



EMEA Edition: Part 1

Introduction

Last year was the EMEA's 10th anniversary of its first full year of granting marketing authorisations. The European Medicines Agency is a decentralised body of the European Union with headquarters in London. It offers a very efficient centralised procedure for the assessment and authorisation of innovative medicines. It does this through a computer network of about 3500 experts throughout the EU, enabling a fast track procedure for medicine licensing. The evaluating committee is required by Regulation to arrive at decisions on authorisation within 210 days. This compares with 500 days for the FDA.

In this issue...

simply click on the links below to view a story

- **Growth of EMEA Authorisations**
- **GSK Top Marketing Authorisation Holder**
- **Rogues Gallery of "bad" connotations**
- **IN at the deep end**

The Growth of EMEA Authorisations

In 1995 (See Table 1 below), its inaugural year, the EMEA granted 2 marketing authorisations that are still valid. For 2006, the figure had risen to 37. With the growth in bio-pharmaceuticals and synthetic pharmaceuticals and with ageing populations throughout the whole of the EU, this increase in EMEA authorisations for innovative products looks likely to continue.

Table 1 Marketing Authorisations (valid 15.02.07) Granted by Year

1995	2
1996	17
1997	15
1998	28
1999	22
2000	34
2001	39
2002	37
2003	19
2004	36
2005	21
2006	37

These Authorisations are held by ninety two different companies or partnerships. Of these, twenty one companies hold 170 Authorisations, or 55% of the total Authorisations, with GSK heading the list with 24 (see Table 2 on page 2)

Table 2 Marketing Authorisations by Holder Quantity

Glaxo Group/GSK/SmithKline/SmithKline Beecham	24	Orion	3	Immunomedics	1
Roche	17	Sanofi Pharma Bristol-Myers Squibb	3	INFAI	1
Novartis	15	Squibb	3	INO Therapeutics	1
Novo Nordisk	14	Takeda	3	Ipsen	1
Eli Lilly	13	Allergan	2	Laboratoire HRA Pharma	1
Bayer	10	Astellas	2	Lilly ICOS	1
Boehringer Ingelheim	9	Howmedica	2	Lipomed	1
Bristol-Myers Squibb	9	Ligand	2	Lundbeck	1
Genzyme	9	NV Organon	2	Merz	1
Merck	9	Nycomed	2	Nicobrand	1
SP Europe	9	Pharmacia-Pfizer	2	Norton Healthcare	1
Pfizer	8	Proctor & Gamble	2	Otsuka	1
Schering/Schering-Plough	8	Sanofi-Pasteur	2	Pharmacia & Upjohn	1
Wyeth	8	UCB/UCB Pharma	2	Pharmion	1
Sanofi-Aventis	7	Appotex Europe	1	Pierre Fabre Med	1
Serono Europe	6	Astra Zeneca	1	QSA Global	1
Abbott	5	Aventis Pasteur	1	Sandoz	1
Alcon	5	Axcan Pharma	1	Sanofi-Synthelabo	1
Amgen	5	Biocodex	1	Sanquin	1
Sanofi Pasteur	5	Bioenvision	1	SBL Vaccine	1
Shire	5	Biogen Idec	1	SkyePharma	1
Aventis Pharma	4	Biolitec Pharma	1	Solstice Neurosciences	1
Gilead	4	Biomarin Europe	1	Swedish Orphan	1
Les Laboratoires Servier	4	BioPartners	1	Teva	1
Orphan Europe	4	Bracco International	1	Topo Target	1
Baxter	3	Canyon	1	Torbet Laboratories	1
CIS Bio	3	Centocor	1	Unigene	1
Dompé Biotec	3	Cephalon	1	Valeant	1
Eisai	3	Elan	1	Zeneus Pharma	1
GE Healthcare	3	Encysive	1	The Medicines Company	1
Janssen Cilag	3	Ferring	1		
		Helsinn Birex	1		

[Back to page 1](#) ▲

Rogues Gallery - Global Linguistic Screening of all EMEA Authorisations

All pharma Marketing Authorisations are nowadays, hopefully, subjected to target market linguistic screening. However, the recent CHMP (Committee for Human Medicinal Products) meeting of the EMEA on February 5th (<http://www.emea.eu.int/pdfs/human/regaffair/032898en.pdf>) goes much further, stipulating that invented names [my emboldening]:

2.3.3 ...should not appear offensive or have a “bad” connotation in **any** of the official EU language.

I would also suggest that we have an obligation to ensure names do not offend the sensibilities of speakers of any of the major world languages. This particularly so in a territory such as the UK with a large and diverse population of second language speakers, many of whom are represented in the medical profession. Sometimes these secondary, negative or “bad”, meanings cause amused or distasteful interest for relevant ex-patriots and second language speakers. For example Hindi and Spanish, two of the most spoken and most widely spoken languages in the world, both appear in our Electric Eel negative list below (Table 3). These are the negative results of a global screening in twenty major European and world languages.

[continued on page 3](#) ▼

Appella
names that build brands

continued from page 2 ▲

Table 3 Electric Eel Negative Screening

(Filter levels 1 – 3 are those from which Appella submits names for longlisting. Level 5 contains negative word triggers and Levels 6 and 7 correspond to negative words by degrees.)

