

Summary Report for Importation of Unlicensed Medicines

01 Jul 2008 – 30 Sep 2008

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PUBLIC DOMAIN DATA

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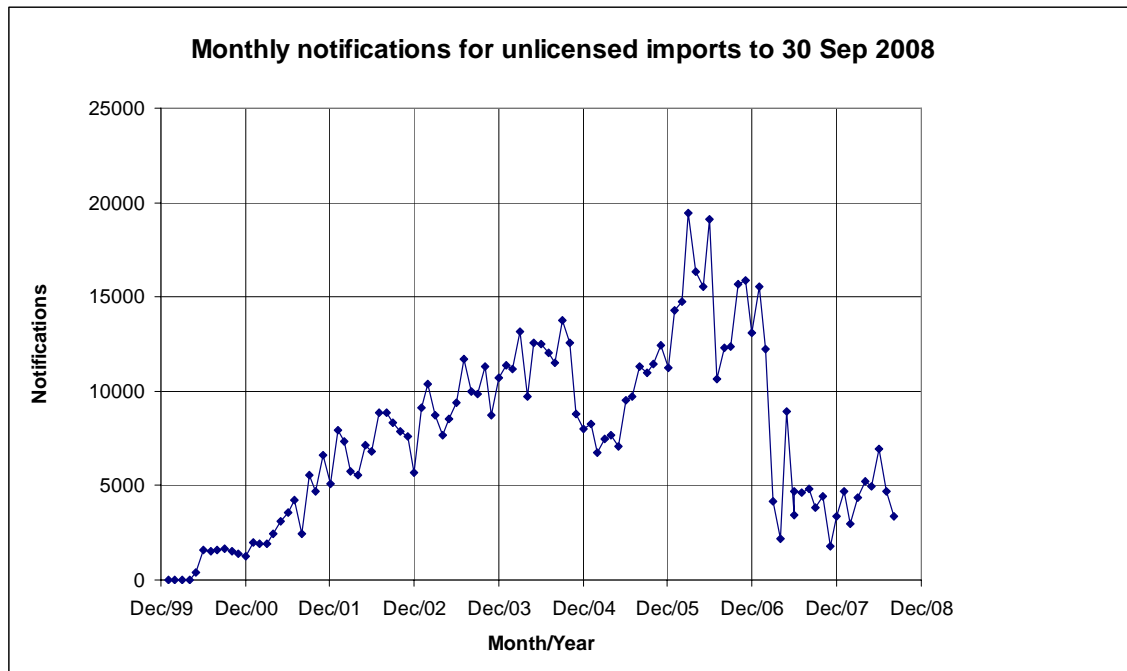
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1 Introduction

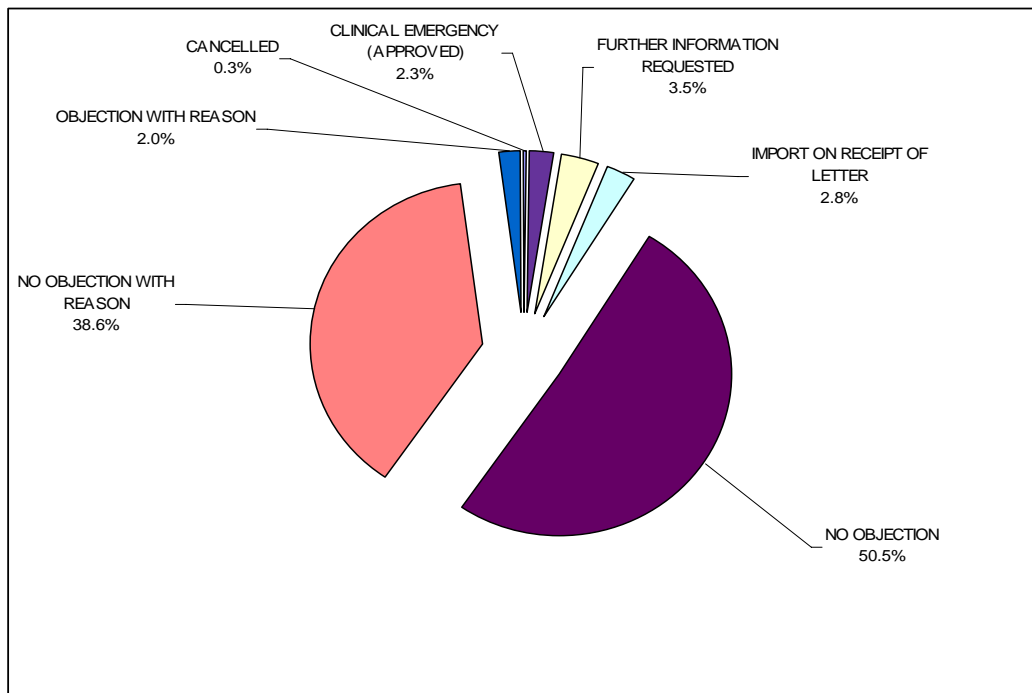
This report provides a review of the Import Notification System (INS) up to the end of September 2008.

2 Notifications for importation

Graph 1 Monthly notifications for unlicensed imports



Graph 2 Breakdown of notifications by status, 01 July – 30 Sep 2008



2.1 Countries of origin of products

Table 1 Breakdown of notifications by country

Rank	Exporting Country	Number of Notifications
1	Germany	3100
2	United States of America	2944
3	Norway	2431
4	France	1172
5	Italy	878
6	Spain	764
7	Sweden	693
8	Austria	471
9	Canada	453
10	Switzerland	410
11	Denmark	342
12	India (Mainly SII Monocomponent Measles and Rubella; also 4 Tresivac SII MMR which attracted Objections due to UK equivalent product)	296
13	The Netherlands	281
14	Belgium	267
15	Australia	203
16	Poland	114
17	Republic of Ireland	75
18	Hungary	40
19	Japan	26
20	New Zealand	9
21	China (Artemether 50 mg only)	8
22	Portugal	7
23	Finland	5
24	Brazil	4
25	British Isles (Incorrectly Notified)	4
26	Greece	3
27	Philippines	1
28	Puerto Rico	1
29	South Africa	1
30	Thailand	1

2.2 Most frequently notified products

Table 2 lists the 50 most frequently notified products in rank order.

Considering the top 10 of these products:

1. Melatonin products. These are used for attention deficit hyperactivity disorder, sleep disturbances and treatment of jet lag. Melatonin products are regarded as supplements in the USA and may not meet normal pharmaceutical standards of GMP. Appropriate warnings to this effect have been issued in non-objection letters. There has recently been a licensed modified release product launched in

the UK and this has led to some changes in the status of melatonin as an imported product. See below for more details.

2. Dicloxacillin 1g Powder For Infusion . No licensed equivalent product available in UK.
3. Co-Proxamol Tabs 325mg/32.5mg. Following cancellation of UK Co-proxamol licences at the end of 2007, there are some prescribers who continue to need this product where no licensed alternative can be found.
4. Benzylpenicillin Powder For Solution, All Doses. No licensed equivalent product available in UK.
5. Acetylcysteine Oral Preparations. These are products with no UK licensed equivalents.
6. Vitamins (Oral & Topical). Vitamin Oral & Topical Preparations. Many of these are probably “lifestyle” products and used as general supplements or for skincare. It is almost impossible to check whether there are UK equivalents.
7. Trabectedin Powder For Infusion, All Doses. No licensed equivalent product available in UK.
8. Cefotaxim Powder For Solution For Injection 1& 2g. Import for supply elsewhere in EU (there is an equivalent UK licensed product).
9. Allergy Patch/Prick Tests. There are a large number of specific patch tests that have no UK licensed equivalents. Where there are licensed UK equivalents, specialists frequently argue that for reasons of standardisation and clinical comparability it is necessary to use the same brand products for all tests
10. Monocomponent Measles Vaccines. These continue to be in demand in the wake of the controversy surrounding MMR and autism. Although the quantities notified have generally reduced along with those for mumps and rubella, there was a significant increase in notifications in Q3 2008.

