)**: (Ligament disorder (2,086): 1; Arthropathy (0065): 1; Osteomyelitis (1,184): 1; Fracture pathological (0069): 1; Arthritis infective (2,024): 1; Musculoskeletal pain (1,889): 1; Muscle atrophy (0072): 2; Tendon disorder (1,074): 3; Myopathy (0074): 6; Arthritis (0064): 8; Arthralgia (0063): 16; Skeletal pain (1,347): 18; Muscle weakness (1,128): 27; Myalgia (0073): 28; Arthrosis (0066): 28; Deformity (2,209): 50); **4-410 (n 530)** (Hyperaesthesia (0113): 1; Hyperkinesia (0114): 1; Aphasia (0087): 1; Vocal cord paralysis (0942): 1; Brainstem disorder (0810): 1; EEG abnormal (0104): 1; Neuralgia (0124): 1; Choreoathetosis (0090): 1; Polyneuropathy (2,082): 1; Tongue paralysis (0153): 1; Spinal stenosis (1,975): 1; Dystonia (0068): 2; Encephalopathy (0105): 2; Sensory disturbance (0148): 2; Faecal incontinence (0107): 2; Ataxia (0088): 3; Muscle contractions involuntary (0155): 3; Migraine (0121): 3; Neuropathy peripheral (1,313): 5; Speech disorder (0150): 5; Oculogyric crisis (0132): 6; Convulsions (0093): 11; Dysphonia (0103): 12; Stupor (0151): 12; Convulsions grand mal (0095): 14; Dyskinesia (0102): 16; Tremor (0154): 17; Headache (0109): 23; Gait abnormal (0108): 24; Hypertonia (0116): 25; Dysaesthesia (1,491): 25; Hypoaesthesia (0117): 25; Coma (0091): 41; Dizziness (0101): 53; Paraesthesia (0137): 56; Hypokinesia (0118): 132); 6-**431 (n 53):** (Fixed pupils (1,605): 1; Diplopia (0241): 1; Scleritis (0255): 1; Photophobia (0250): 1; Muscae volitantes (1,977): 2; Eye abnormality (0243): 3; Vision abnormal (0257): 7; Lacrimation abnormal (1,049): 17; Conjunctivitis (0238): 20); **7-432 (n 1):** Ear disorder NOS (1,255): 1); 8-433 (n 16): (Taste loss (0266): 1; Parosmia (0265): 2; Taste perversion (0267): 13); 9-**500 (n 599):** (Aggressive reaction (0162): 1; Hallucination (0179): 1; Personality disorder (0192): 1; Catatonic reaction (0169): 1; Anorexia (0165): 2; Somnolence (0197): 4; Mental disorder (1,944): 4; Insomnia (0183): 5; Nervousness (0188): 6; Depression (0172): 7; Confusion (0092): 7; Agitation (0163): 10; Depersonalization (0171): 11; Apathy (0167): 85; Emotional lability (0177): 224; Anxiety (0166): 230); **10-600 (n 792):** (Increased stool urgency (1,843): 1; Haematemesis (0297): 1; Constipation (0204): 1; Flatulence (0285): 1; Pancreatitis (0314): 1; Amylase increate (1,101): 1; Tongue disorder (0330): 2; Saliva increate (0222): 2; Intestinal ischaemia (1,308): 2; Mouth dry (0218): 4; Cheilitis (0270): 5; Mucositis NOS (1,351): 5; Dyspepsia (0279): 5; Dysphagia (0280): 7; Diarrhoea (0205): 7; Tongue oedema

(0331): 9; Abdominal pain (0268): 16; Vomiting (0228): 312; Nausea (0308): 410); **11-700 (n 6)** (Hepatic function abnormal (0348): 1; Bilirubinaemia (0339): 1; Hepatic necrosis (0349): 1; Hepatic enzymes increate (1,346): 1; Jaundice (0356): 2); **12-800 (n 12):** (Hyperglycaemia (0382): 1; Cachexia (0368): 1; Weight decrease (0407): 1; Phosphatase alkaline increate (0404): 1; Glycosuria (0377): 1; Troponin tincreased (2,090): 1; Acidosis lactic (0364): 2; Calcinosis (0369): 2; Oedema pharynx (1,395) :4); **13-900 (n 1):** (Adrenal insufficiency (0410): 1; **14-1,010 (n149):** (Cardio respiratory failure (1899): 1; Hypotension postural (0213): 1; Cardiomegaly (1,320): 1; Blood pressure fluctuation (1,762): 2; Hypertension pulmonary (0211):2; Cardiac failure (0496): 2; Heart disorder (0504): 3; Pulse weak (1,401): 9; Cyanosis (0501): 12; Circulatory failure (0499):14; Hypertension (0210): 30; Hypotension (0212): 72); **15-1,020 (n 10): (**Coronary artery disorder (0426): 1; Fibrosis endocardial (1,274): 2; Angina pectoris (0422): 3; Fibrosis myocardial (1,188): 4); **16-1,030 (n 79):** (AV block (0431): 1; AV block complete (1,378): 1; Arrhythmia nodal (0809): 1; Extrasystoles (0438): 1; Arrhythmia (0433): 7; Palpitation (0221): 7; Bradycardia (0208): 10; Cardiac arrest (0437): 20; Tachycardia (0224): 31); **17-1,040 (n 48):** (Stenosis vein (2,083): 1; Cerebral haemorrhage (0444): 1; Peripheral ischaemia (0454): 1; Vasodilatation (0225): 1; Thrombophlebitis deep (0470): 1; Capillary leak syndrome (1,835): 1; Thrombophlebitis superficial (0479): 1; Phlebitis (0455): 1; Transient ischaemic attack (1,694): 1; Vein disorder (0492): 2; Thrombophlebitis (0466): 3; Flushing (0207): 34); **18-1,100 (n 414):** (Apnoea (0507): 1; Hypoventilation (0518): 1; Sputum increate (0541): 1; Asthma (1,367): 1; Bradypnoea (0510): 1; Pulmonary congestion (1,721): 1; Chronic obstructive airways disease (1,493): 1; Pulmonary infiltration (1,038): 1; Aspiration (1,030): 1; Haemoptysis (0516): 1; Pleural fibrosis(0525): 1; Stridor (0542): 2; Epistaxis (0515): 2; Pneumonia (0528): 2; Pulmonary fibrosis(0532): 2; Laryngismus (0520): 3; Respiratory disorder (0536): 3; Pulmonary disorders (2,032): 4; Hyperventilation (0517): 4; Pharyngitis (0523): 5; Hypoxia (0519): 5; Sinusitis (0540): 5; Pulmonary oedema (0535): 5; Respiratory insufficiency (0537): 6; Respiratory depression (0144): 11; Bronchospasm (0511): 14; Larynx oedema (0522): 16; Laryngitis (0521): 19; Throattightness (1,489): 33; Coughing (0513): 45; Rhinitis (0539): 75; Dyspnoea (0514): 142); **20-1,220 (n 3):** (Leukocytosis (0576): 1; Leucopenia (0908): 1; Lymphoedema (0581): 1); **21-1,230 (n 12):** (Prothrombin decreased (0590): 1; Thrombocytopenia (0594): 1; Haematoma (1,353): 1; Thrombosis arterial (0482): 1; Thrombus intracardiac (2,113): 1; Thrombosis arterio-venous fistula (1,776): 1; Purpura (0459): 3; Embolism pulmonary (0451): 3); **22-1,300 (n 57):** (Micturition urgency (1,497): 1; Urinary tract stenosis (2,317): 1; Nephrosis (0610): 1; Renal failure acute (0618):2; Azotaemia (2,328):3; Renal failure chronic (2,329): 4; Renal function abnormal (0619): 5; Urinary incontinence (0156): 5; Face oedema (0602): 35]; **23-1,410 (n 2):** (Prostatic disorder (0632): 1; Testicular pain (1,500): 1); **25-1,500 (n 1)** (Eye malformation (0689): 1); **27- 1,700 (n 51):** (Histiocytoma (2,046): 1; Bladder carcinoma (0766): 1; Hyperhaemoglobinaemia (0928): 1; Breast neoplasm benign female (1,114): 1; Skin hypertrophy (0038): 47); **28-1,810 (n 1,399):** (Drug hypersensitivity syndrome (2,309): 1; Posture abnormal (2,012): 1; Death (0722): 1; Withdrawal syndrome (0200): 1; Crying abnormal (1,162): 1; Medicine ineffective (1,948): 1; Night sweats (1,898): 1; Multiple organ failure (1,819): 1; Drug interaction (2,356): 2; Allergy (1,058): 3; Choking (1,460): 3; Fever (0725): 5; Back pain (0717): 6; Pallor (0220): 7; Fatigue (0724): 9; Rigors (0731): 11; Oedema mouth (1,485): 13; Oedema generalized (0400): 13; Oedema periorbital (1009): 16; Asthenia (0716): 20; Oedema (0398): 22;

