4,436 REPORTS FROM ITALY, ACCEPTED IN THE WHO UPM COLLABORATING CENTRE THESAURUS VS 181,744 GLOBALLY COLLECTED REPORTS FROM OTHER PARTICIPATING COUNTRIES OF SAME 33 MONITORED CONTRAST AGENT-PRODUCTS OVER THE FIRST 40 YEARS OF THE PROGRAMME.

SIXTH WHO-ITA/ITA-OMS 2010-2011 CONTRIBUTION

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Summary

This contribution, based on the suggestions and results of our earlier studies of the reports sent through the UMC, is a first example of what we believe should be done by the peripheral offices of the individual Member Countries, to orient subsequent activities in relation to the priorities of the regulatory, prescription-related pharmaco-therapeutic decisions, taking into account the local characteristics of the various collections, with reference both to the reasons provided for the administration of biosimilars instead of the standard products and to the improved characterization of the individual ATC classes and subclasses. In addition, a much greater weight should be attributed to feed-back information, which should be given at least the same importance as translational pre-clinical, pre-marketing and standardized clinical data. There is no doubt that the collections even of the Member Countries that have joined more recently would benefit from the more frequent use of objective models to analyze data as the one we have used; such models can and should be introduced in the theory and practice of any epidemiological and pharmaco-toxico-therapeutic study with a global reach.

As an example, the results of the study are summarized based on the SOCD-SADRs profiles for 33 selected contrast agents and 30 SOCD-SADR classes, with

comparison of the adverse reactions and events collected in Italy and in the rest of the World over a 40-year period. Application of the descriptive statistics approach showed that the two situations are found to be largely similar but to display some significant differences too. Clustering patterns do not confirm the optimization of the separation offered by the WHO-SOCD aggregations and the differentiation into ATC-classes and subclasses of these agents.

Key words: WHO International Drug Monitoring, Pharmacovigilance Programme and Uppsala Monitoring Center (UMC). Objective autoclassificative and confirmatory clustering comparisons over 40 years collection of reports from Italy vs those from other participating Countries for same 33 products monitored of the ATC-VO8A (-A: amidotrizoate, meglumine amidotrizoate/sodium amidotrizoate, iodamide, ioglicicate, iotalamate, ioxitalamate, ioxitalamate meglumine/ioxitalamate sodium, and metrizoate; -B: iobitridol, iodixanol, iohexsol, iomeprol, iopamidol, iopentol, iopromide, iotrolan, ioversol, ioxaglate meglumine/ioxaglate sodium, and ioxaglicate; -C: adipiodone meglumine, iobenzamate, iocetamate, iodoxamate, ioglycamate, iopanoate and iotroxate); and V08C-A: gadobenate, gadobutrol, gadodiamide, gadofosveset, gadopentetate, gadoteridol, and gadoxetate) indicated Contrast Agents subclasses.

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"Unfortunately the modern organization of science, founded on a close connection with politics and economic power, from which proceed financing and the attendant acknowledgements of merit entitling to funding, does not allow... clairvoyant wisdom. ... The field ... is clear for a single type of innovations, those that lead to immediate profit (6-12 months) and do not jeopardize pre-existing investments", Emilio del Giudice, Foreword, in Roberto Germano, Aqua, Bibliopolis, Napoli 2006.

Fotti il potere. Gli arcana della politica e dell' umana natura. Andrea Cangini & Francesco Cossiga, Aliberti Editore, 2010/2011, pp 298.

In the third and fourth note of this series [1, 2], as we discussed some characteristics of the use of contrast agents (CA) in Italy—initially spontaneously, voluntary monitored by WHO-ITA / ITA-OMS and later subjected to the National pharmacovigilance system in the framework of the WHO Drug Monitoring Programme—we stressed that the clusters adopted in the 30 System Organ Class Disorders (SOCDs) of (Suspected) Adverse Reaction and event preferred names (SADRs) failed to envisage the early acute phase both of the potentially fatal chronic disease designated as Contrast-induced Nephropathy (CIN) for iodinated CA class ATC-V08A and Nephrogenic Systemic Nephrosis (NSF) for MRI-enhancing product class ATC-V08C, first of all for Gadolinium-based contrast agents (GBCAs). This did not apply to Italy alone, in connection to its 22 SOCDs or, as highlighted by the 218 SOCD-SADR preferred names and/or codes, actually found in the 4,436 SADRs that emerged there from the monitoring of the 33 products then in use, but also in connection to the same 30 SOCDs and the 700 characterizing SOCD-SADRs of the 38,523 SADRs of the NMR-V08C-A products (Cf [1]), as for the 30 SOCDs also found, and the 876 SOCD-SADRs related to the 155,164 SADRs of the iodinated V08A, -A, -B, -C and-D 30 branded products monitored worldwide (Cf [2]).

As regards the same PR22-2010 dataset of the WHO-Uppsala Monitoring Centre (UMC) thesaurus involving the **SADRs from the 33 products sold in Italy, 40 years monitoring having excluded,** these consisting of 22 SOCDs (on 30; 23 on 32) for the same total common 33 products, and the related common SOCD-SADRs now reduced to 4,436 (on 30; being 4,477 on 32), having excluded the 6 reports of the two V08C-B ferrixan and ferumoxil products (See Appendix Nr 6, in [2]), while the remaining "cleaned", that is subtracted SADRs of the mixed 33 products V08A and V08C SADRs over same period amount to 181,744 - that is 189,245 reports for the (38,523 + 155,164) - 4,442, for all the 10 V08C-A paramagnetic RMC CA products of the Appendix Nr 1 in [1], + the 30 products of the V08A iodinated CA class -, but **181,744 only as for the V08C-A 7 Gd chelates, and the 26 V08A -A (8), -B (11) and –C (7) products used in Italy**, which we will present after subjecting them to the same clustering objective autoclassification and confirmatory plots model study previously applied to their comparisons.