Table 2. Top 50 Products by rank order of number of notifications received (by calendar quarter)

Note: These rankings were obtained manually and although believed to be representative may contain errors

Rank	Q3 2007		Q4 2007		Q1 2008		Q2 2008		Q3 2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
1	Melatonin Products, All Strengths and Presentations ³	3331	Melatonin Products, All Strengths and Presentations ⁶	1118	Melatonin Products, All Strengths and Presentations	1773	Melatonin Products, All Strengths and Presentations	2271	Melatonin Products, All Strengths and Presentations	763
2	Patent Blue V 2.5% Solution	456	Co-Proxamol Tabs 325 mg/32.5 mg and Capsules 400 mg/30 mg ⁴	554	Acetylcysteine Oral Preparations	843	Patent Blue V 2.5% Solution	1237	Dicloxacillin 1g Powder For Infusion	683
3	Topical/Oral Local Anaesthetics	399	Acetylcysteine Oral Preparations	551	Vitamins (Oral & Topical)	537	Vitamins (Oral & Topical)	777	Co-Proxamol Tabs 325mg/32.5 mg ⁴	648
4	Vitamin Oral and Topical Preparations	389	Fluorescein Sodium Injections	374	Sulphamethoxypyridazine 500 mg Tablets	391	Co-Proxamol Tabs 325 mg/32.5mg ⁴	622	Benzylpenicillin Powder For Solution, All Doses	614
5	Acetylcysteine Oral Preparations	318	Midodrine Tablets, All Doses	349	Allergy Prick/Patch Tests	333	Bisacodyl Enemas, All Doses	611	Acetylcysteine Oral Preparations	506
6	Allergy Prick/Patch Tests	316	Allergy Prick/Patch Tests	291	All Homoeopathic Products (Abnoba Viscum=174) ²	284	Monocomponent Mumps Vaccines	470	Vitamins (Oral & Topical)	447
7	Monocomponent Measles Vaccines	297	Vitamin Oral And Topical Preparations	291	Midodrine Tablets (All Doses)	254	Acetylcysteine Oral Preparations	444	Trabectedin Powder For Infusion, All Doses	437
8	Monocomponent Mumps Vaccines	254	Monocomponent Mumps Vaccines (Includes 71 Pavivac Notifications) ⁵	265	Etravirine 100mg Oral Tablets (F060)	237	Midodrine 2.5 & 5 mg Tablets	442	Cefotaxim Powder For Solution For Injection 1& 2 g	408
9	Idebenone Tablets 45 mg	250	Topical Local Anaesthetics	255	Patent Blue V 2.5% Solution	208	All Homoeopathic Products (Abnoba Viscum=142) ²	339	Allergy Patch/Prick Tests	384
10	Homoeopathic Abnoba Viscum (Mistletoe) Preparations ²	242	All Homoeopathic Preparations (Abnoba Viscum = 192) ²	230	Sulfadoxine + Pyrimethamine 500 mg + 25 mg Tablets	198	Allergy Prick/Patch Tests	263	Monocomponent Measles Vaccines	361
11	Sodium Nitroprusside 50 mg Injection	236	Progesterone Creams	209	Idebenone 45 mg Tablets	187	Thyroid Oral Preparations	213	All Homoeopathic Products (Abnoba Viscum=146) ²	300
12	Midodrine Hydrochloride Tablets, All Doses	212	Provocholine/ Methacholine preparations	193	Progesterone Creams ("Natural")	181	Progesterone Creams ("Natural")	200	Cefuroxim Powder For Inj All Doses	288
13	Progesterone	209	Triamcinalone Injections	189	Glycopyrronium	149	Monocomponent Measles	191	Midodrine Tablets All	243

Rank	Q3 2007		Q4 2007		Q1 2008		Q2 2008		Q3 2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
	Creams/Gels, All Strengths				Bromide/Glycopyrrolate Tablets All Doses		Vaccines		Doses	
14	Iron Injections	201	<i>Saccharomyces boulardii</i> Capsules 250 mg	182	Labetalol 5mg/ml Injections	149	Labetalol 5 mg/ml Injection Soln	184	Labetalol 5mg/MI Injection Soln 1 X 20 MI	220
15	Glycopyrrolate Oral Preparations, All Doses	191	Monocomponent Rubella Vaccines	174	Bisacodyl Enemas & Suppositories	145	Idebenone 45 mg Tablets	183	Bisacodyl Enemas 10mg/30ml	216
16	Glycopyrrolate Parenteral Preparations, All Doses	182	Fumaric Acid Tablets, All Doses	167	Monocomponent Mumps Vaccines (Includes 32 Pavivac Notifications) ⁵	139	Sulphamethoxypyridazine 500 mg Tablets	181	Lidocaine Topical Preparations (Solutions, Patches, Gels, Sprays)	202
17	Parenteral Local Anaesthetics	174	Glycopyrrolate Bromide Oral Preparations	162	Decitabine 50 mg Injection	132	Glycopyrrolate Bromide/Glycopyrrolate Tablets All Doses	155	Idebenone 45mg Tablets	190
18	Monocomponent Rubella Vaccines	173	Glycopyrrolate Bromide (Incl with Neostigmine) Injections	139	Monocomponent Rubella Vaccines	127	Fumaric Acid Tablets All Doses	146	Monocomponent Rubella Vaccines	190
19	Barium Sulfate Preparations (imaging agents)	157	Gastrozepin 50mg Tablets	125	Lidocaine Gel & Transdermal Patches	123	Hydroxyzine Hydrochloride Tablets 10 & 25 mg	145	Fumaric Acid Tablets, All Doses	185
20	Fumaric Acid Esters Tablets, All Doses	147	Hydroquinone Creams (Incl With Retinoin And Other Ingredients) Cream All Strengths	124	Monocomponent Measles Vaccines	121	Lidocaine Topicals (Incl Gel & Transdermal Patches)	135	Glycopyrrolate Tabs, All Doses	183
21	Insulins, All Types And Doses	132	Idebenone 45mg Tablets	118	<i>Saccharomyces boulardii</i> 250 mg Capsules & Sachets	115	Rifaximin Tablets 200 mg	119	Sodium Chloride 0.9% W/V Soln For Infusion	179
22	Mechlorethamine Hydrochloride 10 mg Injection	122	Monocomponent Measles Vaccines	112	Ubidecarenone 50 mg Caps	111	Pyrazinamide Tablets 500 mg	117	Thyroid Oral Preparations	152
23	Thyroid Oral Preparations	118	Benzathine Penicillin Injections	104	Barium Sulphate Ph Eur Oral Preparations	104	Monocomponent Rubella Virus Vaccines	103	Meropenem Trihydrate 1g Powder For Solution For Infusion	137
24	Fosfomycin Preparations, All Doses And Routes Of Admin	107	Nonoxynol 9 Contraceptive Films & Foams	104	Thyroid Oral Preparations	98	Benzathine Penicillin Injections, All Doses	102	Dexamethasone Sodium Phosphate Injections, All Doses	132