Syncope (0223): 23; Chest pain (0718): 36; Temperature changed sensation (1,705): 36; Anaphylactic shock (0713): 40; Oedema peripheral (0401): 48; Anaphylactic reaction (2,237): 54; Anaphylactoid reaction (0714): 105; Scar (1,522): 138; Malaise (0728): 174; Allergic reaction (0712): 291; Pain (0730): 316); **29-1,820 (n 40):** (Infusion site rash (2,136): 1; Medical device complication (2,139): 1; Application site reaction (0047): 1; Injection site bleeding (1,752): 2; Cellulitis (1,372): 2; Infusion site reaction (2,137): 3; Injection site inflammation (0054): 4; Injection site pain (0057): 7; Injection site rash (1,881): 7; Injection site reaction (0058): 12); **30-1,830 (n 50):** (Infection staphylococcal (1,867): 1; Infection susceptibility increased (1,226): 1; Infection (0736): 1; Abscess (0887): 1; Sepsis (0744): 2; Skin tightness (2,098): 44. **2-Gadobutrol (n 837): 1-100 (n 189):** (Acne (0001): 1; Rash psoriasiform (0031): 1; Bullous eruption (0871): 1; Scleroderma (0971): 1; Erythema multiforme (0014): 1; Skin cold clammy (0932): 1; Dermatitis (0007): 1; Skin discolouration (0036): 1; Skin reaction localised (1,650): 1; Skin necrosis (0060): 1; Rash maculo-papular (0030): 2; Fibrosis skin (2,314): 3; Rash pustular (0032): 3; Skin disorder (0037): 4; Angioedema (0003): 10; Sweating increased (0043): 13; Rash erythematous (0028): 23; Rash (0027): 24; Pruritus (0024): 34; Urticaria (0044): 63); **2-200 (n 6):** (Arthrosis (0066): 1; Arthralgia (0063): 1; Muscle weakness (1,128): 2; Myalgia (0073): 2); **4-410 (n 91):** (Hypokinesia (0118): 1; Hyperkinesia (0114): 1; Sensory disturbance (0148): 1; Tetany (0152): 1; Dystonia (0068): 1; Neurologic disorder NOS (2133): 1; Cramps legs (0939): 1; Oedema cerebral (0891): 1; Encephalopathy (0105): 1; Ptosis (0142): 1; Vertigo (0158): 2; Convulsions grand mal (0095): 2; Muscle contractions involuntary (0155): 3; Stupor (0151): 3; Hypoaesthesia (0117): 4; Dysphonia (0103): 4; Headache (0109): 7; Dysaesthesia (1,491): 7; Tremor (0154): 7; Convulsions (0093): 7; Coma (0091): 11; Paraesthesia (0137): 12; Dizziness (0101): 12); **6-431 (n 10):** (Lacrimation abnormal (1049): 1; Chromatopsia (0237): 1; Mydriasis (0219): 1; Conjunctivitis (0238): 3; Vision abnormal (0257): 4); **7-432 (n 3):** (Hearing decreased (1368): 1; Ear disorder NOS (1,255): 1; Tinnitus (0264): 1); **8-433 (n 3):** (Taste loss (0266): 1; Taste perversion (0267): 2); **9-500 (n 9):** (Hallucination (0179): 1; Amnesia (0164): 1; Somnolence (0197): 1; Insomnia (0183): 1; Anxiety (0166): 1; Sleep disorder (0195): 1; Agitation (0163): 3); **10-600 (n 129):** (Flatulence (0285): 1; Gastric ulcer (0287): 1; Constipation (0204): 1; Stomatitis (0327): 1; Dyspepsia (0279): 2; Mouth dry (0218): 2; Diarrhoea (0205): 3; Dysphagia (0280): 3; Cheilitis (0270): 4; Tongue oedema (0331): 4; Abdominal pain (0268): 5; Mucositis NOS (1,351): 5; Vomiting (0228): 40; Nausea (0308): 57); **11-700 (n 1)** (Hepatocellular damage (0353): 1); **12-800 (n 3):** (Glucose tolerance abnormal (0376): 1; Oedema pharynx (1,395): 2); **14-1,010 (n 43):** (Cardiac failure left (0497): 1; Blood pressure fluctuation (1,762): 1; Hypertension (0210): 5; Cardiovascular disorders (2,031): 6; Cyanosis (0501): 7; Circulatory failure (0499): 9; Hypotension (0212): 14); **15-1,020 (n 3):** (Myocardial ischaemia (0429): 1; Angina pectoris (0422): 2); **16-1,030 (n 21):** (Arrhythmia (0433): 2; Palpitation (0221): 2; Bradycardia (0208): 3; Cardiac arrest (0437): 6; Tachycardia (0224): 8); **17-1,040 (n 28):** (Peripheral ischaemia (0454): 1; Cerebrovascular disorder (0445): 1; Vasculitis (0085): 1; Vein pain (0494): 1; Flushing (0207): 24); **18-1,100 (n 111):** (Pneumonia (0528): 1; Alveolitis allergic (1,019): 1; Hypoxia (0519): 1; Pulmonary disorders (2,032): 2; Respiratory insufficiency (0537): 2; Stridor (0542): 2; Pharyngitis (0523): 3; Respiratory disorder (0536): 3; Pulmonary oedema (0535): 4; Laryngitis (0521): 6; Throat tightness (1,489): 6; Respiratory depression (0144): 7; Rhinitis (0539): 8; Bronchospasm (0511): 8; Larynx oedema (0522): 9; Coughing (0513): 9; Dyspnoea (0514): 39); **19-1,210 (n 1):** (Anaemia (0544): 1): **20-**

1,220 (n 2): (Granulocytopenia (0572): 1; Leucopenia (0908): 1); **21-1,230 (n 2):** (Embolism pulmonary (0451): 1; Thrombocytopenia (0594): 1); **22-1,300 (n 19):** (Nephropathy toxic (0609): 1; Oliguria (0612): 1; Azotaemia (2,328): 1; Renal failure acute (0618): 1; Anuria (0596): 1; Urinary retention (0157): 1; Renal function abnormal (0619): 1; Creatinine clearance decreased (0598): 1; Renal pain (0621): 2; Face oedema (0602): 9); **24-1,420 (n 1):** (Vaginal discomfort (1,505): 1); **28- 1,810 (n 160):** (Choking (1,460): 1; Halitosis (0990): 1; Asthenia (0716): 1; Multiple organ failure (1,819): 1; Pain (0730): 1; Oedema generalised (0400): 1; Leg pain (1,439): 2; Chest pain (0718): 2; Drug level increased (1,281): 2; Back pain (0717): 3; Oedema peripheral (0401): 3; Fatigue (0724): 3; Fever (0725): 5; Oedema periorbital (1,009): 6; Rigors (0731): 6; Pallor (0220): 6; Oedema (0398): 7; Oedema mouth (1,485): 8; Anaphylactoid reaction (0714): 8; Syncope (0223): 9; Anaphylactic shock (0713): 12; Temperature changed sensation (1,705): 16; Anaphylactic reaction (2,237): 18; Malaise (0728): 19; Allergic reaction (0712): 19); **29-1,820 (n 2)** (Injection site necrosis (0056): 1; Injection site pain (0057): 1). **3-Gadodiamide (n 5,434): 1-100 (n 1,073):** (Acne (0001): 1; Papilloma (1,486): 1; Photosensitivity reaction (0022): 1; Livedo reticularis (1,410): 1; Skin depigmentation (0035): 1; Nail disorder (0020): 1; Dermatitis herpetiformis (1,549): 1; Skin reaction localised (1,650): 1; Erythema induratum (0912): 1; Psoriasis (1,398): 1; Dermatitis contact (0049): 1; Rash psoriaform (0031): 1; Epidermal necrolysis (0013): 1; Skin cold clammy (0932): 2; Rash pustular (0032): 2; Hyperkeratosis (0966): 3; Bullous eruption (0871): 4; Skin necrosis (0060): 4; Dermatitis (0007): 4; Skin atrophy (0034): 5; Alopecia (0002): 5; Scleroderma (0971): 5; Pigmentation abnormal (0973): 6; Eczema (0012): 6; Angioedema (0003): 7; Skin nodule (0061): 7; Skin ulceration (0041): 10; Sweating increased (0043): 13; Dermatitis exfoliative (0008): 14; Skin exfoliation (1,199): 22; Skin dry (1,123): 27; Rash maculo-papular (0030): 33; Skin disorder (0037): 47; Skin discolouration (0036): 63; Induration (1,891): 63; Rash erythematous (0028): 64; Rash (0027): 75; Pruritus (0024): 136; Urticaria (0044): 147; Fibrosis skin (2,314): 286); **2-200 (n 330):** (Ligament disorder (2,086): 1; Fracture pathological (0069): 1; Fasciitis necrotising (1,746): 1; Bone disorder (0067): 1; Osteomyelitis (1,184): 1; Avascular necrosis bone (2,222): 1; Fasciitis (1,707): 1; Osteitis (1,882): 1; Synovitis (0864): 2; Tendon disorder (1,074): 3; Fracture (2,190): 3; Musculoskeletal pain (1,889): 5; Myositis (0748): 5; Myopathy (0074): 5; Muscle atrophy (0072): 6; Rhabdomyolysis (1,210): 8; Arthritis (0064): 13; Arthropathy (0065): 14; Skeletal pain (1,347): 17; Arthralgia (0063): 38; Arthrosis (0066): 39; Muscle weakness (1,128): 44; Myalgia (0073): 46; Deformity (2,209): 74); **3-300 (n 10):** (Auto-antibody response (1,096): 1; Collagenosis (1,077): 3; Antinuclear factor test positive (1,082): 3; LE syndrome (0081): 3); **4-410 (n 593):** (Oculogyric crisis (0132): 1; Vocal cord paralysis (0942): 1; Optic ischaemic neuropathy (1,978): 1; Hydrocephalus (0692): 1; Optic neuritis (0136): 1; Neuralgia (0124): 1; Ptosis (0142): 1; Migraine (0121): 1; Spinal stenosis (1,975): 1; Cognitive disorders (1,877): 1; Trigeminal disorders (2,169): 1; Meningism (0120): 2; Vertigo (0158): 2; Neuropathy (0130): 2; Hemiparesis (0111): 2; Tongue paralysis (0153): 2; Hyperaesthesia (0113): 2; Paresis (0141): 2; CSF abnormal (0098): 2; Coordination abnormal (0097): 3; Hyperkinesia (0114): 3; Muscle contractions involuntary (0155): 3; Stupor (0151): 3; Speech disorder (0150): 3; Paralysis (0138): 4; Ataxia (0088): 4; Neurologic disorder NOS (2,133): 5; Aphasia (0087): 5; Coma (0091): 5; Sensory disturbance (0148): 6; Neuropathy peripheral (1,313): 8; Dysphonia (0103): 10; Tremor (0154): 11; Convulsions (0093):12; Dysaesthesia (1,491):19; Convulsions grand mal (0095):21; Dyskinesia