The 33 products monitored in Italy vs the same products submitted worldwide, having been subtracted those correspondent reported from Italy, over the same 40 years, subdivided on the basis of the ATC classification as shown below, will be reported in mixed alphabetic order - since their listing order is irrelevant for the algorithm application - fully documented in the Appendices Nr 3 and 6 – corrected as above indicated - of the fourth Note (Cf [2]), and Appendix Nr 1 of the third (in [1]), with the frequencies of the SOCD-SADRs of each of them, common to the italian

market vs those sold globally otherwise, both presented in brackets here - the first number (in bold) of any product representing it in the general alphabetic order, and the second in the indicated ATC subclass frequency increasing order related to the national italian collection -: V08C-A: **9**.1. Gadoxetate (1; 97); **6**.2. Gadofosveset (5; 58); **5**.3. Gadodiamide (15; 5,419); **4**.4. Gadobutrol (42; 795); **8**.5. Gadoteridol (52; 3,376); **7**.6. Gadopentetate (113; 20,089); and **3**.7. Gadobenate (253; 5,128); VO8A-A (including two "biosimilars"): **33**.1. Metrizoate (3; 686); **31**.2. Ioxitalamate (5; 413); **30**.3. Ioxitalamate meglumine/ioxitalamate sodium (5; 1,793); **16**.4. Ioglicicate (19; 146); **24**.5. Iotalamate (27; 14,026); **2**.6. Amidotrizoate (42; 25,956); **32**.7. Meglumine amidotrizoate/sodium amidotrizoate (87; 18,503); and **13**.8. Iodamide (194; 554); -B (including one "biosimilar"): **29**.1. Ioxaglicate (2; 231); **25**.2. Iotrolan (6; 767); **28**.3. Ioxaglate meglumine/ioxaglate sodium (21; 4,946); **22**.4. Iopentol (24; 410); **27**.5. Ioversol (105; 7,465); **18**.6. Iohexol (202; 19,670); **11**.7. Iobitridol (201; 1,428); **14**.8. Iodixanol (317; 4,498); **20**.9. Iopamidol (600; 17,090); **23**.10. Iopromide (952;18,435); and **19**.11. Iomeprol (1,020; 3,597); -C: **10**.1. Iobenzamate (1; 620); **17**.2. Ioglycamate (4; 874); **15**.3. Iodoxamate (5; 522); **12**.4. Iocetamate (5; 188); **1**.5. Adipiodone meglumine (5; 2,716); **21**.6. Iopanoate (6; 478); and **26**.7. Iotroxate (97; 770).

1. Comparison of the number of the reports for 30 SOCD-SADR

Classes during the 40 years period 1968-2010, between Italy and the World minus Italy.

The data are organized in two directions: the 30 SOCD-ADR classes for the treatment of the ADRs, and 33 chosen contrast agents as a kind of representative sample of the contrast agents. From the technical point of view, the data are given as two 30x33 matrices, **M2AA** and **M2BB**, the first one for Italy, and the second for the rest of the World. (See Appendix Nr 1.). The 30 rows in each matrix stand for the SOCD-ADR classes, the columns for the 33 agents, and the cells contain the corresponding number of reports. The Italian situation will be confronted with the situation of the World minus Italy, from these two directions:

I. By comparing the 30 SOCD-ADR totals of reports in the two situations, by techniques mainly of descriptive statistics.

II. By comparing the two situations, by means of clustering of the 33 agents and noting similarities and differences.

1.1. Comparison based on descriptive statistics.

The values obtained are the totals of the number of reports for the 33 chosen contrast agents detailed above. These values, as well as values derived from them, are given in TABLE 1 as follows.

TABLE 1: Comparison of SOCD Italy vs World minus Italy

Nr Crt	SOCD Class	Totals Italy	Totals World less Italy	Profile Italy	Profile World less Italy	Cumsum Italy	Cumsum World-Italy
1	100	1609	53120	0.3627	0.2923	0.3627	0.2923
2	200	7	1554	0.0016	0.0086	0.3643	0.3008
3	300	0	19	0	0.0001	0.3643	0.3009
4	410	269	15652	0.0606	0.0861	0.4249	0.3871
5	420	0	1	0	0.0000	0.4249	0.3871
6	431	47	2505	0.0106	0.0138	0.4355	0.4008
7	432	4	246	0.0009	0.0014	0.4364	0.4022
8	433	3	348	0.0007	0.0019	0.4371	0.4041
9	500	34	5525	0.0077	0.0304	0.4448	0.4345
10	600	582	20068	0.1312	0.1104	0.5760	0.5449
11	700	7	265	0.0016	0.0015	0.5775	0.5464
12	800	2	611	0.0005	0.0034	0.5780	0.5498
13	900	1	107	0.0002	0.0006	0.5782	0.5503
14	1010	279	9100	0.0629	0.0501	0.6411	0.6004
15	1020	8	679	0.0018	0.0037	0.6429	0.6041
16	1030	124	5769	0.0280	0.0317	0.6709	0.6359
17	1040	125	5273	0.0282	0.0290	0.6991	0.6649
18	1100	680	24242	0.1533	0.1334	0.8523	0.7983
19	1210	0	115	0	0.0006	0.8523	0.7989
20	1220	2	206	0.0005	0.0011	0.8528	0.8001
21	1230	9	570	0.0020	0.0031	0.8548	0.8032
22	1300	76	6030	0.0171	0.0332	0.8720	0.8364
23	1410	0	9	0	0.0000	0.8720	0.8364
24	1420	0	39	0	0.0002	0.8720	0.8366
25	1500	0	29	0	0.0002	0.8720	0.8368
26	1600	0	6	0	0.0000	0.8720	0.8368
27	1700	0	285	0	0.0016	0.8720	0.8384
28	1810	530	26762	0.1195	0.1473	0.9914	0.9856
29	1820	37	2099	0.0083	0.0115	0.9998	0.9972
30	1830	1	510	0.0002	0.0028	1.0000	1.0000
Grand Total		**4436**	**181744**				