Rank	Q3 2007		Q4 2007		Q1 2008		Q2 2008		Q3 2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
25	Pyrazinamide 500 mg Tablets	101	Patent Blue V 2.5% Solution	103	Pyrazinamide Tablets 500 mg	93	Benzbromarone Tablets 100 mg	101	Certolizumab Pegol 200mg/MI	130
26	Hydroquinone Topical Preparations Incl. With Tretinoin, Hydrocortisone And Other Ingredients (These Are Not Included Under Vitamin Preps)	100	Acetazolamide Injection 500 mg	101	Clindamycin Suspension 75 mg/5 ml	90	Ubidecarenone 50 mg Caps	100	Pyrazinamide Tablets 500 Mg	128
27	Sodium Cromoglicate Inhalation Preparations	96	Labetalol 5 mg/MI Injections	84	Betamethasone Injections	85	Probenicid 500 mg Tabs	97	Ferucarbotran 756mg In 1.4ml	123
28	Cefradine 500 mg & 1 G Injections	94	Stanozolol Tablets 2 mg	82	Acetazolamide Parenterals	83	Etravirine 100 mg Oral Tablets	79	Progesterone Creams ("Natural") All Strengths	116
29	Sulphamethoxypyridazine 500 mg Tablets	82	Benzbromarone 50 & 100 mg Tablets	70	Thalidomide 50 & 100 mg Tablets	83	Trabectedin Infusions, All Strengths	78	Sultiame Tablets 50 & 200 Mg	114
30	Acetazolamide Sodium 500 mg Injections	72	Etravirine 100mg Oral Tablets (F060)	70	Povidone Iodine Preparations, All Topical Routes Of Administration	74	Sodium Cromoglicate 2% 0.5 ml Eye Drops Single Dose Unit	70	Rifaximin Tablets 200 Mg	107
31	Chloramphenicol Ophthalmic Preparations	70	Phenylbutazone 100 & 200 mg Tablets	69	Hydroquinone Creams (Incl With Retinoin and Other Ingredients) All Strengths	74	Methylnaltrexone Bromide 20 mg/ml Injection	70	Benzbromarone Tablets 100 Mg	98
32	Gemtuzumab Ozogamicin Injections	67	Prochlorperazine Suppositories	69	Phenylbutazone 100 & 200 mg Tablets	64	Clenbuterol 0.059 mg Oral Liquid	68	Etravirine 100mg Tablets	95
33	Bisacodyl Enemas	67	Pristinamycin Tablets 500 mg	62	Streptozocin Powder For Injection	62	Hydroquinone Creams (Incl With Retinoin and Other Ingredients) All Strengths	67	Bupivacaine With Adrenaline Injections	80
34	Indometacin Sodium 1 mg Pow/Sol For Inj	66	Nystatin Tablets & Vaginal Tablets	61	Fumaric Acid 30 & 120 mg Tablets	60	Povidone-Iodine Eye Soln 5% 30 ml Single Use	61	Hydroquinone Creams Including With Tretinoin, Hydrocortisone Etc.	77
35	Benzbromarone 100 mg Tablets	66	Pyrazinamide 500mg Tabs	60	Certolizumab Pegol Reconstituted In Vial To 200 mg/MI	59	Iron (III) -Hexacyanoferrate (II) 500 mg Capsules	60	Biperiden 2mg Tabs	74
36	Nonoxynol 9 Foams And Films	64	Certolizumab Pegol 200mg/ml	59	Sodium Chloride Ophthalmic 5% Ointments	55	Sodium Nitroprusside 50 mg Injection	58	Benzathine Benzylpenicillin Powder For Injection All Doses	72

Rank	Q3 2007		Q4 2007		Q1 2008		Q2 2008		Q3 2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
37	Vitamin Injections	61	Rifaximin Tablets 200 mg	59	Benzathine Penicillin Injections	54	All Insulins	55	Indigo Carmine Injection 20mg/5ml (0.4%)	71
38	Etravirine 100 mg Oral Tablets	60	Thyroid Oral Preparations	57	Defibrotide 200 & 400 mg Capsules	54	Sultiame Tablets 50 mg	52	Ubidecarenone 50mg Caps	70
39	Prochlorperazine Suppositories, All Strengths	58	Betamethasone Parenterals	56	Isoprenaline 200 mcg/ml Inj	48	Tuberculin Purified Protein Derivative 5 IU/0.1 ml Lyophilized	51	Tetanus Immunoglobulins/Toxoid	69
40	Benzathine Penicillin Injections, All Strengths	57	Local Anaesthetic Injections	56	Vitamins (Parenteral)	48	Glycopyrronium Bromide + Neostigmine Methylsulphate 0.5 mg + 2.5 mg/ml Inj	48	Pirenzepine 50mg Tablets	67
41	Triamcinolone Hexacetonide Injections, All Strengths	57	Megestrol Acetate Tablets, All Doses	56	Oxytetracycline Hydrochloride + Hydrocortisone Ophthalmic Preparations	47	Flunitrazepam 1 mg Tablets	48	Nitrofurazone Dressings And Ointments	65
42	Etilefrine Oral Preparations	56	Bisacodyl Enemas 10 mg/30 ml	54	Gastrozepin 50mg Tablets	43	Polidocanol/Lauromacrogol Intravenous Injections All Strengths	46	Carmustine Injections All Doses	64
43	Urokinase Injections, All Doses ¹	53	Sodium Chloride Parenterals, Incl With Additives	54	Benzbromarone Tablets 100 mg	41	Pirenzepine 50 mg Tablets	44	Bethanechol Chloride Tablets 10 & 25mg	60
44	Hydroxyprogesterone Caproate 250 mg Injections	49	Etonogestrel + Ethinylestradiol Vaginal Rings	51	Sargramostim Lyophilized 250 mcg Injection	41	Indigo Carmine Injections	42	Hydroxyzine Hydrochloride Tablets All Doses	59
45	Iloprost Trometamol Injections & Infusions	48	Loxapine 25, 50 & 100 mg tablets	46	Betamethasone Sodium Phosphate 0.1% Drops	40	Decitabine 50 mg Injection	42	Betamethasone 4mg/ml Injection	58
46	Promazine Hydrochloride Tablets, All Doses	45	Lauromacrogol 400 (Polidocanol) Injections	45	Stanozolol 2 mg Tablets	40	Invalid Notifications	41	Iloprost Injection 50 Mcg	58
47	Nefazodone Tablets, All Doses	42	Sodium Cromoglicate Inhalers, Eye drops, Nebulisers	43	Iron (III) -Hexacyanoferrate (II) 500 mg Capsules	37	Dydrogesterone 10 mg Tabs	41	Thioridazine Oral Preparations	54
48	Flucytosine Tablets 500 mg	42	Stiripentol Oral Preparations	43	Rifaximin Tablets 200 mg	37	Procaine Penicillin Injections 1, 200, 000 U/ml	40	Azacididine Lyophilised Powder	53
49	Heparin Calcium Injections	41	Thioridazine Oral	42	Lauromacrogol 400	36	Ferucarbotran 756mg in	40	Trimetazine 20mg Tablets	53

Rank	Q3 2007		Q4 2007		Q1 2008		Q2 2008		Q3 2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
	(All Strengths)		Preparations		(Polidocanol) Injection Solutions		1.4ml			
50	Thioridazine Oral Preparations	41	Albendazole Tablets 400 mg	41	Gabapentin Oral Solution 250 mg/5 ml	35	Pancuronium Bromide Injections All Strengths	38	Ampicillin Injections All Strengths	52

Notes:

1. UK licensed Urokinase available from 8th Dec 2006, but unlicensed dosages are still being notified
2. Total homoeopathic notifications for Q3, 2007=278 (rank=6). Abnoba viscum products are used for supportive therapy in cancer. Cautionary letter to importers draws attention to ethical issues.
3. The increase in Melatonin notifications in Q3 2007 was largely due to a single importer.
4. Co-Proxamol licences were withdrawn in the UK at the end of 2007.
5. Notifications for Pavivac mumps vaccine attract objections to import in accordance with CSM/CHM advice

2.3 Vaccines

It may be noted that for vaccines, where any second administration is more than 3 months after the first, the maximum quantity permitted per notification is 25 unit doses.

Table 3 gives a summary of vaccine notifications for Q3/2007 to Q3/2008.