(0102): 22; Hypoaesthesia (0117): 26; Headache (0109): 33; Hypertonia (0116): 39; Dizziness (0101): 39; Gait abnormal (0108): 55; Paraesthesia (0137): 61; Hypokinesia (0118): 166); **6-431 (n 43):** (Eye muscle paralysis (1,429): 1; Diplopia (0241): 1; Lacrimation abnormal (1,049): 1; Keratitis (0246): 1; Eye pain (0244): 2; Blindness (0232): 2; Eye abnormality (0243): 2; Photophobia (0250): 2; Vision abnormal (0257): 11; Conjunctivitis (0238): 20); **7-432 (n 6):** (Hearing decreased (1,368): 1; Hyperacusis (0261): 1; Tinnitus (0264): 1; Deafness (0258): 3); **8-433 (n 39):** (Taste loss (0266): 5; Taste perversion (0267): 34); **9-500 (n 735):** (Communication disorder (1,970): 1; Suicide ideation (2,363): 1; Drug abuse (0175): 1; Personality disorder (0192): 1; Catatonic reaction (0169): 2; Depersonalization (0171): 4; Aggressive reaction (0162): 4; Somnolence (0197): 4; Nervousness (0188): 4; Anorexia (0165): 5; Amnesia (0164): 5; Agitation (0163): 6; Mental disorder (1,944): 6; Hallucination (0179): 9; Confusion (0092): 10; Insomnia (0183): 14; Depression (0172): 15; Apathy (0167): 98; Emotional lability (0177): 264; Anxiety (0166): 281); **10-600 (n 419):** (Haemorrhoids (0298): 1; Intestinal fistula (1,806): 1; Bowel motility disorder (1,842): 1; Intestinal gangrene (0301): 1; Haemorrhage rectum (1,014): 1; Stomatitis ulcerative (0328): 1; Diseases of oesophagus (1,059): 1; Diarrhoea, Clostridium difficile (1,201): 1; Gastric ulcer haemorrhagic perforated (0289): 1; Intestinal ischaemia (1,308): 1; Stomatitis (0327): 1; Melaena (0306): 1; GI haemorrhage (0294): 1; Oesophageal ulceration (0311): 1; Eructation (0283): 1; Oesophageal varices (1,036): 1; Constipation (0204): 2; Pancreatitis (0314): 2; Dyspepsia (0279): 2; Gastroenteritis (0293): 2; Saliva increased (0222): 4; Diarrhoea (0205): 8; Tongue oedema (0331): 8; Mouth dry (0218): 8; Dysphagia (0280): 9; Abdominal pain (0268): 13; Nausea (0308): 171; Vomiting (0228): 174); **11-700 (n 25):** (Cholelithiasis (0343): 1; Hepatitis viral (1,723): 1; SGPT increased (0360): 1; SGOT increased (0359): 1; Hepatic necrosis (0349): 2; Hepatic cirrhosis (0347): 2; Bilirubinaemia (0339): 2; Hepatitis cholestatic (0351): 2; Hepatic function abnormal (0348): 3; Hepatic enzymes increased (1,346): 3; Jaundice (0356): 7); **12-800 (n 39):** (Gout (0378): 1; Electrolyte abnormality (0374): 1; Acidosis lactic (0364): 1; Creatine phosphokinase increased (0791): 1; Hypokalaemia (0391): 1; Diabetic ulcer (2,015): 1; Hypophosphataemia (1,064): 1; Dehydration (0370): 1; LDH increased (0394): 1; Oedema pharynx (1,395): 1; Lipodystrophy (0830): 1; Hypercalcaemia (0380): 2; Acidosis (0363): 2; Hypoproteinaemia (0827): 2; Cachexia (0368): 3; Calcinosis (0369): 5; Weight decrease (0407): 6; Hypocalcaemia (0387): 8); **13-900 (n 7):** (Panniculitis (1,416): 1; Pituitary neoplasm benign (1,291): 1; Adrenal insufficiency (0410): 2; Hyperparathyroidism (0921): 3); **14-1,010 (n 79):** (ECG abnormal (0502): 1; Vascular graft occlusion (2,109): 1; Cardiovascular disorders (2,031): 1; Cyanosis (0501): 2; Hypotension postural (0213): 2; Hypertension pulmonary (0211): 3; Cardiomegaly (1,320): 4; Circulatory failure (0499): 4; Heart disorder (0504): 6; Cardiac failure (0496): 10; Hypertension (0210): 15; Hypotension (0212): 30); **15-1,020 (n 25):** (Aortic stenosis (0424): 1; Cardiomyopathy (0425): 1; Angina pectoris (0422): 1; Endocarditis (0427): 1; Fibrosis endocardial (1,274): 2; Heart valve disorders (1,228): 2; Myocardial infarction (0428): 2; Myocardial ischaemia (0429): 2; Coronary artery disorder (0426): 3; Pericarditis (0430): 3; Fibrosis myocardial (1,188): 7); **16-1,030 (n 56):** (AV block (0431): 1; AV block complete (1,378): 1; Extrasystoles (0438): 1; QT prolonged (1,361): 1; Arrhythmia nodal (0809): 2; Arrhythmia (0433): 2; Bradycardia (0208): 3; Tachycardia ventricular (0230): 3; Fibrillation atrial (0439): 5; Palpitation (0221): 9; Cardiac arrest (0437): 10; Tachycardia (0224): 18); **17-1,040 (n 72):** (Stenosis vein (2,083): 1; Arteriosclerosis (0771): 1; Thrombophlebitis (0466): 1; Cerebral

ischaemia (1,987): 1; Transient ischaemic attack (1,694): 1; Vein pain (0494): 1; Vasculitis (0085): 1; Phlebitis (0455): 1; Vein distended (0493): 1; Vein disorder (0492): 2; Gangrene (0911): 2; Thrombophlebitis deep (0470): 3; Cerebral haemorrhage (0444): 3; Cerebrovascular disorder (0445): 6; Peripheral ischaemia (0454): 6; Vasodilatation (0225): 18; Flushing (0207): 23); **18-1,100 (n 264):** (Pneumonitis (1,141): 1; Upper respiratory tract infection (0543): 1; Hypoxia (0519): 1; Sleep apnoea (1,515): 1; Bronchitis (0805): 1; Apnoea (0507): 1; Sinusitis (0540): 1; Atelectasis (1,197): 1; Hyperventilation (0517): 1; Pulmonary infiltration (1,038): 1; Pleural fibrosis (0525): 2; Respiratory depression (0144): 2; Asthma (1,367): 2; Pleural effusion (0524): 2; Pulmonary congestion (1,721): 3; Respiratory disorder (0536): 3; Laryngitis (0521): 3; Stridor (0542): 3; Pulmonary oedema (0535): 6; Pulmonary disorders (2032): 6; Pulmonary fibrosis (0532): 7; Laryngismus (0520): 7; Respiratory insufficiency (0537): 8; Bronchospasm (0511): 8; Throat tightness (1,489): 10; Pneumonia (0528): 11; Larynx oedema (0522): 14; Pharyngitis (0523): 17; Coughing (0513): 26; Rhinitis (0539): 32; Dyspnoea (0514): 82); **19-1,210 (n 25):** (Anaemia normocytic (0557): 1; Haemolysis (0560): 1; Haemosiderosis (1,427): 1; Serum iron increased (1,294): 2; Anaemia (0544): 4; Blood dyscrasia (1,946): 4; Iron metabolism disorder (0777): 4; Erythrocytes abnormal (1,251): 8); **20-1,220 (n 3):** (Lymphangitis (0580): 1; Lymphadenopathy (0577): 1; Lymphoedema (0581): 1); **21-1,230 (n 21):** (Haemorrhage NOS (0452): 1; Prothrombin decreased (0590): 1; Coagulation factor decreased (1,122): 1; Bleeding time increased (0584): 1; Thrombus intracardiac (2,113): 1; Haematoma (1,353): 1; Thrombosis (0481): 1; Thrombosis cerebral (0486): 1; Thrombosis arterio-venous fistula (1,776): 1; Embolism aortic (2,041): 2; Embolism cerebral (0448): 2; Embolism pulmonary (0451): 2; Thrombocytopenia (0594): 2; Purpura (0459): 4); **22-1,300 (n 77):** (Nephrosclerosis (1,177): 1; Nephrosis (0610): 1; Glomerulonephritis (0603): 1; Renal papillary necrosis (0622): 1; Urine abnormal (0629): 1; Urinary incontinence (0156): 1; Nephritis interstitial (0608): 1; Urinary tract stenosis (2,317): 1; Oliguria (0612): 2; Nephropathy toxic (0609): 2; Renal cyst (1,138): 2; Dysuria (0601): 2; Renal function abnormal (0619): 3; Renal tubular necrosis (0624): 6; Renal failure chronic (2,329): 11; Face oedema (0602): 13; Renal failure acute (0618): 14; Azotaemia (2,328): 14); **23-1,410 (n 2):** (Hernia inguinal (1,482) :1; Prostatic disorder (0632) :1); **24-1,420 (n 3):** (Menstrual disorder (0657): 1; Genital ulceration (1,387): 1; Oligohydramnios (1,432): 1); **25-1,500 (n 2):** (Drug exposure in pregnancy (2,221): 1; Foetal maturation impaired (0961): 1); **26-1,600 (n 1):** (Hypoplasia cerebellar (1,574): 1); **27-1,700 (n 85):** (Breast neoplasm benign female (1,114) :1; Bladder carcinoma (0766) :1; Histiocytoma (2,046) :1; Brain neoplasm NOS (1,862): 1; Skin hypertrophy (0038): 81); **28-1,810 (n 1,270):** (Influenza-like symptoms (1,222): 1; Wound drainage increased (1,715): 1; Allergy (1,058): 1; Hypovolaemia (0929): 1; Therapeutic response decreased (0878): 1; Therapeutic response increased (0874): 1; Drug level below therapeutic (2,172): 1; Choking (1,460): 1; ESR increased (0723): 1; Nasal polyp (0985): 1; C-reactive protein increased (2,351): 1; Posture abnormal (2,012): 1; Granulomatous lesion (0876): 1; Resistance (1,950): 1; Drug level increased (1,281): 1; Tenderness NOS (1,911): 1; Ascites (0715): 2; Sudden death (1,134): 2; Withdrawal syndrome (0200): 2; Night sweats (1,898): 2; Oedema mouth (1,485): 3; Multiple organ failure (1,819): 4; Condition aggravated (0965): 4; Pallor (0220): 5; Leg pain (1,439): 7; Oedema periorbital (1,009): 7; Medicine ineffective (1,948): 7; Death (0722): 7; Back pain (0717): 9; Anaphylactic reaction (2,237): 9; Temperature changed sensation (1,705): 9; Fever (0725): 13; Syncope (0223): 13; Rigors (0731): 13; Oedema generalised (0400): 20;