Column 2 details the 30 SOCD-ADRs classes (the Nr Crt of Column 1 may be taken instead);

Column 3 gives the values for Italy (some of them are 0, for ADRs which did not occur);

Column 4 gives the values for the World, after subtracting those for Italy;

Column 5 gives the profile for Italy (totals divided by the column Grand Total);

Column 6 gives the profile for World minus Italy;

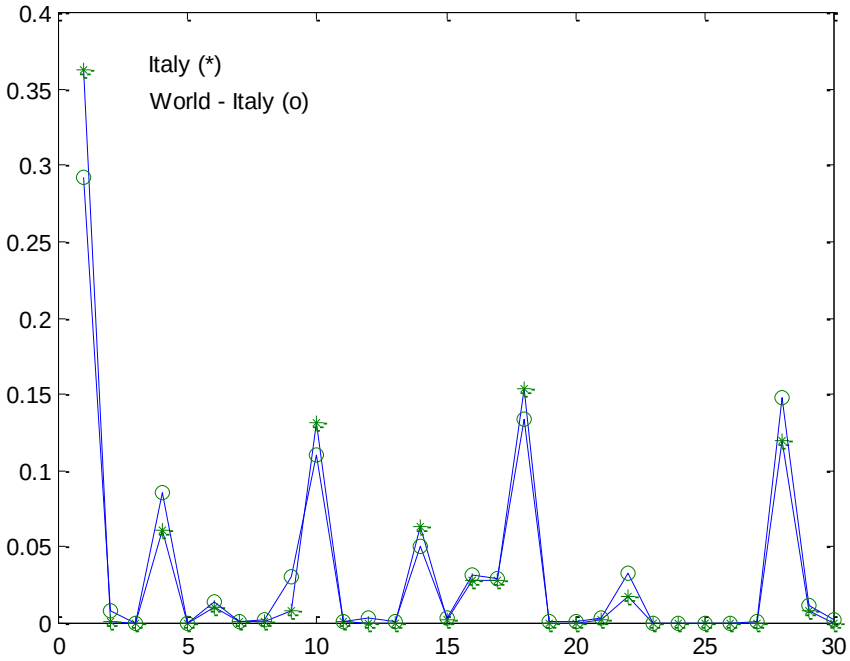
Column 7 gives the cumulative profile for Italy;

Column 8 gives the cumulative profile for the World minus Italy.

Note that the profile values, which sum to 1, can be interpreted as a probability distribution and the increasing values of cumsum, as a cumulative distribution function.

The Figure 1 displays on the same plot the profiles of Italy and of the World less Italy. As abscissas are taken not the values of the SOCD-ADRs, but their indices, which does not change anything.

Figure 1: Profiles

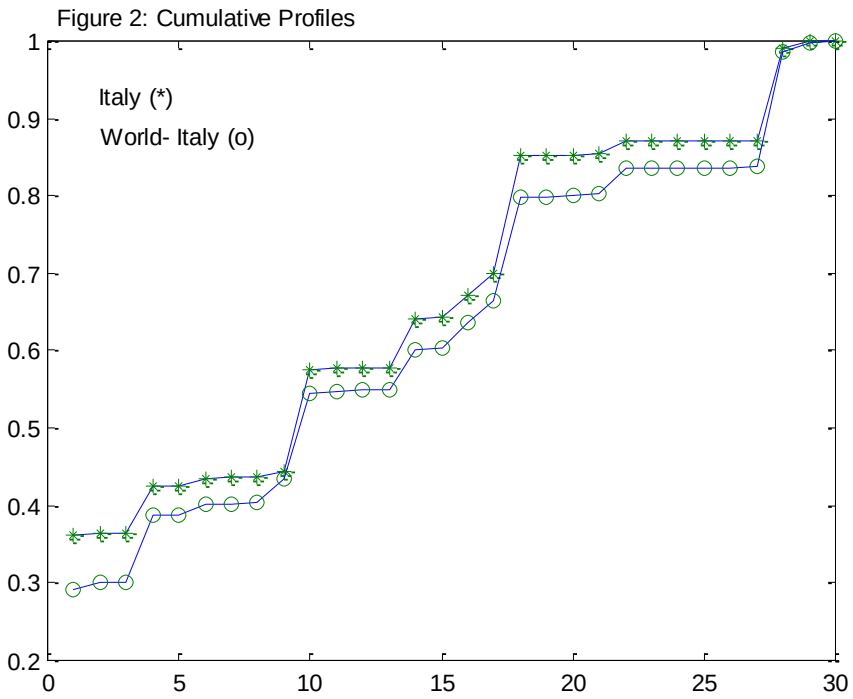


The two **profiles appear to be very similar**.

A more thorough examination shows however that **they are not identical**.

This can be seen first on Figure 2, where **the two cumulative profiles** are plotted together, and they **appear to be slightly different**.

Then, Columns 3 and 4 form a 30x2 contingency table. After adding the value .5 to all the elements of this table, one can apply a standard chi square test.



One obtains Pearson Chi Square=356.26 and Wilks Chi Square=420.5, two concordant values. As the critical Chi Square for a cdf = .95 and df = 29 is 42.56, **our 30x2 table does not display independence**, and **the two columns are not strictly proportional.**

1.2. Comparison based on the clustering patterns of the 33 basic contrast agents in the two situations.

We give here the TABLE 2, relevant here for identifying the agents, which will be given in the following only by their number, as in this table.