Table 3 Vaccines/Immunoglobulins notified by rank order of number of notifications by Calendar Quarter

Rank	Quarter 3/2007		Quarter 4/2007		Quarter 1/2008		Quarter 2/2008		Quarter 3/2008	
	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
1	Monocomponent Measles Vaccines	297	Monocomponent Mumps Vaccines (Includes 71 Pavivac Notifications ¹)	265	Monocomponent Mumps Vaccines (Includes 32 Pavivac Notifications) ¹	139	Monocomponent Mumps Vaccines	470	Monocomponent Measles Vaccines	364
2	Monocomponent Mumps Vaccines	254	Monocomponent Rubella Vaccines	174	Monocomponent Rubella Vaccines	127	Monocomponent Measles Vaccines	191	Monocomponent Rubella Vaccines	192
3	Monocomponent Rubella Vaccines	173	Monocomponent Measles Vaccines	112	Monocomponent Measles Vaccines	121	Monocomponent Rubella Vaccines	103	Tetanus Vaccine	36
4	Diphtheria, Tetanus, Pertussis	21	Tetanus Toxoid Vaccine Adsorbed	18	Tuberculin Purified Protein Derivative	21	Tuberculin Purified Protein Derivative	51	Inactivated Polio Vaccine	33
5	BCG Bacillus Calmette-Guerin	20	Tuberculin Purified Protein Derivative	13	Diphtheria and Tetanus Combined Vaccine	16	Tetanus (Adsorbed) Vaccines	26	Tetanus Immunoglobulin 250iu Injection	31
6	Diphtheria And Tetanus Vaccine	15	Haemophilus Influenzae Type B	11	Tetanus (Adsorbed) Vaccines	15	Tetanus Immunoglobulin	21	Diphtheria And Tetanus Vaccines	25
7	Typhoid Vaccine (Live Oral Strain TY21A)	12	Human Normal Immunoglobulins	9	Rabbit Anti-Human Thymocyte Immunoglobulin	8	Diphtheria/tetanus/polio single dose vaccines	18	Diphtheria Vaccine	18
8	Equine Antihuman Thymocyte Immunoglobulin (Lymphoglobulin)	8	Inactivated Poliomyelitis Vaccine	9	Technetium (Tc99m) Polyclonal Human Immunoglobulin G Injection	6	Diphtheria tetanus & pertussis combined vaccine single dose	8	Human Normal Immunoglobulin	9
9	Rabbit Anti-Human Thymocyte Immunoglobulin	8	Rotavirus Vaccine (Rotateq Solution Live Oral Pentavalent Vaccine)	8	Hepatitis B Immunoglobulin	5	Immunoglobulin infusions	8	Monocomponent Mumps Vaccine (Jeryl Lynn Strain)	7
10	Tetanus Immunoglobulin	8	Meningitis Vaccine	6	Inactivated Polio Vaccine	5	Human normal immunoglobulin intramuscular	5	Diphtheria And Tetanus Toxoids and Acellular Pertussis Vaccine	6
11	Tetanus Vaccine	8	Lymphocyte Immune Globulin Anti-Thymocyte	4	Tetanus Immunoglobulin	4	Polio inactivated vaccine	5	Tuberculin PPD	6
12	Hepatitis B Immunoglobulin	7	Technetium (Tc99m) Polyclonal Human Immunoglobulin G	4	Bacillus Calmette Guerin	3	Haemophilus influenzae Type B	4	Tick-Borne Encephalitis Vaccine	5

	Quarter 3/2007		Quarter 4/2007		Quarter 1/2008		Quarter 2/2008		Quarter 3/2008	
Rank	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
			Injection							
13	Anti D Immunoglobulin Human	4	Tetanus Immunoglobulin	4	Haemophilus Influenzae Type B	3	Varicella virus vaccine, live, attenuated	4	Measles, Mumps And Rubella Virus Vaccine Live U.S.P (Lyophilised)	4
14	Diphtheria, Tetanus, Polio	4	Equine Antihuman Thymocyte Immunoglobulin	2	Diphtheria Toxin II3 Fusion Protein	2	Meningococcal polysaccharide-diphtheria toxoid conjugate group	3	Meningococcal Polysaccharide-Diphtheria Toxoid Conjugate Group	4
15	Diphtheria, Tetanus, Pertussis And Polio	3	Typhoid Vaccine (Live Oral Strain TY21A, Enteric Capsule)	2			Technetium (Tc99m) polyclonal human immunoglobulin g injection	2	Haemophilus Influenzae Type B Vaccine	3
16	Haemophilus Influenzae Type B	3	Botulism Immune Globulin Intravenous	1			BCG vaccine	1	Rabies Vaccines	2
17	Technetium (Tc99m) Polyclonal Human Immunoglobulin G Injection	3	Cytomegalovirus Immune Globulin Human (CMV-IgIV)	1			Haemophilus B conjugate vaccine	1	Cytomegalovirus Immunoglobulin (Cytotect CP Biotest) Solution For Infusion 5%	1
18	Tuberculin PPD	2	Diphtheria And Tetanus Vaccine	1			Lyophilized rabies vaccine	1	Hepatitis B Vaccine (Recombinant DNA) Vaccine	1
19	Cholera Vaccine	1	Hepatitis B Immunoglobulin	1			Tick-borne encephalitis vaccine	1		
20	Hepatitis B Vaccine (Recombinant DNA)	1	BCG Bacillus Calmette-Guerin	1						
21	Immune Globulin Intravenous (Human) 10%	1								
22	Immunoglobulin A	1								
23	Influenza Vaccine (Inactivated)	1								
24	Polio Vaccine Inactivated	1								

	Quarter 3/2007		Quarter 4/2007		Quarter 1/2008		Quarter 2/2008		Quarter 3/2008	
Rank	Product	No.	Product	No.	Product	No.	Product	No.	Product	No.
25	Tick-Borne Encephalitis (Inactivated)	1								

Notes:

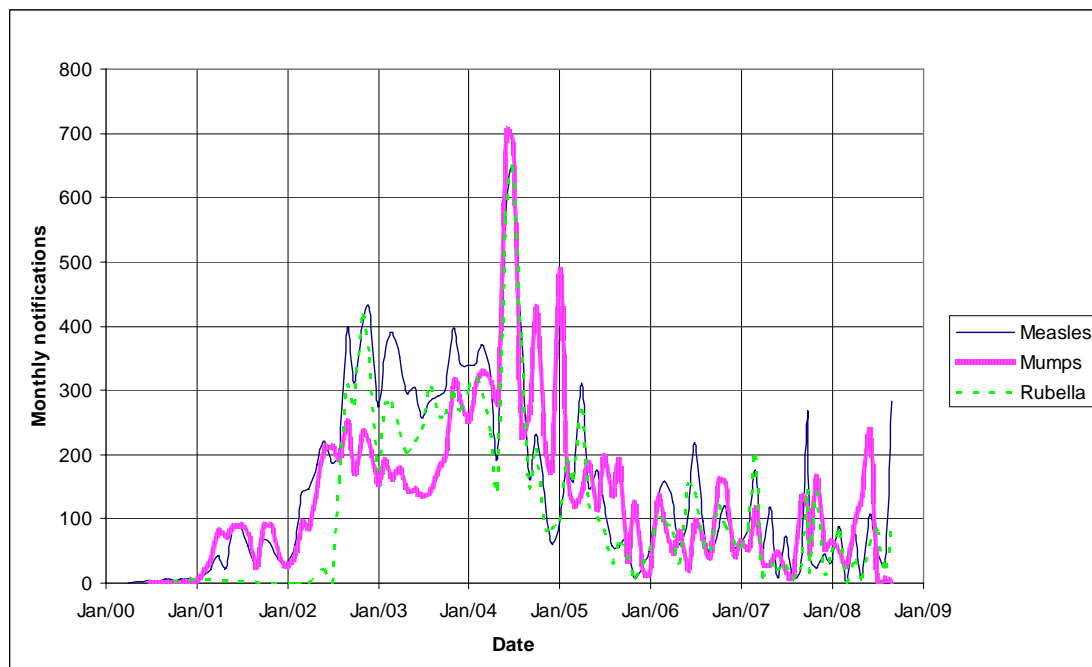
1. Pavivac mumps vaccines attract objections to import on CSM/CHM advice.