Anaphylactic shock (0713): 21; Fatigue (0724): 21; Oedema (0398): 31; Asthenia (0716): 33; Allergic reaction (0712): 36; Anaphylactoid reaction (0714): 45; Chest pain (0718): 45; Oedema peripheral (0401): 98; Scar (1,522): 168; Malaise (0728): 215; Pain (0730): 403); **29-1,820 (n 28):** (Infusion site reaction (2,137): 1; Injection site pruritus (1,880): 1; Injection site rash (1,881): 2; Injection site inflammation (0054): 5; Injection site pain (0057): 6; Injection site reaction (0058): 6; Cellulitis (1,372): 7); **30-1,830 (n 102):** (Infection fungal (0739): 1; Moniliasis (0741): 1; Infection (0736): 1; Infection bacterial (0738): 1; Infection viral (0740): 1; Infection susceptibility increased (1,226): 1; Abscess (0887): 2; Infection staphylococcal (1,867): 4; Sepsis (0744): 26; Skin tightness (2,098): 64**). 5-Gadofosveset (n 63): 1-100 (n 5):** (Rash erythematous (0028): 1; Urticaria (0044): 1; Pruritus (0024): 3); **4-410 (n 10):** (Hypoaesthesia (0117): 1; Dysphonia (0103): 1; Tremor (0154): 1; Stupor (0151): 1; Coma (0091): 2; Headache (0109): 2; Paraesthesia (0137): 2; Conjunctivitis (0238): 2); **9-600 (n 6):** (Ileus paralytic (0215): 1; Vomiting (0228): 1; Abdominal pain (0268): 1; Nausea (0308): 3); **14-1,010 (n 5):** (Circulatory failure (0499): 1; Hypotension (0212): 1; Pulse weak (1,401): 1; Cardiac failure (0496): 2); **15-1,020 (n 2):** (Myocardial infarction (0428): 2); **16-1,030 (n 5):** (Cardiac arrest (0437): 2; Tachycardia (0224): 3); **17-1,040 (n 3):** (Peripheral ischaemia (0454): 1; Flushing (0207): 2); **18-1,100 (n 14):** (Bronchospasm (0511): 1; Pulmonary congestion (1,721): 1; Rhinitis (0539): 3; Coughing (0513): 4; Dyspnoea (0514): 5); **22-1,300 (n 1):** (Urinary incontinence (0156): 1); **28-1,810 (n 9):** (Chest pain (0718): 1; Allergic reaction (0712): 1; Anaphylactoid reaction (0714): 1; Syncope (0223): 1; Tolerance decreased (0761): 1; Temperature changed sensation (1,705): 1; Malaise (0728): 3); **29-1,820 (n 1):** (Injection site pruritus (1,880): 1). **5-Gadopentetic acid (n 20,202): 1-100 (n 4,180):** (Acne (0001): 1; Onychomycosis (1,638): 1; Skin odor abnormal (0039): 1; Papilloma (1,486): 1; Furunculosis (0016): 1; Seborrhoea (0033): 1; Dermatitis lichenoid (0010): 1; Skin fragility (1,782): 1; Urticaria acute (0045): 2; Hypotrichosis (0828): 2; Dermatitis contact (0049): 2; Stevens Johnson syndrome (0042): 2; Skin depigmentation (0035): 2; Skin reaction localised (1,650): 3; Rash pustular (0032): 3; Erythema multiforme (0014): 3; Livedo reticularis (1,410): 3; Skin atrophy (0034): 3; Pigmentation abnormal (0973): 4; Eyelid skin disorder (2,253): 4; Skin necrosis (0060): 5; Dermatitis (0007): 6; Alopecia (0002): 7; Eczema (0012): 7; Skin cold clammy (0932): 8; Hyperkeratosis (0966): 8; Scleroderma (0971): 9; Skin nodule (0061): 15; Skin ulceration (0041): 17; Dermatitis exfoliative (0008): 18; Bullous eruption (0871): 28; Skin exfoliation (1,199): 29; Skin dry (1,123): 40; Angioedema (0003): 57; Induration (1,891): 74; Skin disorder (0037): 75; Rash maculo-papular (0030): 85; Skin discolouration (0036): 98; Sweating increased (0043): 185; Fibrosis skin (2,314): 189; Rash erythematous (0028): 344; Rash (0027): 399; Pruritus (0024): 847; Urticaria (0044): 1,589); **2-200 (n 402):** (Crepitations (1,922): 1; Fasciitis (1,707): 1; Chondrocalcinosis (2,228): 1; Osteoporosis (0076): 1; Bone disorder (0067): 1; Avascular necrosis bone (2,222): 1; Fracture pathological (0069): 1; Fasciitis plantar (1,558): 1; Arthritis infective (2,024): 2; Myositis (0748): 2; Ligament disorder (2,086): 2; Osteomyelitis (1,184): 2; Fracture (2,190): 3; Tendon disorder (1,074): 6; Myopathy (0074): 6; Muscle atrophy (0072): 7; Musculoskeletal pain (1,889): 8; Arthropathy (0065): 13; Skeletal pain (1,347): 23; Arthritis (0064): 24; Arthrosis (0066): 47; Muscle weakness (1,128): 50; Myalgia (0073): 57; Arthralgia (0063): 58; Deformity (2,209): 84); **3-300 (n 4):** (Graft versus host disease (1,770): 1; Collagenosis (1,077): 1; LE syndrome (0081): 2); **4-410 (n 2,088):** (Hyporeflexia (0850): 1; Spinal stenosis (1,975): 1; Meningism (0120): 1; CSF abnormal (0098):

1; Myasthenia gravis-like syndrome (1,063): 1; Encephalomyelitis (0974): 1; Myelitis (0123): 1; Hemiplegia (0112): 1; Nerve root lesion (1,104): 1; Convulsions aggravated (0094): 1; Neuritis (0125): 1; Extrapyramidal disorder (0106): 1; Oculomotor nerve paralysis (0133): 1; Dementia (0100): 1; Polyneuropathy (2,082): 1; Hyperkinesia (0114): 1; Reflexes abnormal (1,451): 1; Vocal cord paralysis (0942): 2; Meningitis (0955): 2; Demyelination (1,547): 2; Cerebral atrophy (1,181): 2; EEG abnormal (0104): 2; Cerebral disorder (1,960): 2; Neuralgia (0124): 2; Hypotonia (0119): 2; Neuropathy (0130): 2; Paresis (0141): 2; Blepharospasm (1,168): 2; Cognitive disorders (1,877): 3; Hemiparesis (0111): 3; Cramps legs (0939): 3; Hyperaesthesia (0113): 4; Faecal incontinence (0107): 4; Neurologic disorder NOS (2,133): 4; Tongue paralysis (0153): 4; Oedema cerebral (0891): 5; Nystagmus (0131): 5; Tetany (0152): 5; Dystonia (0068): 5; Coordination abnormal (0097): 6; Visual field defect (0159): 7; Oculogyric crisis (0132): 8; Aphasia (0087): 9; Paralysis (0138): 10; Migraine (0121): 10; Encephalopathy (0105): 10; Sensory disturbance (0148): 13; Ataxia (0088): 13; Vertigo (0158): 16; Muscle contractions involuntary (0155): 17; Neuropathy peripheral (1,313): 17; Dyskinesia (0102): 26; Speech disorder (0150): 37; Dysphonia (0103): 50; Stupor (0151): 54; Hypertonia (0116): 67; Gait abnormal (0108): 70; Convulsions (0093): 77; Dysaesthesia (1,491): 79; Hypoaesthesia (0117): 91; Convulsions grand mal (0095): 96; Tremor (0154): 97; Coma (0091): 121; Hypokinesia (0118): 211; Headache (0109): 238; Paraesthesia (0137): 254; Dizziness (0101): 300); **6-431 (n 329):** (Photopsia (1,172): 1; Conjunctival disorder (2,008): 1; Blindness temporary (1,280): 1; Lacrimal gland disorder (0216): 1; Keratoconjunctivitis (0247): 1; Photophobia (0250): 2; Mydriasis (0219): 2; Fixed pupils (1,605): 2; Corneal deposits (1,081): 2; Blindness (0232): 3; Eye abnormality (0243): 6; Diplopia (0241): 12; Eye pain (0244): 20; Vision abnormal (0257): 41; Lacrimation abnormal (1,049): 76; Conjunctivitis (0238): 158); **7-432 (n 26):** (Hearing decreased (1,368): 1; Vestibular disorder (1,126): 1; Hyperacusis (0261): 1; Deafness (0258): 4; Ear disorder NOS (1,255): 4; Ear ache (0260): 5; Tinnitus (0264): 10); **8-433 (n 101):** (Taste loss (0266): 3; Parosmia (0265): 6; Taste perversion (0267): 92); **9-500 (n 1,111):** (Intentional self-injury (2,364): 1; Manic reaction (0186): 1; Communication disorder (1,970): 1; Mental deficiency (0187): 1; Drug abuse (0175): 1; Psychosis (0193): 2; Paroniria (0191): 2; Personality disorder (0192): 2; Hallucination (0179): 3; Catatonic reaction (0169): 3; Hysteria (0180): 3; Delirium (0099): 4; Neurosis (0189): 5; Sleep disorder (0195): 6; Concentration impaired (1,127): 6; Anorexia (0165): 6; Thinking abnormal (0199): 7; Mental disorder (1,944): 10; Aggressive reaction (0162): 13; Insomnia (0183): 15; Amnesia (0164): 16; Depression (0172): 20; Nervousness (0188): 25; Depersonalization (0171): 42; Somnolence (0197): 45; Confusion (0092): 46; Agitation (0163): 49; Apathy (0167): 117; Emotional lability (0177): 302; Anxiety (0166): 357); **10-600 (n 2,887):** (Haemorrhoids (0298): 1; Haemorrhage intraabdominal (1,419): 1; Amylase increased (1,101): 1; Gastroenteritis (0293): 1; Haematemesis (0297): 1; Diverticula (1,908): 1; Hiccup (0300): 1; Enanthema (0281): 1; Increased stool frequency (1,844): 1; Eructation (0283): 1; Increased stool urgency (1,843): 1; Gastritis (0291): 1; Intestinal ischaemia (1,308): 1; Duodenitis (1,217): 1; Intestinal obstruction (0302): 1; Gastric dilatation (0286): 1; Irritable bowel syndrome (1,531): 1; Encopresis (2,162): 1; Melaena (0306): 1; Teeth-grinding (1,086): 1; Oesophageal ulceration (0311): 1; Tooth disorder (0336): 2; Glossitis (0295): 2; Gastro-intestinal disorder NOS (1,262): 2; Tenesmus (0231): 2; Intestinal gangrene (0301): 2; Diarrhoea, Clostridium difficile (1,201): 2; Stomatitis ulcerative (0328): 2;