TABLE 2: List of 33 CAs chosen for comparison of Italy vs World less Italy

	Substance (ATC)	Total Italy	Total World less Italy
1	Adipiodone meglumine (V08AC)	**5**	2716
2	Amidotrizoic acid (V08AA)	42	25956
3	Gadobenic acid (V08CA)	253	5128
4	Gadobutrol (V08CA)	42	795
5	Gadodiamide (V08CA)	15	5419
6	Gadofosveset (V08CA)	**5**	**58**
7	Gadopentetic acid (V08CA)	113	20089
8	Gadoteridol (V08CA)	52	3376
9	Gadoxetic acid (V08CA)	**1**	97
10	Iobenzamic acid (V08AC)	**1**	620
11	Iobitridol (V08AB)	201	1428
12	Iocetamic acid (V08AC)	**5**	**188**
13	Iodamide (V08AA)	194	554
14	Iodixanol (V08AB)	317	4498
15	Iodoxamic acid (V08AC)	**5**	522
16	Ioglicic acid (V08AA)	19	**146**
17	Ioglycamic acid (V08AC)	**4**	874
18	Iohexol (V08AB)	202	19670
19	Iomeprol (V08AB)	1020	3597
20	Iopamidol (V08AB)	600	17090
21	Iopanoic acid (V08AC)	**6**	478
22	Iopentol (V08AB)	24	410
23	Iopromide (V08AB)	952	18435
24	Iotalamic acid (V08AA)	27	14026
25	Iotrolan (V08AB)	**6**	767
26	Iotroxic acid (V08AC)	97	770
27	Ioversol (V08AB)	105	7465
28	Ioxaglate meglumine/Ioxaglate sodium (V08AB)	21	4946
29	Ioxaglic acid (V08AB)	**2**	**231**
30	Ioxitalamate meglumine/Ioxitalamate sodium (V08AA)	**5**	1793
31	Ioxitalamic acid (V08AA)	**5**	413
32	Meg. amidotrizoate/Sodium amidotrizoate (V08AA)	87	18503
33	Metrizoic acid (V08AA)	**3**	686
	Grand Total	**4436**	**181744**

Belonging of CAs to the two classes V08A and V08C, and the four subclasses of substances:

V08AA: 2 13 16 24 30 31 32 33

V08AB: 11 14 18 19 20 22 23 25 27 28 29

V08AC: 1 10 12 15 17 21 26

V08CA: 3 4 5 6 7 8 9

The agents with too little reports, form the two sets:

scarceA=[1 6 9 10 12 15 17 21 25 29 30 31 33] for Italy, M2AA

scarceB=[6 12 16 29] for World outside Italy, M2BB

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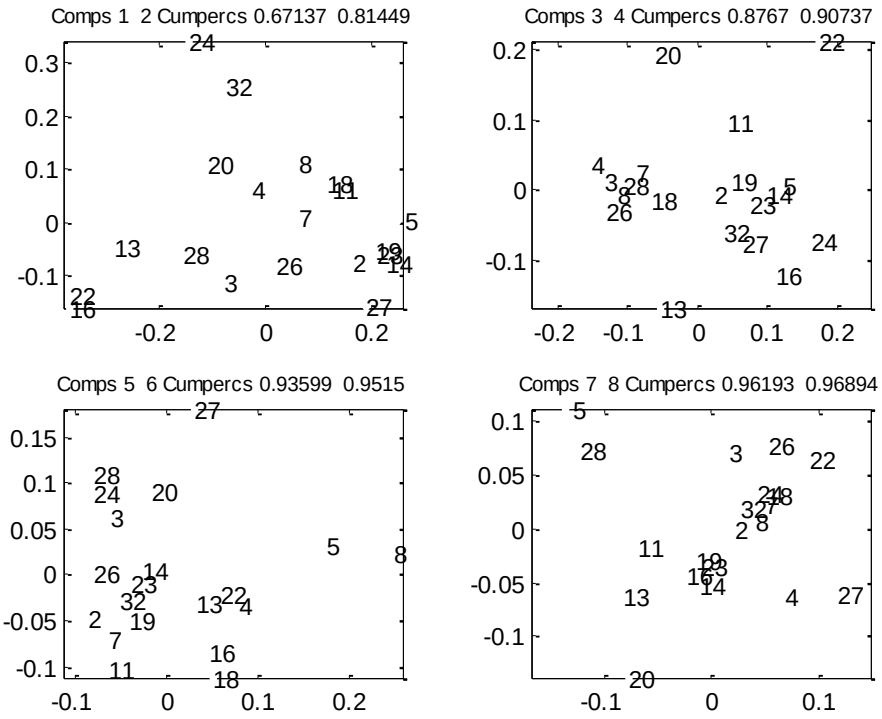
1.2.1. Drug Clustering for M2AA

X=M2AA'; scarce=scarceA; ALLCLUSTERSFINAL(X,scarce);

rich = 2 3 4 5 7 8 11 13 14 16 18 19 20 22 23 24 26 27 28 32

Follow 4 confirmatory plots



GAUGES and CORRELATIONS

0.2958	0.825
0.27386	0.85
0.22361	0.9

0.19365 0.925

0.15811 0.95

0.1118 0.975

VALUES VALID THROUGHOUT

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Summary of clusters and correlations

20 28	0.94058
20 28 32	**at least 0.89193**
13 16	0.94555
13 16 22	**at least 0.85278**
7 26	0.98653
7 18 26	at least 0.96563
5 8	**0.89796**
2 14 19 23	at least 0.98427
2 11 14 19 23	at least 0.96814
2 7 11 14 18 19 23 26	at least 0.94297
2 3 4 7 11 14 18 19 23 26 27	**at least 0.85681**

The blue clusters are 'essential': they include the others as sub-sets

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PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