2.3.1 Measles, Mumps and Rubella Vaccines

Following public concern arising from alleged association between the use of the combined MMR vaccine and the incidence of autism in inoculated children, large numbers of notifications for importation of monocomponent vaccines were received. In February 2004 the purported link between MMR vaccination and autism was discredited in the media. Graph 3 reflects the evolution of the issue, and a broad decline in notifications may be noted, probably commencing in early 2004, although partially masked by a mid-2004 peak as noted in the footnote to Graph 3.

The number of notifications since Jan 2006 has been variable, with wide fluctuations. Recently, there appears to be a steep increase in monocomponent measles vaccine notifications, but very few notifications for mumps and little change for rubella.

Graph 3 Monthly notifications for monocomponent measles, mumps and rubella vaccines to end of September 2008



Note: The peak around June 2004 follows legal advice that the MHRA must accept multiple notifications for the same product in any one day. Previously, the MHRA had only accepted one notification per product per day.

Frequently, importers, concerned professionals and members of the public enquire about which monocomponent measles, mumps and rubella vaccines are acceptable for import and which are likely to meet objection to notifications for import. Table 4 provides a summary of these products. This list has been derived from the INS database and has been subject to manual consolidation. It is possible that the table may contain some errors resulting from this process.

As the table uses data back to the year 2000, names of products and manufacturers may no longer be current.

Table 4 Summary of import status of monocomponent and bi-component measles, mumps and rubella vaccines notified since 2000

Proprietary Name	Non-Proprietary Product Name	Manufacturer /Supplier Name	Exporting Country	Importation status & comments
MUMPS VACCINES				
Hoshino Strain (Chick Cell)	Mumps Vaccine	The Kitasato Institute	Japan	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Imovax Vaccine(Urabe AM-9 Strain)	Live Attenuated Mumps Vaccine (Urabe Am-9 Strain)	Pasteur Merieux Serums & Vaccines	France	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Imovax Vaccine (Live Attenuated Urabe Strain)	Live Attenuated Mumps Vaccine (Urabe Strain)	Pasteur Merieux Connaught	France	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Miyahara Strain Mumps Virus (Live Attenuated)	Mumps Vaccine	Kaketsuken Institute	Japan	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Mumps Vaccine Hoshino Strain	Attenuated Live Mumps Virus	Daiichi Pharmaceutical Company Limited	Japan	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Mumpsvox (Jeryl Lynn Strain)	Single Dose Mumps Virus Vaccine (Jeryl Lynn Strain)	All	Canada/EU/Switzerland/USA	No objection
Pavivac (Jeryl Lynn Strain) Injection Pwdr/Sol	Mumps Vaccine (Jeryl Lynn Strain)	Sevapharma	Czech Republic	Objection: Lack of assurance of quality and safety/ CSM advice
Pavivac (Jeryl Lynn Strain) Injection Pwdr/Sol	Mumps Vaccine (Jeryl Lynn Strain)	Sevapharma	Slovak Republic	Objection: Lack of assurance of quality and safety/ CSM advice
Single Dose Mumps L-Zagreb Strain	Mumps Vaccine L-Zagreb Strain	Institute Of Immunology Zagreb	Croatia	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
Vaxipar (Urabe Strain)	Mumps Vaccine (Urabe Strain)	Novartis Vaccines And Diagnostics Srl	Italy	Objection: Suspected higher risk of aseptic meningitis than Jeryl Lynn strain
MEASLES VACCINES				
Attenuvax (Enders Edmonston Strain)	Measles Vaccine Edmonston Strain	All	EU/Switzerland/USA	No objection
Masern-Impfstoff Merieux (Schwarz Strain)	Measles (Schwarz Strain)	All	EU	No objection
Measles AIK-C Strain Injection	Measles Vaccine (Live Attenuated)	Daiichi Pharmaceutical Company Limited	Japan	Outstanding further information request (2006)
Measles Vaccine	Measles Vaccine	Aventis Behring GmbH	Germany	No objection
Measles Vaccine	Measles Vaccine	Krebs GmbH	Germany	No objection
Measles Vaccine Edmonston-Zagreb Strain	Measles (Live) Edmonston-Zagreb Strain	Institute Of Immunology Zagreb	Croatia	Outstanding further information requests (2002)
Moraten Berna	Measles (Live) Edmonston-Zagreb Strain	Berna Biotech Limited	Switzerland	No objection
Moraten Berna Measles Vaccine	Measles Vaccine	Grapharma BV	Netherlands	No objection
Morbilvax Lyophilised Inj 1 Vial&Solv 1x0.5ml	Measles (Schwarz Strain)	All	EU/Switzerland	No objection
More Attenuated Enders' Strain Measles Vaccine	Measles Virus Vaccine Live	Merck & Co Inc	United States Of America	No objection
Moru-Viraten Injection 1x0.5ml Dose	Measles + Rubella	Berna	Canada	No objection
Movivac (Schwarz Strain) Lyophilized Vaccine 5x2	Measles Vaccine (Schwarz Strain)	Sevapharma	Czech Republic	Objection: Lack of assurance of safety/quality
M-Vac SII Measles (Live) Edmonston-	Measles (Live) Edmonston-	Serum Institute Of India Limited	India	No objection

Proprietary Name	Non-Proprietary Product Name	Manufacturer /Supplier Name	Exporting Country	Importation status & comments
Zagreb Strain	Zagreb Strain			
Rimevax 0.5ml Injection	0.5 MI Single Dose Measles Vaccine (Schwarz Strain 1000 Dicc50)	Smithkline Beecham	EU/Switzerland	No objection
Rouvax	Measles (Schwarz Strain)	Aventis Behring GmbH	EU/USA	No objection
RUBELLA VACCINES				
Ervevax Rubella Vaccine	Rubella (Wistar RA 27/3 Strain)	Smithkline Beecham	EU/Switzerland	No Objection
Gunevax Subcutaneous Injection	Rubella (Wistar RA 27/3 Strain)	Novartis Vaccines and Diagnostics SRL	EU	No Objection
Meruvax II Injection	Rubella (Wistar RA 27/3 Strain)	All	EU/Switzerland/ USA	No Objection
Moru-Viraten Injection	Measles + Rubella	Berna	Canada	No Objection
Roeteln Impstoff Merieux	Rubella (Wistar RA 27/3 Strain)	All	EU/Switzerland	No Objection
Rosovax Rubella Vaccine	Wistar RA 27/3 Strain	Nuovo Istituto Sieroterapico	Italy	No Objection
Rubeaten Berna	Rubella Vaccine	Berna Biotech Limited	EU/Switzerland/ USA	No Objection
Rubella Vaccine	Rubella Vaccine	Cofares	Spain	No Objection
Rubella Vaccine Takahashi Strain	Attenuated Live Bastard Measle	Daiichi Pharmaceutical Company Limited	Japan	Outstanding further information requests (2007)
Rubella Vaccine Wistar Ra 27/3	Rubella Vaccine (Wistar RA 27/3 Strain)	Institute Of Immunology Zagreb	Croatia	Outstanding requests for further information (2002)
Rubella Virus Vaccine (Takahashi Strain)	Rubella Takahashi Strain (Live)	Kaketsuken Institute	Japan	Objection on grounds of lack of assurance of quality & safety
Rubella Virus Vaccine (Takahashi Strain)	Rubella Takahashi Strain (Live)	The Kitasato Institute	Japan	Outstanding requests for further information (2006), but info provided to date would lead to objection on grounds of lack of assurance of quality & safety
Rubelleovac Rubella Vaccine	Rubella (Wistar RA 27/3 Strain)	Berna Biotech Limited	EU/Switzerland/ USA	No Objection
Rudivax	Rubella Virus Vaccine Live	Sanofi Pasteur MSD	EU/Switzerland/ USA	No Objection
R-Vac (R-Vax) SII Rubella	Rubella Vaccine (Live B.P.) Lyophilised	Serum Institute Of India Limited (SII)	India	No Objection
Vac Antirubeola SKF Injection	Rubella (Wistar RA 27/3 Strain)	Smithkline Beecham Sa	Spain	No Objection

2.4 Other products

2.4.1 Melatonin

Melatonin products are the most frequently notified category of unlicensed imports. At the beginning of June 2008, a licensed 2 mg modified release melatonin tablet, Circadin (Lundbeck), became available in the UK.