Oesophagitis (0309): 2; GI haemorrhage (0294): 3; Flatulence (0285): 3; Gingivitis (1,083): 3; Tooth ache (1,376): 3; Tongue disorder (0330): 4; Pancreatitis (0314): 4; Gastroesophageal reflux (1,149): 5; Constipation (0204): 6; Stomatitis (0327): 6; Dyspepsia (0279): 10; Mucositis NOS (1,351): 13; Saliva increased (0222): 19; Cheilitis (0270): 28; Mouth dry (0218): 38; Diarrhoea (0205): 41; Tongue oedema (0331): 63; Abdominal pain (0268): 91; Dysphagia (0280): 104; Nausea (0308): 1,140; Vomiting (0228): 1,266); **11-700 (n 36):** (Gallbladder disorder (0345): 1; Gamma-GT increased (1,334): 1; Hepatic necrosis (0349): 1; Hepatic failure (0933): 1; Hepatic function abnormal (0348): 2; Hepatitis (0350): 2; Cholelithiasis (0343): 2; Bilirubinaemia (0339): 2; SGPT increased (0360): 3; Hepatocellular damage (0353): 4; SGOT increased (0359): 4; Hepatic enzymes increased (1,346): 5; Jaundice (0356): 8); **12-800 (n 94):** (Hypomagnesaemia (0798): 1; Xerophthalmia (0943): 1; Hyponatraemia (0392): 1; Cachexia (0368): 1; Hypophosphataemia (1,064): 1; Growth retarded (0379): 1; Insulin increased (2,339): 1; Hyperuricaemia (0385): 1; Ketosis (0393): 1; Diabetic ulcer (2,015): 1; Lipase increased (1,621): 1; Anion gap abnormal (1,589): 1; Phosphatase alkaline increased (0404): 1; Hypercalcaemia (0380): 1; Troponin t increased (2,090): 1; Hypocalcaemia (0387): 2; Dehydration (0370): 2; Acidosis (0363): 2; Fluid overload (1,018): 2; Creatine phosphokinase increased (0791): 2; Glucose tolerance abnormal (0376): 2; Thirst (0405): 2; Phosphatase alkaline decreased (2,056): 2; Weight decrease (0407): 3; Gout (0378): 3; Hyperkalaemia (0383): 3; Calcinosis (0369): 3; Hypoglycaemia (0389): 4; Hypokalaemia (0391): 5; Hyperglycaemia (0382): 9; Oedema pharynx (1,395): 33); **13-900 (n 9):** (Hypoparathyroidism (1,306): 1; Hypothyroidism (0417): 1; Diabetes insipidus (0411): 1; Myxoedema (0418): 1; Adrenal insufficiency (0410): 1; Thyroid disorder (0419): 1; Endocrine disorder NOS (1,252): 1; TSH increased (1,831): 2); **14-1,010 (n 606):** (Cardio-respiratory failure (1,899): 1; Vascular graft occlusion (2,109): 1; Aneurysm (0915): 1; Cardiac failure right (0498): 1; Hypertension portal (1,042): 1; Hypertension pulmonary (0211): 2; Cardiomegaly (1,320): 3; ECG abnormal (0502): 4; Hypotension postural (0213): 5; Blood pressure fluctuation (1,762): 7; Heart disorder (0504): 7; ECG abnormal specific (0503): 8; Cardiovascular disorders (2,031): 10; Pulse weak (1,401): 10; Cardiac failure (0496): 21; Cyanosis (0501): 46; Circulatory failure (0499): 77; Hypertension (0210): 142; Hypotension (0212): 259); **15-1,020 (n 52):** (Endocarditis (0427): 1; Thrombosis coronary (0488): 1; Aortic stenosis (0424): 1; Pericarditis (0430): 1; Aortic valve incompetence (1,761): 1; Cardiomyopathy (0425): 1; Mitral stenosis (1,554): 1; Cardiac enzymes increased (1,888): 1; Pericardial effusion (0910): 1; Fibrosis endocardial (1,274): 2; Heart valve disorders (1,228): 2; Mitral insufficiency (0899): 2; Coronary artery disorder (0426): 3; Fibrosis myocardial (1,188): 4; Myocardial ischaemia (0429): 6; Angina pectoris (0422): 8; Myocardial infarction (0428): 16); **16-1,030 (n 422):** (Arrhythmia nodal (0809): 1; AV block (0431): 2; T wave inversion (1,688): 2; Arrhythmia ventricular (0435): 2; QT prolonged (1,361): 2; Heart block (0441): 2; Adams Stokes syndrome (0432): 2; Bundle branch block (0436): 3; AV block complete (1,378): 4; Extrasystoles (0438): 5; Tachycardia ventricular (0230): 5; Tachycardia supraventricular (0229): 6; Fibrillation ventricular (0440): 7; Fibrillation atrial (0439): 14; Arrhythmia (0433): 19; Palpitation (0221): 33; Bradycardia (0208): 48; Cardiac arrest (0437): 85; Tachycardia (0224): 180); **17-1,040 (n 640):** (Stenosis vein (2,083): 1; Haemorrhage stroke (1,989): 1; Vein distended (0493): 1; Ocular haemorrhage (1,004): 1; Compartment syndrome (2,220): 1; Phlebitis deep (0456): 1; Haemorrhage anterior chamber eye

(0926): 1; Subarachnoid haemorrhage (0463): 1; Gangrene (0911): 1; Thrombophlebitis cerebral vein (0469): 1; Cerebral ischaemia (1,987): 1; Transient ischaemic attack (1,694): 1; Arteriosclerosis (0771): 2; Cerebral infarction (1,986): 2; Thrombophlebitis superficial (0479): 2; Renal artery occlusion (1,546): 2; Thrombophlebitis arm superficial (0468): 2; Vascular disorder (0491): 3; Vasculitis (0085): 3; Vein pain (0494): 3; Vasospasm (0226): 3; Thrombophlebitis deep (0470): 4; Cerebral haemorrhage (0444): 5; Thrombophlebitis arm (0467): 5; Cerebrovascular disorder (0445): 14; Vein disorder (0492): 14; Peripheral ischaemia (0454): 16; Thrombophlebitis (0466): 20; Phlebitis (0455): 63; Flushing (0207): 163; Vasodilatation (0225): 302); **18-1,100 (n 2,751):** (Larynx pain (1,648): 1; Airways obstruction (1,749): 1; Chest X-ray abnormal (0512): 1; Pleural fibrosis (0525): 1; Atelectasis (1,197): 1; Pneumothorax (0531): 1; Bronchial obstruction (1,820): 1; Pulmonary collapse (0979): 1; Sputum disorder (1,976): 1; Pulmonary infiltration (1,038): 1; Bronchospasm aggravated (1,066): 1; Respiratory distress syndrome (2,252): 1; Breath sounds decreased (1,716): 1; Sleep apnoea (1,515): 1; Pleural effusion (0524): 2; Bradypnoea (0510): 2; Aspiration (1030): 2; Bronchitis (0805): 3; Pneumonitis (1,141): 3; Haemoptysis (0516): 3; Upper respiratory tract infection (0543): 3; Asphyxia (0508): 4; Hypoventilation (0518): 4; Epistaxis (0515): 5; Chronic obstructive airways disease (1,493): 6; Pulmonary fibrosis (0532): 7; Sputum increased (0541): 7; Pulmonary disorders (2,032): 8; Pulmonary congestion (1,721): 9; Sinusitis (0540): 10; Asthma (1,367): 13; Pneumonia (0528): 14; Hypoxia (0519): 18; Hyperventilation (0517): 21; Respiratory disorder (0536): 22; Pulmonary oedema (0535): 27; Apnoea (0507): 31; Respiratory insufficiency (0537): 43; Respiratory depression (0144): 56; Stridor (0542): 59; Larynx oedema (0522): 73; Laryngitis (0521): 97; Throat tightness (1,489): 97; Pharyngitis (0523): 100; Bronchospasm (0511): 143; Laryngismus (0520): 151; Coughing (0513): 281; Rhinitis (0539): 554; Dyspnoea (0514): 859); **19-1,210 (n 18):** (Haemolysis (0560): 1; Haemosiderosis (1,427): 1; Serum iron increased (1,294): 1; Anaemia haemolytic direct Coomb's test negative (0549): 1; Anaemia haemolytic (0548): 2; Splenomegaly (0569): 2; Anaemia (0544): 4; Iron metabolism disorder (0777): 6); **20-1,220 (n 29):** (Granulocytopenia (0572): 1; Lymphopenia (0845): 1; Leucopenia (0908): 1; Eosinophilia (0571): 2; Lymphoedema (0581): 2; Lymphadenopathy (0577): 4; Lymphangitis (0580): 8; Leukocytosis (0576): 10); **21-1,230 (n 50):** (Purpura thrombocytopenic (1,348): 1; Thrombus intracardiac (2,113): 1; Thrombosis arterio-venous fistula (1,776): 1; Haemorrhage retroperitoneal (1,214): 1; Thrombosis venous arm (1,370): 1; Prothrombin decreased (0590): 2; Coagulation factor decreased (1,122): 2; Embolism arterial (0447): 2; Coagulation disorder (0586): 3; Disseminated intravascular coagulation (1,175): 3; Thrombocytopenia (0594): 4; Haematoma (1,353): 4; Thrombosis (0481): 7; Embolism pulmonary (0451): 7; Purpura (0459): 11); **22-1,300 (n 530):** (Pyelonephritis (0614): 1; Urine abnormal (0629): 1; Oliguria (0612): 1; Polyuria (0613): 1; Micturition urgency (1,497): 1; Creatinine clearance decreased (0598): 1; Nephrosclerosis (1,177): 1; Renal cyst (1,138): 1; Nephritis (0607): 1; Renal tubular disorder (0623): 1; Urinary tract stenosis (2,317): 1; Urinary retention (0157): 1; Albuminuria (0595): 2; Urinary crystals (1,461): 2; Renal interstitial fibrosis (1,328): 2; Strangury (0625): 2; Micturition frequency (0606): 2; Renal calculus (0617): 3; Renal tubular necrosis (0624): 3; Nephropathy toxic (0609): 3; Dysuria (0601): 3; Haematuria (0604): 5; Anuria (0596): 6; Renal pain (0621): 8; Urinary tract infection (0628): 8; Renal failure chronic (2,329): 15; Renal function abnormal (0619): 15; Azotaemia (2,328): 17; Urinary

incontinence (0156): 23; Renal failure acute (0618): 25; Face oedema (0602): 374); **23-1,410 (n 2):** (Prostatic disorder (0632): 1; Testicular pain (1,500): 1); **24-1,420 (n 5):** (Menstrual disorder (0657): 1; Breast pain (1,839): 1; Pre-eclampsia (1,702): 1; Lactation puerperal decreased (0946): 1; Pregnancy unintended (0663): 1); **25-1,500 (n 11):** (Heart malformation (0691): 1; Ventricular septal defect (0707): 1; Vascular malformation peripheral (0764): 1; Naevus (0948): 2; Abortion (0634): 2; Drug exposure in pregnancy (2,221): 4); **26-1,600 (n 1):** (Birth premature (0637): 1); **27-1,700 (n 84):** (Histiocytoma (2,046): 1; Bladder carcinoma (0766): 1; Neoplasm NOS (1,259): 1; Breast neoplasm benign female (1,114): 1; Uterine fibroid (0857): 1; Brain neoplasm NOS (1,862): 1; Skin hypertrophy (0038): 78); **28-1,810 (n 3,061):** (Abdomen enlarged (0711): 1; Wound drainage increased (1,715): 1; Infection TBC (0923): 1; Ascites (0715): 1; Hernia NOS (1,832): 1; Serum sickness (0733): 1; Chest pain precordial (0719): 1; Granulomatous lesion (0876): 1; Oedema dependent (0399): 1; ESR increased (0723): 1; Posture abnormal (2,012): 1; Medicine ineffective (1,948): 2; Carpal tunnel syndrome (1,397): 2; Withdrawal syndrome (0200): 2; Anaesthetic complication (2,160): 2; Multiple organ failure (1,819): 3; Therapeutic response increased (0874): 3; Hyperpyrexia (0894): 3; Night sweats (1898): 3; Hypothermia (0727): 4; Leg pain (1,439): 4; Crying abnormal (1,162): 4; Tenderness NOS (1,911): 4; Sudden death (1,134): 4; Chest pain substernal (0720): 8; Drug hypersensitivity syndrome (2,309): 8; C-reactive protein increased (2,351): 8; Influenza-like symptoms (1,222): 8; Allergy (1,058): 10; Condition aggravated (0965): 13; Back pain (0717): 27; Oedema mouth (1,485): 28; Choking (1,460): 29; Oedema generalised (0400): 32; Oedema periorbital (1,009): 46; Death (0722): 53; Pallor (0220): 60; Asthenia (0716): 64; Fever (0725): 65; Fatigue (0724): 65; Anaphylactic reaction (2,237): 74; Oedema (0398): 85; Anaphylactic shock (0713): 106; Allergic reaction (0712): 114; Rigors (0731): 122; Anaphylactoid reaction (0714): 126; Syncope (0223): 137; Temperature changed sensation (1,705): 141; Oedema peripheral (0401): 170; Scar (1,522): 201; Malaise (0728): 311; Chest pain (0718): 320; Pain (0730): 579); **29-1,820 (n 551):** (Injection site pruritus (1,880): 1; Injection site anaesthesia (1,917): 1; Neovascularisation (1,474): 2; Medical device complication (2,139): 2; Injection site necrosis (0056): 2; Infusion site rash (2,136): 2; Injection site bleeding (1,752): 2; Application site reaction (0047): 3; Injection site infection (1,910): 4; Injection site urticaria (1,968): 4; Infusion site reaction (2,137): 5; Injection site bruising (1,753): 6; Cellulitis (1,372): 8; Injection site mass (0055): 14; Injection site inflammation (0054): 28; Injection site rash (1,881): 31; Injection site pain (0057): 191; Injection site reaction (0058): 245); **30-1,830 (n 122):** (Herpes simplex (0867): 1; Infection susceptibility increased (1,226): 1; Infection fungal (0739): 1; Healing impaired (0896): 1; Abscess (0887): 2; Infection bacterial (0738): 3; Infection staphylococcal (1,867): 5; Infection (0736): 8; Sepsis (0744): 12; Skin tightness (2,098): 88. **6-Gadoteric acid (n 8): 1-100 (n 1):** (Urticaria (0044): 1); **4-410 (n 2):** (Dysaesthesia (1,491): 1; Paraesthesia (0137): 1); **10-600 (n 3):** (Vomiting (0228): 1; Nausea (0308): 2); **18-1,100 (n 2):** (Dyspnoea (0514): 1; Throat tightness (1,489): 1). **7-Gadoteridol (n 3,428): 1-100 (n 504):** (Heat rash (1,469): 1; Hyperkeratosis (0966): 1; Erythema induratum (0912): 1; Papilloma (1,486): 1; Skin reaction localised (1,650): 1; Pigmentation abnormal (0973): 1; Eyelid skin disorder (2,253): 1; Scleroderma (0971): 1; Rash pustular (0032): 2; Skin depigmentation (0035): 2; Skin atrophy (0034): 2; Dermatitis (0007): 2; Bullous eruption (0871): 2; Urticaria acute (0045): 2; Skin cold clammy (0932): 3; Skin necrosis (0060): 3; Skin nodule (0061): 3; Skin ulceration (0041): 5; Angioedema (0003): 7; Skin