18 24 0.8250	16 28 0.8797	5 27 0.9241
20 22 0.8276	19 32 0.8800	11 20 0.9271
4 24 0.8278	19 20 0.8830	**3 13 0.9285**
27 28 0.8296	2 20 0.8830	4 32 0.9289
11 24 0.8307	19 28 0.8841	4 28 0.9325
7 24 0.8318	11 28 0.8857	**3 20 0.9334**
13 18 0.8325	2 32 0.8862	2 5 0.9344
3 22 0.8328	18 28 0.8896	**5 18 0.9360**
22 28 0.8435	8 14 0.8928	18 32 0.9363
4 5 0.8485	**3 8 0.8968**	7 32 0.9373
14 20 0.8502	26 32 0.8974	**5 11 0.9382**

14	32	0.8502	2	8	0.8991	**7**	**8**	**0.9391**
14	28	0.8553	13	26	0.8993	13	28	0.9401
8	27	0.8569	**5**	**7**	**0.9008**	7	20	0.9438
20	23	0.8620	8	32	0.9030	7	28	0.9447
3	16	0.8659	8	20	0.9047	4	20	0.9511
13	20	0.8689	4	13	0.9053	26	28	0.9581
13	32	0.8706	8	11	0.9067	4	8	0.9584
20	24	0.8719	8	23	0.9079	5	23	0.9590
23	32	0.8738	18	20	0.9088	8	18	0.9606
3	32	0.8751	2	28	0.9108	24	32	0.9607
5	26	0.8758	20	26	0.9166	**5**	**19**	**0.9632**
23	28	0.8764	8	19	0.9166	5	14	0.9641
7	13	0.8773	8	26	0.9211	**3**	**28**	**0.9760**
8	28	0.8792	11	32	0.9230			

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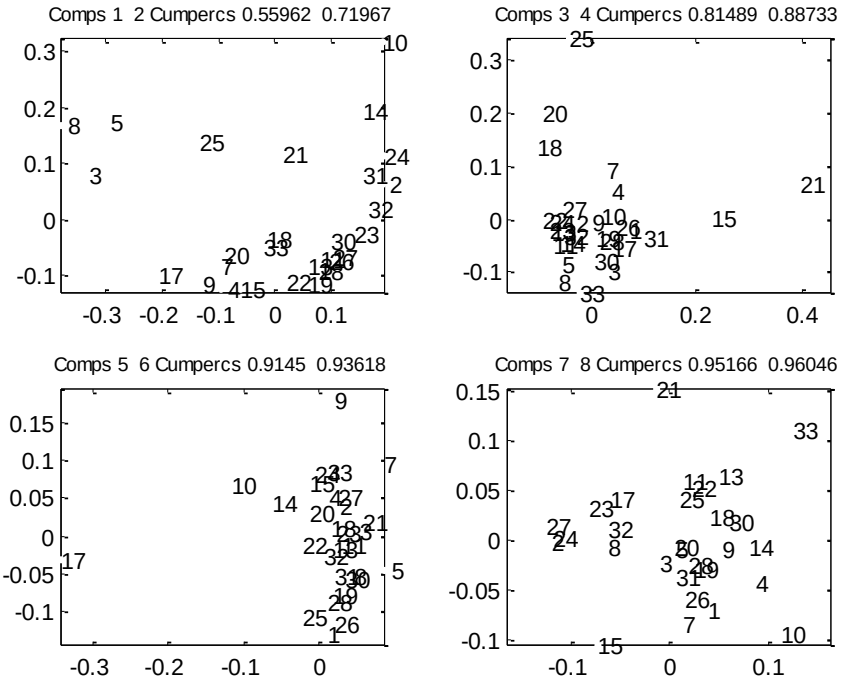
1.2.2. Drug Clustering for M2BB

X=M2BB'; scarce=scarceB; ALLCLUSTERSFINAL(X,scarce);

rich = 1 2 3 4 5 7 8 9 10 11 13 14 15 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 33

Follow **4 confirmatory plots**



GAUGES and CORRELATIONS

0.2958 0.825

0.27386 0.85

0.22361 0.9

0.19365 0.925

0.15811 0.95

0.1118 0.975

VALUES VALID THROUGHOUT

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Summary of clusters and correlations

4 7	0.98204
4 7 20	at least 0.96931
3 5	0.96758
2 23 27 32	at least 0.98218
1 11 13 19 26 28 30	at least 0.9817
1 2 11 13 19 22 23 26 27 28 30 32	at least 0.95578
1 2 11 13 18 19 22 23 26 27 28 30 31 32	at least 0.92268
1 2 4 7 11 13 18 19 20 22 23 24 26 27 28 30 31 32 33	at least 0.87346
1 2 4 7 9 11 13 14 18 19 20 22 23 24 26 27 28 30 31 32 33	at least 0.83119

The blue designs the chosen 'essential' clusters.

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PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

10 18 0.8254	5 22 0.8508	9 17 0.8924
1 5 0.8265	17 26 0.8551	21 31 0.8941
1 25 0.8289	11 17 0.8552	17 22 0.8970
15 24 0.8291	**3 20 0.8566**	15 31 0.8976
25 26 0.8297	10 11 0.8577	15 23 0.8999
13 25 0.8315	7 17 0.8586	15 33 0.9034
5 28 0.8325	10 26 0.8588	4 17 0.9065
10 19 0.8326	5 20 0.8592	**3 4 0.9071**
7 8 0.8335	17 33 0.8610	**3 7 0.9089**
3 30 0.8344	4 25 0.8617	10 32 0.9113
1 3 0.8364	1 21 0.8636	13 15 0.9115
22 25 0.8367	13 17 0.8641	3 9 0.9125
3 28 0.8370	21 26 0.8649	15 22 0.9137
3 11 0.8379	3 17 0.8658	11 15 0.9157
5 19 0.8388	17 20 0.8681	18 25 0.9163