Historically, most imported melatonin products are non-pharmaceutical products from the United States of America, where melatonin products are classed as supplements, not medicines. These products may not be manufactured to the standards of Good Manufacturing Practice normal for pharmaceuticals.

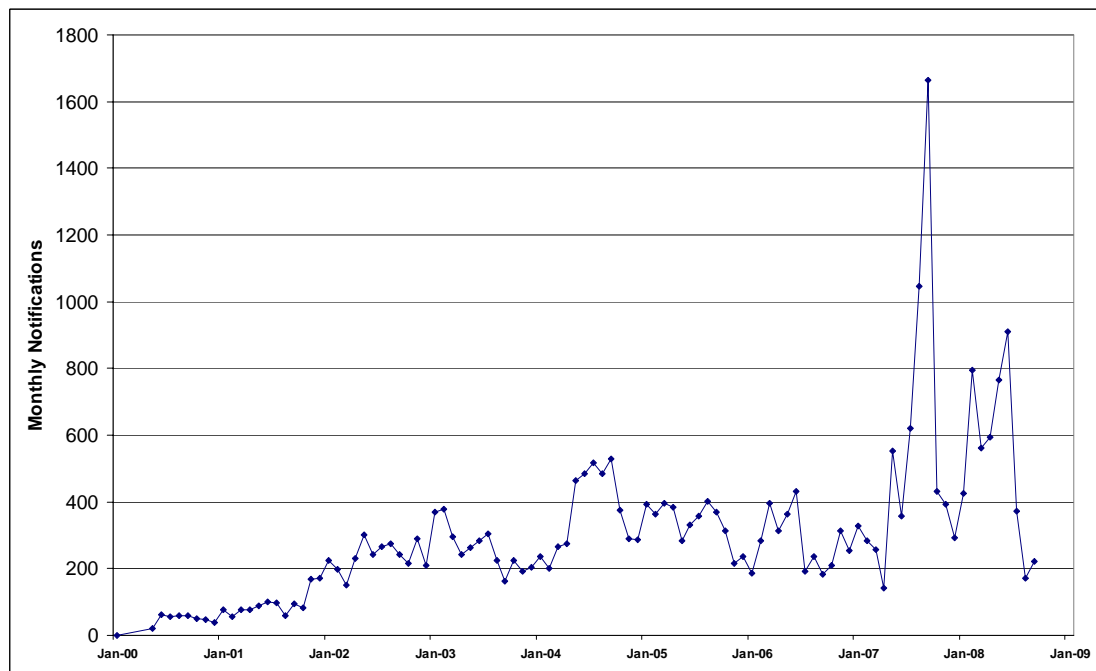
It is therefore important to ensure that the licensed product available in the UK is used wherever possible. It is recognised, however, that there may be individual patients for

whom the UK product cannot meet their clinical needs. In particular, there may be some need for alternative dosage forms, or strengths, or for an immediate release product.

A search conducted by MHRA Information Services confirmed that in addition to the licensed product available in the UK, there is also a licensed immediate release product available elsewhere in the European Union. This product is Bio-Melatonin 3 mg Tablets, licensed in Hungary and has been previously notified. No other products were identified.

Graph 4 shows the number of melatonin notifications monthly since 2000.

Graph 4 Monthly notifications for melatonin products



The decrease in notifications after June 2008 follows the introduction of Circadin and subsequent MHRA requests of importers for further information concerning the clinical needs for imported unlicensed melatonin products.

Tables 5 and 6 show melatonin notifications during Q2 & 3 2008 by product name and also generically.

Table 5 Melatonin Products Notified in Q2 & 3 2008 (Ranked by Q3 2008)

Product Name	Manufacturer Name	Country	Number Of Notifications	
			Q2/2008	Q3/2008
Melatonin Capsules 3 mg	Life Extension Buyers Inc	USA	425	219
Melatonin Tablets 3 mg (Bio-Melatonin)	Pharma Nord	Licensed in Hungary (EU). Manfd in Denmark (EU)	55	118
Melatonin Tablets 3 mg	Natrol	USA	67	69
Melatonin Capsules 5 mg	Biotech	USA	92	68
Melatonin Oral Liquid 1 mg/ml	Source Natural	USA	87	45
Melatonin Capsules 2.5 mg	Tyson	USA	53	38

Product Name	Manufacturer Name	Country	Number Of Notifications	
			Q2/2008	Q3/2008
Melatonin Life Extension Capsules 3 mg 6h Timed release	Prolongevity Life Extension	USA	0	34
Melatonin Capsules 1 mg	Life Extension Buyers Inc	USA	40	29
Melatonin Tablets 5 mg	Natrol	USA	20	20
Melatonin Tablets 3 mg	Source Natural	USA	14	18
Melatonin Capsules 3 mg Prolonged Release (Life Extension)	Life Extension Buyers Inc	USA	159	17
Melatonin Tablets 1 mg	Source Natural	USA	9	17
Melatonin Tablets 1 mg	Natrol	USA	16	16
Melatonin Capsules 10 mg	Life Extension Buyers Inc	USA	6	11
Melatonin Oral Liquid 1 mg/4 ml	Natrol	USA	10	8
Melatonin Capsules 5 mg	Enzyme Process	USA	8	8
Melatonin Tablets 2.5 mg Sublingual	Source natural	USA	0	8
Melatonin Tablets 3 mg	Natures Bounty	USA	4	4
Melatonin Capsules 5 mg	Par	USA	0	4
Melatonin Tablets 1 mg	Physiologics	USA	0	4
Melatonin (Horizon) Tablets 3 mg	Source Natural	USA	0	3
Melatonin Tablets 5 mg	Mason	USA	6	1
Melatonin B6 5 mg Tablet	Mason	USA	0	1
Melatonin Tablets 3 mg (Vytalonin)	Formulation Technology Inc.	USA	903	0
Melatonin Capsules 3 mg	Thorne Research	USA	71	0
Melatonin Capsules 5 mg	Thorne Research	USA	52	0
Melatonin Tablets 3 mg	Basic Organics	USA	39	0
Melatonin Tablets 5 mg	Life Extension Buyers Inc	USA	24	0
Melatonin Capsules 2 mg	Medinova Inc	USA	17	0
Melatonin Tablets 3 mg	Medinova Inc	USA	13	0
Melatonin Capsules 3 mg	Medinova Inc	USA	13	0
Melatonin Tablets 1 mg	Medinova Inc	USA	10	0
Melatonin Capsules 1 mg	Medinova Inc	USA	10	0
Melatonin Tablets 2 mg	Medinova Inc	USA	7	0
Melatonin Tablets 5 mg	Medinova Inc	USA	6	0
Melatonin Capsules 5 mg	Medinova Inc	USA	6	0
Melatonin Capsules 2 mg Prolonged Release (Prothera)	Prothera Incorporated	USA	6	0
Melatonin Capsules 10 mg	Forest Natural Inc	USA	5	0
Melatonin Capsules 10 mg	Vital Nutrients	USA	5	0
Melatonin Tablets 2 mg Prolonged Release (Circadin)	Lundbeck	Now has EU Licence	4	0
Melatonin Tablets 1 mg	Natures Bounty	USA	4	0
Melatonin Tablets 3mg Prolonged Release (Source Natural)	Source Natural	USA	3	0
Melatonin Capsules 3 mg	Douglas Labs	USA	2	0
Total			2271	763

Table 6 Notifications for melatonin products in Q2 & Q3 2008 by generic name. Ranked by Q3 2008