exfoliation (1,199): 10; Dermatitis exfoliative (0008): 11; Skin dry (1,123): 13; Skin disorder (0037): 14; Sweating increased (0043): 15; Rash maculo-papular (0030): 18; Induration (1,891): 27; Rash (0027): 33; Skin discolouration (0036): 34; Rash erythematous (0028): 42; Urticaria (0044): 80; Fibrosis skin (2,314): 81; Pruritus (0024): 85); **2-200 (n 166):** (Arthropathy (0065): 1; Fracture pathological (0069): 1; Osteomyelitis (1,184): 1; Ligament disorder (2,086): 1; Muscle atrophy (0072): 2; Myositis (0748): 2; Tendon disorder (1,074): 3; Myopathy (0074): 3; Arthritis (0064): 7; Skeletal pain (1,347): 11; Arthralgia (0063): 14; Myalgia (0073): 21; Muscle weakness (1,128): 24; Arthrosis (0066): 27; Deformity (2,209): 48); **4-410 (n 384):** (Hyperaesthesia (0113): 1; Hyperkinesia (0114): 1; Brain stem disorder (0810): 1; Muscle contractions involuntary (0155): 1; Coordination abnormal (0097): 1; Neuralgia (0124): 1; Hemiplegia (0112): 1; Quadriplegia (0143): 1; Cramps legs (0939): 1; Spinal stenosis (1,975): 1; Torticollis (0077): 1; Tongue paralysis (0153): 1; Ataxia (0088): 2; Vertigo (0158): 2; Hypotonia (0119): 2; Sensory disturbance (0148): 2; Aphasia (0087): 3; Oculogyric crisis (0132): 3; Headache (0109): 4; Neuropathy peripheral (1,313): 5; Speech disorder (0150): 5; Tremor (0154): 6; Convulsions (0093): 7; Convulsions grand mal (0095): 9; Stupor (0151): 10; Dysphonia (0103): 10; Dyskinesia (0102): 16; Hypoaesthesia (0117): 17; Dysaesthesia (1,491): 17; Coma (0091): 18; Dizziness (0101): 20; Gait abnormal (0108): 22; Hypertonia (0116): 23; Paraesthesia (0137): 38; Hypokinesia (0118): 131); **6-431 (n 28):** (Fixed pupils (1,605): 1; Eye pain (0244): 1; Eye abnormality (0243): 2; Mydriasis (0219): 2; Vision abnormal (0257): 3; Lacrimation abnormal (1,049): 5; Conjunctivitis (0238): 14); **7-432 (n 2):** (Ear disorder NOS (1,255): 1; Tinnitus (0264): 1); **8-433 (n 2):** (Taste perversion (0267): 2); **9-500 (n 585):** (Aggressive reaction (0162): 1; Thinking abnormal (0199): 1; Snoring (1,511): 1; Personality disorder (0192): 1; Catatonic reaction (0169): 1; Anorexia (0165): 2; Nervousness (0188): 3; Confusion (0092): 3; Insomnia (0183): 4; Mental disorder (1,944): 4; Depression (0172): 6; Agitation (0163): 7; Depersonalization (0171): 9; Somnolence (0197): 10; Apathy (0167): 84; Emotional lability (0177): 222; Anxiety (0166): 226); **10-600 (n 217):** (Dyspepsia (0279): 1; Stomatitis (0327): 1; Gastritis (0291): 1; Constipation (0204): 1; GI haemorrhage (0294): 1; Cheilitis (0270): 1; Haemorrhage rectum (1,014): 1; Glossitis (0295): 2; Mucositis NOS (1,351): 2; Saliva increased (0222): 2; Mouth dry (0218): 5; Diarrhoea (0205): 5; Abdominal pain (0268): 6; Dysphagia (0280): 9; Tongue oedema (0331): 9; Vomiting (0228): 63; Nausea (0308): 107); **11-700 (n 4):** (Hepatic necrosis (0349): 1; Jaundice (0356): 1; Hepatic enzymes increased (1,346): 2); **12-800 (n 12):** (Cachexia (0368): 1; Acidosis (0363): 1; Weight decrease (0407): 1; Hypokalaemia (0391): 1; Hypoglycaemia (0389): 2; Calcinosis (0369): 2; Oedema pharynx (1,395): 4); **13-900 (n 1):** (Adrenal insufficiency (0410): 1); **14-1,010 (n 115):** (Cardiomegaly (1,320): 1; Heart murmur (1,471): 1; Heart disorder (0504): 1; ECG abnormal (0502): 2; Hypertension pulmonary (0211): 2; Blood pressure fluctuation (1,762): 3; Cardiac failure (0496): 4; Pulse weak (1,401): 5; Cyanosis (0501): 7; Hypertension (0210): 15; Circulatory failure (0499): 21; Hypotension (0212): 53); **15-1,020 (n 9):** (Coronary artery disorder (0426): 1; Myocardial infarction (0428): 1; Angina pectoris (0422): 1; Fibrosis endocardial (1,274): 2; Fibrosis myocardial (1,188): 4); **16-1,030 (n 48):** (Fibrillation cardiac (0442): 1; AV block (0431): 1; Torsade de pointes (1,431): 1; Palpitation (0221): 1; Arrhythmia nodal (0809): 1; QT prolonged (1,361): 1; Fibrillation atrial (0439): 1; Tachycardia ventricular (0230): 1; Fibrillation ventricular (0440): 2; Bradycardia (0208): 10; Tachycardia (0224): 12; Cardiac arrest (0437): 16); **17-1,040 (n 24):** (Cerebral haemorrhage (0444): 1; Vein disorder (0492): 1; Peripheral ischaemia (0454): 1;

Cerebral ischaemia (1,987): 1; Vasodilatation (0225): 1; Flushing (0207): 19); **18-1,100 (n 243):** (Hypopnoea (1,712): 1; Sinusitis (0540): 1; Pleural fibrosis (0525): 1; Bronchial obstruction (1,820): 1; Apnoea (0507): 1; Epistaxis (0515): 1; Pneumonitis (1,141): 1; Asthma (1,367): 1; Pulmonary congestion (1,721): 1; Hyperventilation (0517): 1; Pulmonary infiltration (1,038): 1; Chronic obstructive airways disease (1,493): 1; Respiratory disorder (0536): 1; Pneumonia (0528): 2; Pulmonary fibrosis (0532): 2; Yawning (0201): 2; Pulmonary oedema (0535): 2; Laryngismus (0520): 2; Pharyngitis (0523): 2; Respiratory distress syndrome (2,252): 2; Pulmonary disorders (2,032): 3; Respiratory depression (0144): 6; Bronchospasm (0511): 7; Stridor (0542): 7; Laryngitis (0521): 8; Respiratory insufficiency (0537): 10; Larynx oedema (0522): 11; Throat tightness (1,489): 17; Coughing (0513): 21; Rhinitis (0539): 39; Dyspnoea (0514): 87); **19-1,210 (n 1):** (Anaemia (0544): 1); **20-1,220 (n 2):** (Leukocytosis (0576): 1; Lymphoedema (0581): 1); **21-1,230 (n 8):** (Prothrombin decreased (0590): 1; Purpura thrombocytopenic (1,348): 1; Thrombus intracardiac (2,113): 1; Thrombosis arterio-venous fistula (1,776): 1; Purpura (0459): 2; Disseminated intravascular coagulation (1,175): 2); **22-1,300 (n 36):** (Azotaemia (2,328): 1; Urinary tract stenosis (2,317): 1; Renal function abnormal (0619): 1; Micturition disorder (0605): 1; Urinary incontinence (0156): 1; Renal failure acute (0618): 3; Face oedema (0602): 28); **23-1,410 (n 1):** (Prostatic disorder (0632): 1); **24-1,420 (n 1):** (Breast pain (1,839): 1); **25-1,500 (n 2):** (Atrial septal defect (0677): 1; Drug exposure in pregnancy (2,221): 1); **26-1,600 (n 1):** (Hypoglycaemia neonatal (0960): 1); **27-1,700 (n 46):** (Breast neoplasm benign female (1,114): 1; Histiocytoma (2,046): 1; Bladder carcinoma (0766): 1; Skin hypertrophy (0038): 43); **28-1,810 (n 938):** (Multiple organ failure (1,819): 1; Granulomatous lesion (0876): 1; Withdrawal syndrome (0200): 1; Fever (0725): 1; Night sweats (1,898): 1; Posture abnormal (2,012): 1; Choking (1,460): 2; Drug hypersensitivity syndrome (2,309): 2; Rigors (0731): 3; Back pain (0717): 3; Death (0722): 3; Oedema mouth (1,485): 5; Fatigue (0724): 7; Pallor (0220): 10; Oedema periorbital (1,009): 11; Oedema generalised (0400): 11; Anaphylactic shock (0713): 14; Syncope (0223): 15; Oedema (0398): 16; Temperature changed sensation (1,705): 17; Asthenia (0716): 21; Chest pain (0718): 28; Anaphylactic reaction (2,237): 33; Anaphylactoid reaction (0714): 35; Oedema peripheral (0401): 41; Allergic reaction (0712): 56; Scar (1,522): 133; Malaise (0728): 159; Pain (0730): 307); **29-1,820 (n 3):** (Injection site inflammation (0054): 1; Cellulitis (1,372): 1; Injection site rash (1,881): 1); **30-1,830 (n 45):** (Infection staphylococcal (1,867): 1; Infection susceptibility increased (1,226): 1; Abscess (0887): 1; Skin tightness (2,098): 42). 8-**Gadoversetamide (2,836): 1-100 (n 371):** (Papilloma (1,486): 1; Pigmentation abnormal (0973): 1; Acne (0001): 1; Acanthosis (1,052): 1; Onychomycosis (1,638): 1; Alopecia (0002): 1; Epidermal necrolysis (0013): 1; Dermatitis contact (0049): 1; Rash pustular (0032): 1; Livedo reticularis (1,410): 1; Skin depigmentation (0035): 2; Skin atrophy (0034): 2; Bullous eruption (0871): 3; Hyperkeratosis (0966): 3; Skin necrosis (0060): 3; Sweating increased (0043): 3; Urticaria (0044): 4; Skin nodule (0061): 4; Scleroderma (0971): 4; Skin ulceration (0041): 6; Skin exfoliation (1,199): 11; Dermatitis exfoliative (0008): 13; Rash (0027): 14; Rash maculo-papular (0030): 18; Skin dry (1,123): 19; Rash erythematous (0028): 20; Skin disorder (0037): 24; Induration (1,891): 30; Pruritus (0024): 32; Skin discolouration (0036): 38; Fibrosis skin (2,314): 108); **2-200 (n 216):** (Ligament disorder (2,086): 1; Fracture pathological (0069): 1; Tendinitis (1,001): 1; Arthritis infective (2,024): 1; Chondrocalcinosis (2,228): 1; Arthropathy (0065): 1; Avascular necrosis bone (2,222): 1; Osteoporosis (0076): 2; Muscle atrophy (0072): 2; Musculoskeletal pain (1,889): 2;