8	9	0.8390	15	17	0.8684	15	27	0.9182
10	27	0.8394	5	33	0.8693	10	31	0.9194
5	30	0.8399	**5**	**18**	**0.8696**	2	10	0.9212
19	21	0.8402	**4**	**5**	**0.8749**	15	30	0.9234
17	30	0.8412	17	28	0.8752	9	15	0.9279
1	10	0.8417	10	30	0.8765	20	25	0.9300
10	13	0.8417	5	9	0.8765	10	24	0.9328
3	**13**	**0.8423**	2	15	0.8768	15	26	0.9414
3	15	0.8433	7	25	0.8774	15	28	0.9428
3	**19**	**0.8477**	3	33	0.8790	7	15	0.9448
5	**11**	**0.8478**	1	17	0.8791	1	15	0.9477
21	28	0.8481	17	19	0.8829	15	19	0.9489
5	13	0.8483	15	18	0.8842	4	15	0.9505
17	18	0.8486	10	23	0.8843	10	14	0.9648
21	30	0.8487	15	20	0.8855	**3**	**8**	**0.9661**
10	28	0.8489	15	21	0.8885	**5**	**8**	**0.9763**
3	**22**	**0.8492**	15	32	0.8895			
3	**18**	**0.8503**	**5**	**7**	**0.8907**			

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1.2.3. For examination/comparison of M2AA, M2BB.

Summary of (essential) clusters and correlations for M2AA

1. **20 28 32** at least 0.89193

2. **13 16 22** at least 0.85278

3. **5 8** 0.89796

4. **2 3 4 7 11 14 18 19 23 26 27** at least 0.85681

Summary of (essential) clusters and correlations for M2BB

1. **3 5** 0.96758

2. **1 2 4 7 11 13 18 19 20 22 23 24 26 27 28 30 31 32 33** at least 0.87346

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1.2.4. Comments:

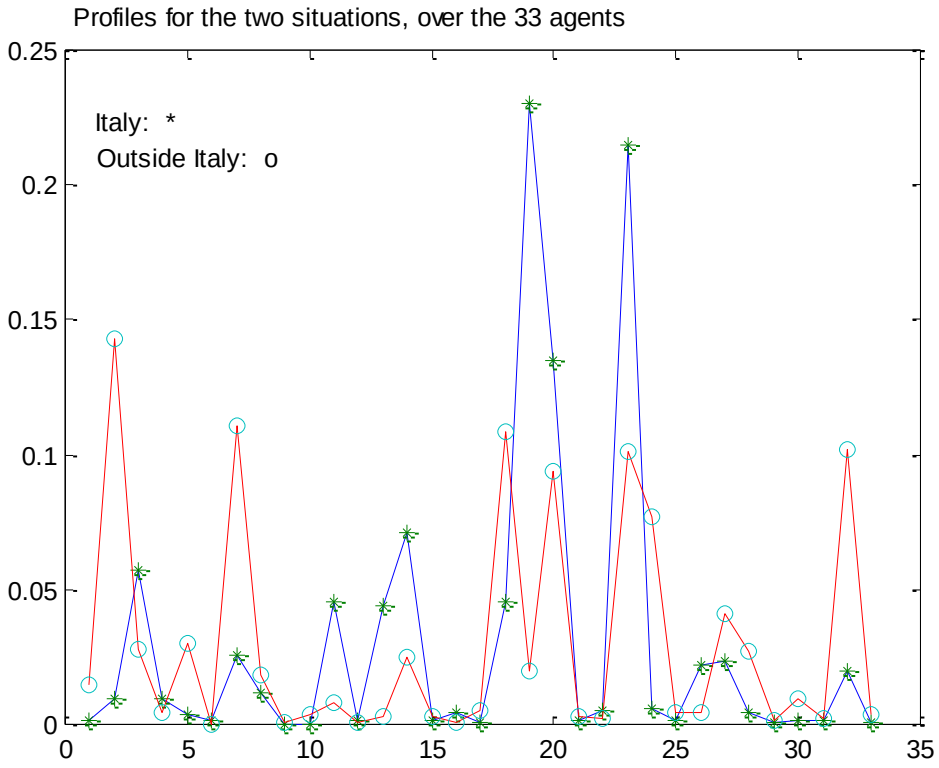
One would expect the cluster- and pairs of interest structure of M2BB to be superior to that of M2AA. We find this true, at least approximately.

a) The cluster 2 of M2BB contains all the 4 clusters of M2AA, except for agents 3, 5, 8 and 16.

b) Still, among the possibly of interest pairs of M2BB, there are the pairs (5 8), (3 4), (3 7), (3 11), (3 18) and (3 19). This reduces the missing pairs including 3, to (3 2), (3 14), (3 23), (3 26), and (3 27), which come in addition to missing pairs (13 16) and (16 22) containing 16.

c) We may mention here that the 11 possibly of interest pairs common to M2AA and M2BB, (3 8), (3 13), (3 20), (3 22), (3 28), (4 5), (5 7), (5 11), (5 18), (5 19), (7 8) have all at least one element in class V08CA.

FIGURE 3: Profiles for the two situations, over 33 agents.



d) If we would have chosen the descriptive statistics option in this case, we would reach the same conclusion: the picture in the case of Italy and that for the World outside Italy show similarity, but imperfectly.

3. Discussion

As in our earlier contributions in this series, no further comment is offered in this Section beside those provided at the conclusion of the analyses. We insist on the need for a better, objective upgrading of the definitions of the WHO-SOCD aggregations into 30, 32 or a different number of groups, as well as on ATC sub-classes (and, in the latter case of related classes, too). In this work, contrast agents of the V08-A and –C classes for these indications have for the first time been associated and compared to biosimilars, originators and reference products (See [3]).