Generic Name	Number of Notifications	
	Q2 2008	Q3 2008
Melatonin Capsules 3 mg	511	219
Melatonin Tablets 3 mg	1095	212
Melatonin Capsules 5 mg	158	80
Melatonin Capsules 3 mg Modified Release (Life Extension)	159	51
Melatonin Oral Liquid 1 mg/ml	87	45
Melatonin Capsules 2.5 mg	53	38
Melatonin Tablets 1 mg	39	37
Melatonin Capsules 1 mg	50	29
Melatonin Tablets 5 mg	56	24
Melatonin Capsules 10 mg	16	11
Melatonin Oral Liquid 1 mg/4 ml	10	8
Melatonin Tablets 2.5 mg (Sublingual)	0	8
Melatonin + Vit B6 Tablets 5 mg	0	1
Melatonin Capsules 2 mg	17	0
Melatonin Tablets 2 mg	7	0
Melatonin Capsules 2 mg Modified Release (Prothera)	6	0
Melatonin Tablets 2 mg Modified Release (Circadin)	4	0
Melatonin Tablets 3 mg Modified Release (Source Natural)	3	0
Total	2271	763

These data show that the largest category of unlicensed product is 3 mg immediate release products and it is accepted that these may be required in cases where the modified release UK product will not meet patients' clinical needs. There is the possibility that 3 mg immediate release capsules or other dosage forms such as sublingual tablets, lozenges or drops may be required for patients that cannot swallow tablets. This latter category of patients is likely to include only a small number of adults for whom alternative solid dosage products may be suitable and some paediatric patients for whom drops or capsule contents (including modified release) may be most suitable.

MHRA policy in respect of the products previously notified is from 01 June 2008:

- An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.
- Although the MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the clinical need, even "off-label", it should be used in preference to an unlicensed product. Licensed products available in the UK have been assessed for quality safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is a better risk position than in the use of an un-assessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It

should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label.

- If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.
- If none of these options will suffice, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise unassessed (GMP inspection of specials manufacturers is not product specific). There may also be other pharmaceutical products available which are unlicensed in the country of origin.
- The least acceptable products are those that are unlicensed in the country of origin, and which are not classed as medicines in the country of origin (but are in the UK). Hence the use of melatonin products from the USA, where melatonin products are classed as supplements, not pharmaceuticals and may not be made to expected standards of pharmaceutical GMP, should be avoided whenever possible.

Despite attempts to minimise the number of non-pharmaceutical melatonin products notified for importation, a significant number of these products continue to be notified. It is important that prescribers are aware of the issues and written assurances may be sought from prescribers via importers that they are aware that products requested are non-pharmaceuticals and may not be manufactured to recognised standards of pharmaceutical Good Manufacturing Practice.

2.4.2 Thalidomide

A Centrally Authorised Thalidomide product, Thalidomide Pharmion Capsules 50 mg (Celgene) is now available in the UK.

Following the availability of a licensed product within the UK, given the safety concerns over the use of thalidomide, objections will be raised to importation of unlicensed products unless there are exceptional clinical reasons for requiring specific unlicensed products. Similarly, unlicensed UK manufactured products must not be supplied unless there are exceptional **clinical** reasons for requiring specific unlicensed products.

It should be emphasised that cost, convenience, institutional or other non-clinical issues are not legally acceptable reasons for the use of unlicensed products. The licensing system exists in its present form, partly as a result of previous tragic experiences with thalidomide, to ensure the safety of patients. It is therefore especially important, given the safety issues, that the legal requirements are observed. Licensed products have been assessed for quality, safety and efficacy. Unlicensed products have not had the benefit of such assessment, and although, as one enquirer stated, thalidomide is a well characterised molecular entity, this does not give assurance in respect of other safety and quality considerations, such as stability, related compounds, and general product quality and manufacturing practices.

Given the safety concerns with thalidomide, the MHRA considers, as indicated above, that unlicensed thalidomide products should only be used where there are exceptional clinical reasons to do so.

3 Issues arising

3.1 Administrative matters

3.1.1 Process timings – Clinical Emergencies

Normally, Clinical Emergency notifications can be processed within one working day. This can be up to four calendar days if the notification is received on a Friday afternoon. Some notifications can take longer if there are queries or if a medical assessment is required. A small number of notifications originally submitted as non-emergencies have been processed as emergencies resulting from changes in circumstances. These will show extended processing times.

Graph 5 Time (days) to issue Clinical Emergency (Approved) letters from notification date, Q3 2008

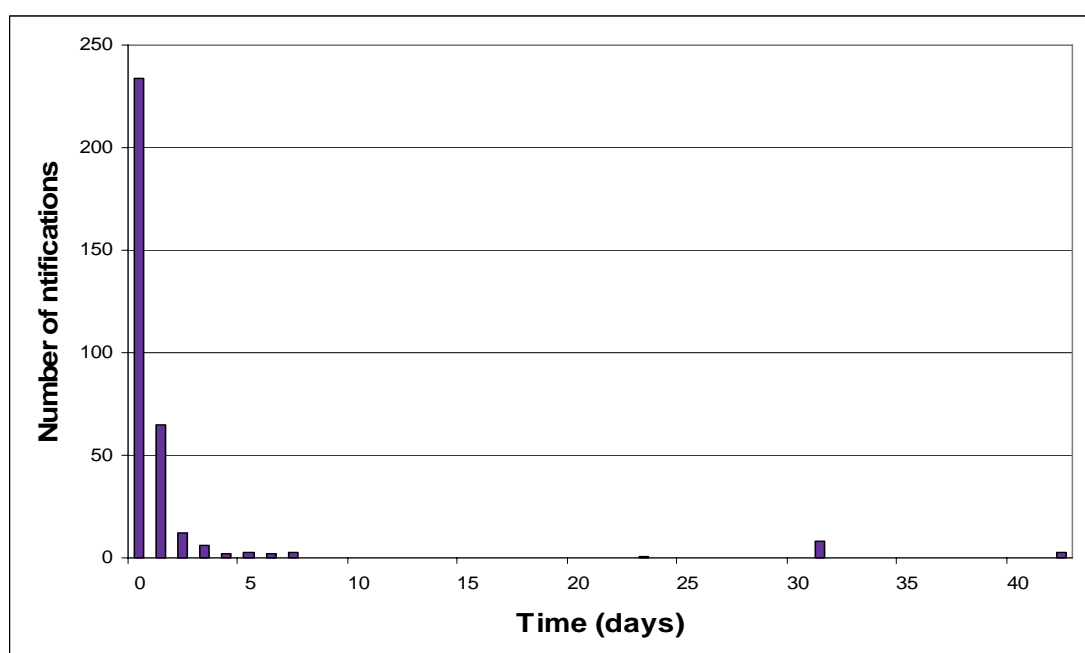


Table 7 Summary of Timings for Issuing Clinical Emergency (CE) Notifications (2007 & Q1 – Q3 2008)

	2007	Q1 2008	Q2 2008	Q3 2008
% ≤ 4 days	88	82	93	94
% ≤ 1 day	74	70	89	88
Total CE Notns	1297	272	367	339

NOTE: The historical figures have been revised following discovery of an error in the search algorithm for these statistics. The percentage values have only changed