Tendon disorder (1,074): 3; Osteomyelitis (1,184): 3; Myopathy (0074): 3; Fracture (2,190): 3; Arthritis (0064): 9; Skeletal pain (1,347): 15; Arthralgia (0063): 17; Myalgia (0073): 24; Muscle weakness (1,128): 28; Arthrosis (0066): 33; Deformity (2,209): 65); **3-300 (n 2):** (Graft versus host disease (1,770): 1; LE syndrome (0081): 1); **4-410 (n 329):** (Hyperkinesia (0114): 1; Aphasia (0087): 1; Neuralgia (0124): 1; Coordination abnormal (0097): 1; Oedema cerebral (0891): 1; Dysphonia (0103): 1; Paresis (0141): 1; Trigeminal disorders (2,169): 1; Sensory disturbance (0148): 1; Hemiparesis (0111): 1; Speech disorder (0150): 1; Tongue paralysis (0153): 1; Spinal stenosis (1,975): 1; Oculogyric crisis (0132): 2; Hyperaesthesia (0113): 2; Cerebral disorder (1,960): 2; Encephalopathy (0105): 2; Stupor (0151): 2; Muscle contractions involuntary (0155): 2; Paralysis (0138): 2; Ataxia (0088): 3; Convulsions (0093): 3; Tremor (0154): 3; Vertigo (0158): 4; Convulsions grand mal (0095): 4; Coma (0091): 5; Dizziness (0101): 7; Neuropathy peripheral (1,313): 7; Headache (0109): 8; Dysaesthesia (1,491): 13; Dyskinesia (0102): 13; Hypoaesthesia (0117): 15; Hypertonia (0116): 21; Gait abnormal (0108): 23; Paraesthesia (0137): 29; Hypokinesia (0118): 144); **6-431 (n 8):** (Keratitis (0246): 1; Lacrimation abnormal (1,049): 1; Eye abnormality (0243): 1; Conjunctivitis (0238): 2; Vision abnormal (0257): 3); **8-433 (n 2):** (Taste perversion (0267): 2); **9-500 (n 620):** (Suicide ideation (2,363): 1; Delirium (0099): 1; Agitation (0163): 1; Aggressive reaction (0162): 1; Personality disorder (0192): 1; Drug abuse (0175): 1; Amnesia (0164): 1; Nervousness (0188): 1; Confusion (0092): 2; Anorexia (0165): 2; Depersonalization (0171): 3; Mental disorder (1944): 4; Somnolence (0197): 4; Insomnia (0183): 6; Depression (0172): 15; Apathy (0167): 87; Emotional lability (0177): 242; Anxiety (0166): 247); **10-600 (n 66):** (GI haemorrhage (0294): 1; Haemorrhage intraabdominal (1,419): 1; Bowel motility disorder (1,842): 1; Haemorrhage rectum (1014): 1; Diarrhoea, Clostridium difficile (1,201): 1; Saliva increased (0222): 1; Diverticula (1,908): 1; Peritonitis (0320): 1; Intestinal ischaemia (1,308): 1; Gastro-intestinal disorder NOS (1,262): 1; Melaena (0306): 1; Duodenitis (1,217): 1; Oesophageal ulceration (0311): 1; Diseases of oesophagus (1,059): 1; Oesophagitis (0309): 1; Haemorrhoids (0298): 2; Pancreatitis (0314): 2; Gastric dilatation (0286): 2; Gastroesophageal reflux (1,149): 2; Diarrhoea (0205): 3; Dysphagia (0280): 3; Mouth dry (0218): 3; Constipation (0204): 3; Vomiting (0228): 9; Abdominal pain (0268): 9; Nausea (0308): 13); **11-700 (n 5):** (Hepatic necrosis (0349): 1; Hepatitis (0350): 1; Jaundice (0356): 1; Cholelithiasis (0343): 2); **12-800 (n 21):** (Gout (0378): 1; Acidosis (0363): 1; Hypercholesterolaemia (0381): 1; Cachexia (0368): 1; Hyperkalaemia (0383): 1; Diabetes mellitus (0371): 1; Hypocalcaemia (0387): 1; Fluid overload (1,018): 1; Acidosis lactic (0364): 1; Diabetic ulcer (2015): 1; Hypophosphataemia (1,064): 1; Hypokalaemia (0391): 1; Calcinosis (0369): 2; Weight decrease (0407): 3; Hypoglycaemia (0389): 4); **13-900 (n 5):** (Hypoparathyroidism (1,306): 1; Adrenal insufficiency (0410): 1; Hypothyroidism (0417): 1; Hyperparathyroidism (0921): 1; Myxoedema (0418): 1); **14-1,010 (n 47):** (Heart disorder (0504): 1; Vascular graft occlusion (2,109): 1; Hypertension portal (1,042): 1; Pulse weak (1,401): 1; ECG abnormal specific (0503): 1; Circulatory failure (0499): 2; Hypertension pulmonary (0211): 3; Hypotension (0212): 5; Cardiomegaly (1,320): 6; Hypertension (0210): 13; Cardiac failure (0496): 13); **15-1,020 (n 23):** (Cardiomyopathy (0425): 1; Pericarditis (0430): 1; Mitral stenosis (1,554): 1; Aortic valve incompetence (1,761): 1; Myocardial infarction (0428): 1; Fibrosis endocardial (1,274): 2; Mitral insufficiency (0899): 2; Aortic stenosis (0424): 2; Heart valve disorders (1,228): 2; Angina pectoris (0422): 2; Coronary artery disorder (0426): 4; Fibrosis myocardial (1,188): 4); **16-1,030**

(n 19): (Arrhythmia (0433): 1; Tachycardia ventricular (0230): 1; Arrhythmia nodal (0809): 1; Tachycardia supraventricular (0229): 1; Palpitation (0221): 1; AV block complete (1,378): 1; QT prolonged (1,361): 1; Fibrillation atrial (0439): 2; Tachycardia (0224): 2; AV block (0431): 2; Bradycardia (0208): 2; Cardiac arrest (0437): 4); **17-1,040 (n 34):** (Haemorrhage stroke (1,989): 1; Thrombophlebitis (0466): 1; Subclavian steal syndrome (2,011): 1; Stenosis vein (2,083): 2; Haemorrhage intracranial (1,068): 2; Cerebral haemorrhage (0444): 2; Vasodilatation (0225): 2; Transient ischaemic attack (1,694): 2; Peripheral ischaemia (0454): 4; Flushing (0207): 4; Thrombophlebitis deep (0470): 4; Vein disorder (0492): 4; Cerebrovascular disorder (0445): 5); **18-1,100 (n 73):** (Atelectasis (1,197): 1; Upper respiratory tract infection (0543): 1; Pneumonitis (1,141): 1; Pulmonary congestion (1,721): 1; Pharyngitis (0523): 1; Chronic obstructive airways disease (1,493): 1; Sinusitis (0540): 1; Pulmonary infiltration (1,038): 1; Pleural fibrosis (0525): 1; Respiratory distress syndrome (2,252): 1; Pulmonary fibrosis (0532): 2; Rhinitis (0539): 2; Coughing (0513): 2; Respiratory depression (0144): 2; Bronchitis (0805): 2; Larynx oedema (0522): 2; Throat tightness (1,489): 2; Stridor (0542): 2; Sleep apnoea (1,515): 3; Pulmonary disorders (2,032): 4; Pulmonary oedema (0535): 6; Pleural effusion (0524): 7; Pneumonia (0528): 7; Respiratory insufficiency (0537): 9; Dyspnoea (0514): 11); **19-1,210 (n 4):** (Splenomegaly (0569): 1; Anaemia (0544): 3); **20-1,220 (n 3):** (Lymphoedema (0581): 1; Leukocytosis (0576): 2); **21-1,230 (n 16):** (Prothrombin decreased (0590): 1; Thrombus intracardiac (2,113): 1; Thrombosis (0481): 1; Haemorrhage NOS (0452): 1; Thrombosis arterial leg (0484): 1; Embolism arterial (0447): 1; Thrombosis arterio-venous fistula (1,776): 1; Purpura (0459): 2; Embolism pulmonary (0451): 2; Embolism aortic (2,041): 2; Thrombocytopenia (0594): 3); **22-1,300 (n 18):** (Azotaemia (2,328): 1; Urinary tract stenosis (2,317): 1; Renal cyst (1,138): 2; Urinary incontinence (0156): 2; Renal function abnormal (0619): 3; Urinary tract infection (0628): 4; Renal failure chronic (2,329): 5); **23-1,410 (n 2):** (Hernia inguinal (1,482): 1; Prostatic disorder (0632): 1); **27-1,700 (n 55):** (Cervical smear test positive (0826): 1; Histiocytoma (2,046): 1; Bladder carcinoma (0766): 1; Breast neoplasm benign female (1,114): 1; Basal cell carcinoma (1,240): 1; Uterine fibroid (0857): 1; Skin neoplasm malignant (1,239): 1; Skin hypertrophy (0038): 48); **28-1,810 (n 814):** (Night sweats (1,898): 1; Nasal polyp (0985): 1; Anaphylactoid reaction (0714): 1; Influenza-like symptoms (1,222): 1; Oedema mouth (1,485): 1; Multiple organ failure (1,819): 1; Pallor (0220): 1; Leg pain (1,439): 1; Posture abnormal (2,012): 1; Therapeutic response increased (0874): 1; Tenderness NOS (1,911): 1; Allergic reaction (0712): 2; Oedema periorbital (1009): 2; Withdrawal syndrome (0200): 2; Temperature changed sensation (1,705): 2; Rigors (0731): 2; Hernia NOS (1,832): 2; Death (0722): 3; Fever (0725): 4; Syncope (0223): 4; Back pain (0717): 5; Chest pain (0718): 5; Fatigue (0724): 9; Oedema generalised (0400): 10; Oedema (0398): 14; Asthenia (0716): 19; Oedema peripheral (0401): 51; Scar (1,522): 148; Malaise (0728): 181; Pain (0730): 338); **29-1,820 (n 13):** (Injection site rash (1,881): 1; Medical device complication (2,139): 1; Injection site reaction (0058): 5; Cellulitis (1,372): 6); **30-1,830 (n 70):** (Infection fungal (0739): 1; Infection bacterial (0738): 1; Infection susceptibility increased (1,226): 1; Herpes zoster (0862): 1; Abscess (0887): 2; Infection (0736): 3; Infection staphylococcal (1,867): 4; Sepsis (0744): 11; Skin tightness (2,098): 46). **9-Gadoxetic acid (n 98): 1-100 (n 20):** (Rash maculo-papular (0030): 1; Rash (0027): 1; Rash erythematous (0028): 1; Skin discolouration (0036): 1; Sweating increased (0043): 3; Urticaria (0044): 6; Pruritus (0024): 7); **4-410 (n 8):** (Dysaesthesia (1,491): 1; Paraesthesia (0137): 1; Hypoaesthesia (0117): 1; Headache