We feel that up-to-date modelling techniques should consistently be applied at the national, regional and central level to supplement and complete the pharmaco-toxicology vigilance data via feed-back monitoring, to add to our knowledge by performing at least complementary research, and to regulate practicalities of drug use and abuse. We hope that our effort will inspire other researchers to follow this approach. This appears to be a jointly identified area of opportunity and collaboration that contributes to represent the so-called third revolution in biomedical science, perhaps not yet cited included (See [4]), but we stress the need to promote effective global convergences.

Appendix Nr 1.

The complete data set files related to the matrices M2AA and M2BB are given. Data result from pooling the Appendices 1 of [1] and 3 of [2] and subtraction of those 33 products listed in the Appendix 6 of [2]. Processing with the Matlab software as in the case of the data reported in Appendix 7 in [2].

M2A (Italy)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
COD Preferred Name of SOCD-SADRs	Adipiodone meglumine (V08AC)	Amidotrizoic acid (V08AA)	Gadobenic acid (V08CA)	Gadobutrol (V08CA)	Gadodiamide (V08CA)	Gadofosveset (V08CA)	Gadopentetic acid (V08CA)	Gadoteridol (V08CA)	Gadoxetic acid (V08CA)	Iobenzamic acid (V08AC)	Iobitridol (V08AB)	Iocetamic acid (V08AC)	Iodamide (V08AA)	Iodixanol (V08AB)	Iodoxamic acid (V08AC)	Ioglicic acid (V08AA)	Ioglycamic acid (V08AC)
100	2	18	78	12	8	2	36	16	1		71	2	39	142	1	3	
200			1								1						
300																	
410		1	16	3	1		6	5			16		4	12			
420																	
431			4	1	1		2	4			1	1		4			
432														1			
433							2							1			
500		1	1				1				1		1				
600	1	6	61	8		2	17	6		1	18		59	27		7	1
700			2											1			
800																	
900																	
1010		3	17	1			7	2			10		23	16	2	3	
1020											2			2			
1030			7				4				7		7	7		1	
1040		1	5	2			3	1			4	1	1	14			
1100	2	6	32	9	3	1	18	13			30		41	39	2	2	1
1210																	
1220																	
1230																	
1300			4	1			1	2			2	1		10		1	
1410																	
1420																	
1500																	
1600																	
1700																	
1810		6	23	5	2		14	3			37		17	39		2	2
1820			2				2				1		2	2			
1830																	
Total	**5**	**42**	**253**	**42**	**15**	**5**	**113**	**52**	**1**	**1**	**201**	**5**	**194**	**317**	**5**	**19**	**4**

	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	
COD Preferred Name of SOCD-SADRs	Iohexol (V08AB)	Iomeprol (V08AB)	Iopamidol (V08AB)	Iopanoic acid (V08AC)	Iopentol (V08AB)	Iopromide (V08AB)	Iotalamic acid (V08AA)	Iotrolan (V08AB)	Iotroxic acid (V08AC)	Ioversol (V08AB)	Ioxaglate meglumine/Ioxaglate sodium (V08AB)	Ioxaglic acid (V08AB)	Ioxitalamate meg/Ioxitalamate sodium (V08AA)	Ioxitalamic acid (V08AA)	Meg. amidotrizoate/Na amidotrizoate (V08AA)	Metrizoic acid (V08AA)	Total
100	71	437	136	1	3	407	4	2	36	53	6	1		2	19		**1609**
200		3	2														**7**
300																	
410	8	49	91	1	3	37	2	2	4	1	2		1		4		**269**
420																	
431	4	6	5			9				4					1		**47**
432		2	1														**4**
433																	**3**
500	3	7	9		1	6				1					2		**34**
600	23	106	95	3	8	82	2		20	14	5		1		9		**582**
700		1				3											**7**
800			1			1											**2**
900						1											**1**
1010	7	48	37		2	72	4		7	4	3				10	1	**279**
1020		3	1														**8**
1030	9	18	19		1	31	2		4	3					4		**124**
1040	4	27	21			26	2	1	1	8					3		**125**
1100	45	153	91		1	132	6		16	10	3	1	2	2	19		**680**
1210																	
1220		1				1											**2**
1230	1	1	4			1				2							**9**
1300	2	15	3		1	30		1							2		**76**
1410																	
1420																	
1500																	
1600																	
1700																	
1810	24	132	81	1	4	102	5		9	4	2		1	1	14		**530**
1820	1	10	3			11				1						2	**37**
1830		1															**1**
Total	**202**	**1020**	**600**	**6**	**24**	**952**	**27**	**6**	**97**	**105**	**21**	**2**	**5**	**5**	**87**	**3**	**4436**