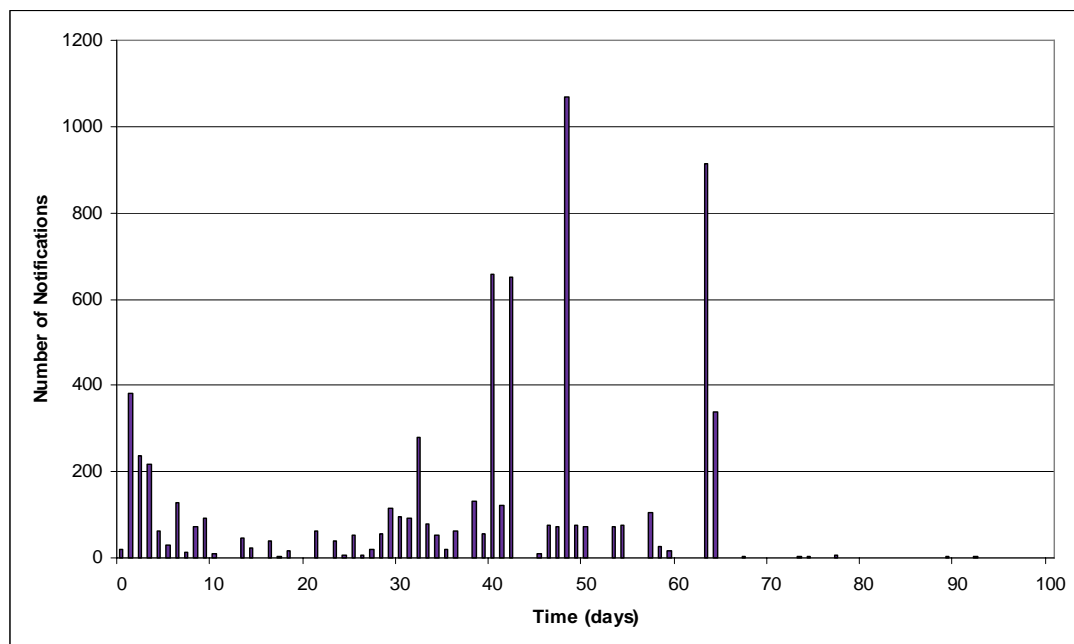
marginally, but the total number of Clinical Emergencies was previously underestimated.

3.1.2 Process timings – Routine notifications

Notifications received on spreadsheets may be given a bulk acknowledgement letter in which case the date is not recorded on the database. Individual notification letters are, however, individually acknowledged as are new notifications submitted on spreadsheets.

Graph 6 shows statistics for individually acknowledged notifications for Q3/2008 and provides an estimate of the time taken to enter data onto the database after the received date stamped on the individual notifications. In previous reports, time from notification date to acknowledgment date has been reported. It was hoped that using the notification received date would provide better quality data. Unfortunately, some of the received date stamps are illegible and in this case the received date is recorded as being the same as the notification date. Some importers do not submit their notifications until some time after the stated notification date on their notifications. Hence the figures for entry lag may be incorrect in cases where there the notification was in fact received well after the notification date. It is not possible to determine the proportion of such notifications from data held on the INS database.

Graph 6 Time taken to issue Acknowledgement Letters after receipt, Q3 2008

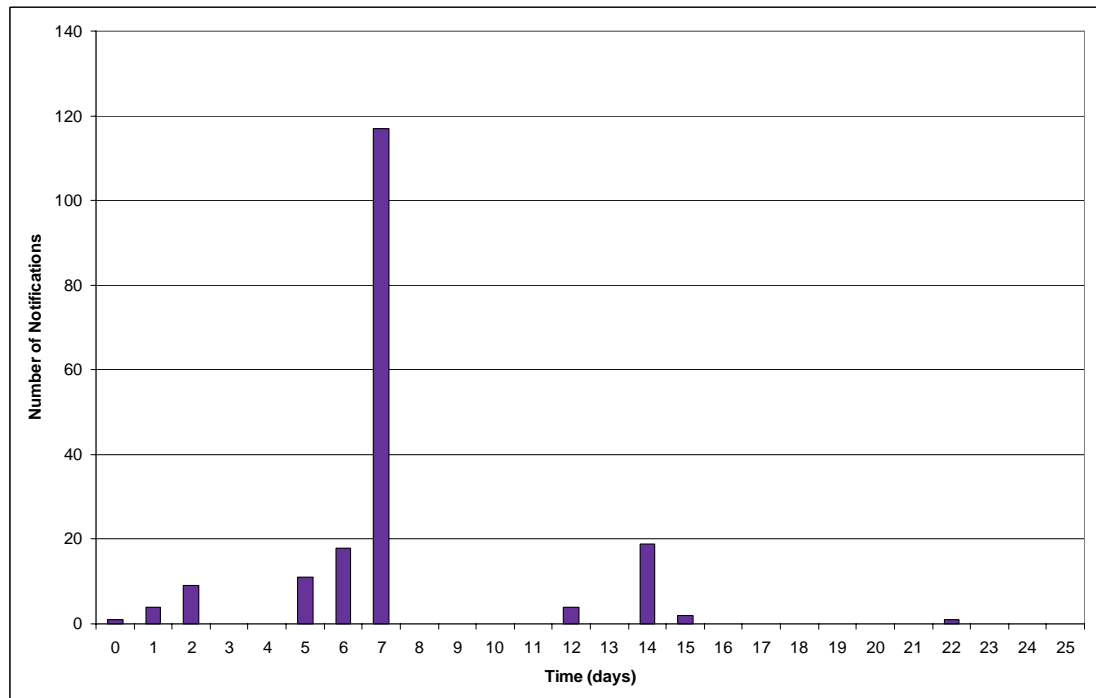


The large peaks observed in Graph 6 at around 42, 48 and 64 days are due to the necessity to obtain further information required to complete entry of new products notified on single spreadsheets from specific importers. Items notified on spreadsheets will not be acknowledged until all issues required to complete entry on the INS database are resolved. For this reason, importers are advised to ensure that separate spreadsheets are submitted for previously un-notified products, thus avoiding delays for previously notified products.

The Imports Notification Section has proposed a target of 15 working days (21 calendar days) for issue of acknowledgment letters following receipt of notifications.

Graph 7 provides data on the time to issue objection letters, where these are required, after the acknowledgement date. The target for these critical letters is within 28 days from the date of acknowledgment, as specified by SI 2005/2789. All objection letters were issued within 28 days.

Graph 7 Time taken to issue objection letters after initial acknowledgment, Q3 2008



Where individual acknowledgement letters were issued, 95.7% of No Objection with Reason letters were issued within 28 days of acknowledgment. Most of these letters are repeats of previously issued information, and although it is desirable to issue these letters within 28 days, it is not critical as there is no objection to import.

Similarly, where acknowledgment letters were issued, 98% of Further Information Requests were issued with 28 days of acknowledgment. Some Further Information requests are made without issuing acknowledgment letters. The letters issued outside of the 28 days were to an importer already in receipt of letters for the same products issued within 28 days of acknowledgment. This is an acceptable situation.

3.1.3 Discussion of timings

It is especially important to issue letters of objection and further information requests within the statutory 28 days from the date of acknowledgment. All critical letters fell within the 28 day requirement.

Efforts continue to try and reduce the time to enter data and issue acknowledgment letters. The analysis of timings is, however, difficult owing to unavoidable delays caused by the need to obtain further data before entry can proceed and due to other difficulties in interpreting timings recorded on the database.

3.1.4 IT issues

Work continues to address previously reported IT issues. Introduction of upgrades and “fixes” will follow successful User Acceptance Testing.

3.1.5 Summary Report – public domain data

For reasons of transparency, ease of patient access and awareness within the health professions, a public domain report including the top 50 listings will continue to be issued. This report also provides a means of informing interested parties of current issues.

3.2 Strategy for the future

3.2.1 Review of unlicensed medicines legislation

As noted in previous reports, a review of unlicensed medicines legislation continues. A consultation document was published in February 2008 seeking views and comments on this review from stakeholders.

Meetings with stakeholders have taken place as part of the consultation process and the information obtained is currently under assessment. It is anticipated that a further round of consultation, which may include proposals for a revised notification system for supply of unlicensed medicines will be made in Q1-Q2, 2009.

3.2.2 Staffing

As the use of temporary staff to support the Import Notifications unit has now been discontinued, processing of notifications may be subject to some variability due to staff leave or occasional illness.

4 Conclusions

The Import Notification System is operating substantially within the requirements of SI 2005/2789.

Melatonin products continue to be the most frequently notified unlicensed imported products, although the number has decreased following MHRA efforts to reduce the number of imported non-pharmaceutical products. These efforts will continue.

The importance of minimising the use of unlicensed thalidomide products is emphasised, given the availability of a licensed formulation in the UK and the well known safety issues with this compound.