(0109): 2; Dizziness (0101): 3); **6-431 (n 1):** (Lacrimation abnormal (1,049): 1); **8-433 (n 1):** (Parosmia (0265): 1); **9-500 (n 3):** (Anxiety (0166): 1; Agitation (0163): 1; Confusion (0092): 1); **10-600 (n 12):** (Dyspepsia (0279): 1; Stomatitis ulcerative (0328): 1; Diarrhoea (0205): 2; Vomiting (0228): 2; Nausea (0308): 6); **11-700 (n 2):** (Hepatic function abnormal (0348): 1; Hepatitis cholestatic (0351): 1); **14-1,010 (n 2):** (Cardiovascular disorders (2,031): 2); **15-1,020 (n 2):** (Angina pectoris (0422): 1; Myocardial ischaemia (0429): 1); **16-1.030 (n 4):** (Arrhythmia (0433): 1; Tachycardia (0224): 3); **1,040 (n 3)**: (Peripheral ischaemia (0454): 1; Flushing (0207): 1; Vasospasm (0226): 1); **18-1,100 (n 15):** (Pulmonary oedema (0535): 1; Respiratory disorder (0536): 1; Hyperventilation (0517): 1; Rhinitis (0539): 1; Throat tightness (1,489): 1; Dyspnoea (0514): 10); **22-1,300 (n 1):** (Face oedema (0602): 1); **28-1,810 (n 20):** (Fever (0725): 1; Choking (1,460): 1; Anaphylactic reaction (2,237): 1; Anaphylactoid reaction (0714): 1; Malaise (0728): 1; Syncope (0223): 1; Oedema peripheral (0401): 1; Back pain (0717): 1; Pallor (0220): 1; Allergic reaction (0712): 2; Chest pain (0718): 2; Temperature changed sensation (1,705): 2; Rigors (0731): 5); **29-1,820 (n 4):** (Injection site pain (0057): 1; Injection site rash (1,881): 1; Injection site anaesthesia (1,917): 1; Injection site reaction (0058): 1). **10-Mangafodipir (n 9): 4-410 (n 1):** (Headache (0109):1); **14-1,010 (n 1):** (Hypotension (0212): 1); **17-1,040 (n 2):** (Flushing (0207): 2); **18-1,100 (n 2):** (Chest X-ray abnormal (0512): 1; Pneumonia (0528): 1); **28-1,810 (n 3):** (Condition aggravated (0965): 1; Anaphylactoid reaction (0714): 1; Fever (0725): 1).

Appendix Nr. 2. The 700 SOCD-ADRs effectively appearing in the RMN 10 paramagnetic product list of Appendix Nr. 1.

The basic Matlab file containing 2364 rows x 10 columns (the 10 columns corresponding to the 10 products) had been then reduced to the equivalent 700x 10 matrix file (without the null rows). In this table are given the index numbers of the 700 ADRs effectively present.

This table is to be read across and down. The format of 70 rows and 10 columns was chosen for printing convenience only; t**he 10 columns of this table are not related in any way with the 10 contrast media treated** (we could print the same data as a 140x5 matrix, for instance).

1	**2**	**3**	**7**	**8**	**10**	**12**	**13**	**14**	**16**
20	**22**	**24**	**27**	**28**	**30**	**31**	**32**	**33**	**34**
35	**36**	**37**	**38**	**39**	**41**	**42**	**43**	**44**	**45**
47	**49**	**54**	**55**	**56**	**57**	**58**	**60**	**61**	**63**
64	**65**	**66**	**67**	**68**	**69**	**72**	**73**	**74**	**76**
77	**81**	**85**	**87**	**88**	**90**	**91**	**92**	**93**	**94**
95	**97**	**98**	**99**	**100**	**101**	**102**	**103**	**104**	**105**
106	**107**	**108**	**109**	**111**	**112**	**113**	**114**	**116**	**117**
118	**119**	**120**	**121**	**123**	**124**	**125**	**130**	**131**	**132**

133	**136**	**137**	**138**	**141**	**142**	**143**	**144**	**148**	**150**
151	**152**	**153**	**154**	**155**	**156**	**157**	**158**	**159**	**162**
163	**164**	**165**	**166**	**167**	**169**	**171**	**172**	**175**	**177**
179	**180**	**183**	**186**	**187**	**188**	**189**	**191**	**192**	**193**
195	**197**	**199**	**200**	**201**	**204**	**205**	**207**	**208**	**210**
211	**212**	**213**	**215**	**216**	**218**	**219**	**220**	**221**	**222**
223	**224**	**225**	**226**	**228**	**229**	**230**	**231**	**232**	**237**
238	**241**	**243**	**244**	**246**	**247**	**250**	**255**	**257**	**258**
260	**261**	**264**	**265**	**266**	**267**	**268**	**270**	**279**	**280**
281	**283**	**285**	**286**	**287**	**289**	**291**	**293**	**294**	**295**
297	**298**	**300**	**301**	**302**	**306**	**308**	**309**	**311**	**314**
320	**327**	**328**	**330**	**331**	**336**	**339**	**343**	**345**	**347**
348	**349**	**350**	**351**	**353**	**356**	**359**	**360**	**363**	**364**
368	**369**	**370**	**371**	**374**	**376**	**377**	**378**	**379**	**380**
381	**382**	**383**	**385**	**387**	**389**	**391**	**392**	**393**	**394**
398	**399**	**400**	**401**	**404**	**405**	**407**	**410**	**411**	**417**
418	**419**	**422**	**424**	**425**	**426**	**427**	**428**	**429**	**430**
431	**432**	**433**	**435**	**436**	**437**	**438**	**439**	**440**	**441**
442	**444**	**445**	**447**	**448**	**451**	**452**	**454**	**455**	**456**
459	**463**	**466**	**467**	**468**	**469**	**470**	**479**	**481**	**482**
484	**486**	**488**	**491**	**492**	**493**	**494**	**496**	**497**	**498**
499	**501**	**502**	**503**	**504**	**507**	**508**	**510**	**511**	**512**
513	**514**	**515**	**516**	**517**	**518**	**519**	**520**	**521**	**522**
523	**524**	**525**	**528**	**531**	**532**	**535**	**536**	**537**	**539**
540	**541**	**542**	**543**	**544**	**548**	**549**	**557**	**560**	**569**
571	**572**	**576**	**577**	**580**	**581**	**584**	**586**	**590**	**594**

595 596 598 601 602 603 604 605 606 607

608 609 610 612 613 614 617 618 619 621

622 623 624 625 628 629 632 634 637 657

663 677 689 691 692 707 711 712 713 714

715 716 717 718 719 720 722 723 724 725

727 728 730 731 733 736 738 739 740 741

744 748 761 764 766 771 777 791 798 805

809 810 826 827 828 830 845 850 857 862

864 867 871 874 876 878 887 891 894 896

899 908 910 911 912 915 921 923 926 928

929 932 933 939 942 943 946 948 955 960

961 965 966 971 973 974 979 985 990 1001

1004 1009 1014 1018 1019 1030 1036 1038 1042 1049

1052 1058 1059 1063 1064 1066 1068 1074 1077 1081

1082 1083 1086 1096 1101 1104 1114 1122 1123 1126

1127 1128 1134 1138 1141 1149 1162 1168 1172 1175

1177 1181 1184 1188 1197 1199 1201 1210 1214 1217

1222 1226 1228 1239 1240 1251 1252 1255 1259 1262

1274 1280 1281 1291 1294 1306 1308 1313 1320 1328

1334 1346 1347 1348 1351 1353 1361 1367 1368 1370

1372 1376 1378 1387 1395 1397 1398 1401 1410 1416

1419 1427 1429 1431 1432 1439 1451 1460 1461 1469

1471 1474 1482 1485 1486 1489 1491 1493 1497 1500

1505 1511 1515 1522 1531 1546 1547 1549 1554 1558

1574 1589 1605 1621 1638 1648 1650 1688 1694 1702

1705 1707 1712 1715 1716 1721 1723 1746 1749 1752

1753 1761 1762 1770 1776 1782 1806 1819 1820 1831

1832 1835 1839 1842 1843 1844 1862 1867 1877 1880

1881 1882 1888 1889 1891 1898 1899 1908 1910 1911

1917 1922 1944 1946 1948 1950 1960 1968 1970 1975

1976 1977 1978 1986 1987 1989 2008 2011 2012 2015

2024 2031 2032 2041 2046 2056 2082 2083 2086 2090

2098 2109 2113 2133 2136 2137 2139 2160 2162 2169

2172 2190 2209 2220 2221 2222 2228 2237 2252 2253

2309 2314 2317 2328 2329 2339 2351 2356 2363 2364

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CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

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