M2B (Rest of the World)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
COD Preferred Name of SOCD-SADRs	Adipiodone meglumine (V08AC)	Amidotrizoic acid (V08AA)	Gadobenic acid (V08CA)	Gadobutrol (V08CA)	Gadodiamide (V08CA)	Gadofosveset (V08CA)	Gadopentetic acid (V08CA)	Gadoteridol (V08CA)	Gadoxetic acid (V08CA)	Iobenzamic acid (V08AC)	Iobitridol (V08AB)	Iocetamic acid (V08AC)	Iodamide (V08AA)	Iodixanol (V08AB)	Iodoxamic acid (V08AC)	Ioglicic acid (V08AA)	Ioglycamic acid (V08AC)
100	785	9478	784	177	1065	3	4144	488	19	373	430	115	174	1910	107	14	121
200	7	44	191	6	330		402	166		1	1		1	18		1	3
300					10		4										
410	190	1448	514	88	592	10	2082	379	8	29	89	5	48	240	22	7	63
420																	
431	29	377	49	9	42	2	327	24	1		12	2	7	47	4	6	9
432	3	21	1	3	6		26	2		1	2			2	2		
433	1	14	16	3	39		99	2	1		4		1	2			1
500	44	283	598	9	735		1110	585	3	4	36		6	46	11	1	12
600	430	3000	731	121	419	4	2870	211	12	48	156	19	63	302	124	24	97
700	7	10	4	1	25		36	4	2	1	2			3			18
800		41	14	3	39		94	12			6	1		26			2
900		7	1		7		9	1			1			2			1
1010	264	1207	132	42	79	5	599	113	2	25	81	2	36	173	36	17	143
1020	8	61	10	3	25	2	52	9	2		6		1	28	2	1	5
1030	83	814	72	21	56	5	418	48	4	4	51		14	125	22	7	55
1040	59	877	43	26	72	3	637	23	3	13	22	1	5	139	15	8	15
1100	312	3949	382	102	261	13	2733	230	15	19	208	8	86	342	81	21	100
1210		7		1	25		18	1						3			
1220		17	3	2	3		29	2			3	1		15			
1230	4	65	12	2	21		50	8		2	6	6		20			1
1300	56	1029	53	18	77	1	529	34	1	53	55	7	6	302	11	4	17
1410		1	2		2		2	1									
1420	1	11		1	3		5	1						1			
1500		2	1		2		11	2									
1600					1		1	1									
1700		6	51		85		84	46						3	1		
1810	424	2816	1376	155	1268	9	3047	935	20	46	246	21	105	716	82	34	207
1820	9	354	38	2	28	1	549	3	4	1	10		1	22	2	1	4
1830		17	50		102		122	45			1			11			
Total	**2716**	**25956**	**5128**	**795**	**5419**	**58**	**20089**	**3376**	**97**	**620**	**1428**	**188**	**554**	**4498**	**522**	**146**	**874**

	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	
COD Preferred Name of SOCD-SADRs	Iohexol (V08AB)	Iomeprol (V08AB)	Iopamidol (V08AB)	Iopanoic acid (V08AC)	Iopentol (V08AB)	Iopromide (V08AB)	Iotalamic acid (V08AA)	Iotrolan (V08AB)	Iotroxic acid (V08AC)	Ioversol (V08AB)	Ioxaglate meglumine/Ioxaglate sodium (V08AB)	Ioxaglic acid (V08AB)	Ioxitalamate meg/Ioxitalamate sodium (V08AA)	Ioxitalamic acid (V08AA)	Meg. amidotrizoate/Na amidotrizoate (V08AA)	Metrizoic acid (V08AA)	Total
100	5148	985	3670	151	109	5916	5666	173	237	2094	1383	49	599	161	6382	210	**53120**
200	105	4	121	1	1	23	55	2	2	14	17		4	2	32		**1554**
300	1					1		1							2		**19**
410	2671	224	2646	23	34	1160	803	197	56	477	276	21	97	19	1114	20	**15652**
420	1																**1**
431	291	45	293	3	5	245	226	11	10	130	54	2	6	7	222	8	**2505**
432	52	7	49	1		16	11	7	2	7	4		3		15	3	**246**
433	46	6	21		2	51	4	1		23	1		1		9		**348**
500	437	71	533	6	8	291	165	52	7	140	89	8	24	3	197	11	**5525**
600	1844	498	1626	174	39	1903	1170	77	122	826	680	36	258	75	2025	84	**20068**
700	45	7	21	8		16	11	2		7	10	2	4		18	1	**265**
800	93	14	82	4	2	76	14	3		45	14	2	2	2	20		**611**
900	30	7	9		1	8	1		1	3	6				10	2	**107**
1010	918	275	990	7	34	1104	541	37	67	382	381	16	104	25	1246	17	**9100**
1020	101	28	103		1	76	22		1	31	31	1	2		66	1	**679**
1030	662	130	640	4	13	644	297	8	18	415	212	7	49	12	838	21	**5769**
1040	544	108	479	5	7	786	422	18	15	202	121	1	37	3	549	15	**5273**
1100	2405	472	2443	14	63	2796	2363	54	97	1297	602	28	219	40	2389	98	**24242**
1210	7	1	15			11	2	1		5	7			2	8	1	**115**
1220	43	1	32	1	1	12	10	2		7	7	1			14		**206**
1230	88	14	91	2	1	15	44	5	2	26	31		3	3	45	3	**570**
1300	777	107	547	29	12	597	454	35	15	306	226	7	38	3	613	11	**6030**
1410															1		**9**
1420	4	2	2			4	1			1	2						**39**
1500	1		1		1	2				3			1		2		**29**
1600	1		2														**6**
1700	6		2												1		**285**
1810	3011	582	2458	45	72	2582	1494	75	115	903	779	47	330	53	2529	180	**26762**
1820	269	7	182		3	88	237	2	3	117	7	1	12	2	140		**2099**
1830	69	2	32		1	12	13	4		4	6	2		1	16		**510**
Total	**19670**	**3597**	**17090**	**478**	**410**	**18435**	**14026**	**767**	**770**	**7465**	**4946**	**231**	**1793**	**413**	**18503**	**686**	**181744**

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CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product.

Thus the sources of reports accepted by National Centres vary, as do the proportions.

A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO data base.

Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i) of the source of the information,

(ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,

(iii) that the information does not represent the opinion of the World Health Organization.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

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[1] Bradu D, Rossini L. 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). Pharmacologyonline Newsletter 3:728-781(2010).

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[3] Bradu D, Rossini L. Biosimilar branded iodinated contrast agents related to the largest number of reports to the WHO-Pharmacovigilance system over the first 40 years of the Programme. Fifth WHO-ITA/ITA-OMS 2010-2011 contribution. Pharmacologyonline Newsletter 2:submitted as nr 78(2011).

[4] Sharp PA, Langer R. Promoting convergence in biomedical science, Science PolicyForum 333:527(2011).