Negative words and triggers	Marketing Authorisation Holder	Negative meaning definition	Filter Level
Czech			
travatan	Alcon	looks like Czech otrava 'pest' 96% similarity	5
elaprase	Shire	looks like Czech prase 'pig, swine' 83% similarity	6
zerit	Bristol-Myers Squibb	looks like Czech zemřít 'die' 81% similarity	6
plavix	Sanofi-Pharma + Bristol-Myers Squibb	looks like Czech uplavice 'dysentery' 80% similarity	6
Hindi			
viread	Gilead	looks like Hindi virya 'male reproductive fluid: [formal]' 82% similarity	6
Malay			
baraclude	Bristol-Myers Squibb	looks like Malay barah 'cancer' 83% similarity	5
aldara	3M Santé	looks like Malay darah 'blood' 82% similarity	6
Polish			
cymbalta	Eli Lilly	looks like Polish cymbał 'idiot, oaf' 96% similarity	5
sutent	Pfizer	looks like Polish sutener 'pimp; procurer' 94% similarity	6
pedea	Orphan Europe	looks like Polish pedał 1.(bicycle/accelerator/clutch etc.) pedal 2.'faggot, queer' 84% similarity	6
Spanish			
insulatard	Novo Nordisk	looks like Spanish insultar 'insult' 94% similarity	6
sustiva	Bristol-Myers Squibb	looks like Spanish susto 'shock' 88% similarity	4

Chief culprit in the EMEA listings is VIREAD (tenofovir disoproxil fumarate) which, in Hindi, is very similar to virya 'male reproductive fluid'. Other offenders are INSULATARD (Insulin human (rDNA)) looking very similar to insultar 'to insult' in Spanish and the quartet of Authorisations held by Bristol Myers Squibb who risk running a gauntlet of bemusement, if not deprecation, to many Spanish, Czech and Malay speaking professionals. Perhaps most unfortunate of names is ZERIT (stavudine) "for treatment of HIV infected adults and children with progressive or advanced immunodeficiency" which, in Czech is similar to zemřít 'to die'. Even allowing for the difference caused by the fricativation and trilling of the ř of zemřít, there is a high degree of similarity between the two words, a difference of one phoneme (speech sound) and letter towards the end of the word, the least acoustically salient position.

Back to page 1 ▲

IN at the deep end

A more important area of concern is any similarity of proposed invented names, or international names (IN), with INN. A reminder of the WHO's recommendations from Guidelines on the Use of INN for Pharmaceutical Substances (1997):

To avoid confusion, which could jeopardize the safety of patients, trade-marks cannot be derived from INN and, **in particular, must not include their common stems.**

Despite this, the pens are clearly making the biggest rings around the query box marked "similar medical setting, and/or route of use, and/or route of administration?" in the decision tree entitled "IN containing INN stems" used by the Committee for Human Medicinal Products (CHMP) and invented Name Review Group (NRG) of the EMEA. Below is a table of EMEA INs/Trademarks or invented names that contain INN stems.

Table 4 EMEA Marketing Authorisations containing INN stems

Organisations applying for an MA (Marketing Authorisation) are entitled to feel somewhat in the dark with regard to how important it is to keep INN stems out of invented names as there is such conflicting advice. There is the best practice proposal, with reference to WHO guidance on INNs, that there should be "no INN-derived invented names", but then practical advice is given when best practice has not been observed in a six sub-section long item justifying instances of INN stem inclusion. There is, on top of this, the plea to avoid pharmacological confusion in the invented name/trademark/IN:

(CPMP/328/98, Revision 5, London, 5th Feb 2007)

2.1.2 The invented name of a medicinal product should not **convey misleading therapeutic and/or pharmaceutical connotations.**

2.1.3 The invented name of a medicinal product should not be **misleading with respect to the composition of the product.**

Name (not case sensitive)	INN Stem	Description
agenerase	-ase	enzymes;
angiox	-io-	iodine-containing compounds other than contrast media
avaglim	-gli-	previously gly-; antihyperglycaemics
cellcept	cell-	cellulose derivatives; (cell-ate and -cellose)
cetrotide	-tide	peptides and glycopeptides (for special groups of peptides see -actide, -pressin, -relin, -tocin.)
dukoral	-al	aldehyde
dynastat	-stat	enzyme inhibitors
elapraxe	-ase	enzymes
emadine	-ine	alkaloids and organic bases
hexavac	-ac	A420
invirase	-ase	enzymes;

continued on page 5 ▼

Appella
names that build brands

continued from page 4 ▲

ionsys	io-	iodine-containing contrast media
kiovig	-io-	iodine-containing compounds other than contrast media
noxafil	-afil	inhibitors of PDE5 with vasodilator action
onsenal	-al	aldehyde
opatanol	-ol	for alcohols and phenols
posaconazole	-conazole	systemic antifungal agents, miconazole derivatives
rebetol	-ol	for alcohols and phenols
refludan	-dan	cardiac stimulants, pimobendan derivatives
replagal	-al	aldehyde
sifrol	-ol	for alcohols and phenols
somavert	som-	growth hormone derivatives
suboxone	-one	ketones
telmisartan	-sartan	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
temodal	-al	aldehyde
valtropin	-pin	tricyclic compounds; dipine: see -dipine; -zepine: antidepressant/neuroleptic; C.O.O.O -apine: psychoactive; A.3.1.0 cilpine: antiepileptic; -oxepin, -oxopine, -sopine, -tepine
vistide	-tide	peptides and glycopeptides (for special groups of peptides see -actide, -pressin, -relin, -tocin.)
xenical	-al	aldehyde

Perhaps, not surprisingly, problems do seem to arise when selecting proposed names. The commonest inconsistencies occur with INN stems comprising two letters in a frequently occurring sequence in the vocabulary e.g. -al 'aldehyde' (INN description) & -io- 'iodine-containing compounds other than contrast media', -io- 'iodine-containing compounds'. Words like *replagal* (Aug 2001, date of MA) *onsenal* (Oct 2003)) and *kiovig* might simply be using the sequences as innocent components in made-up names but, just because they are made-up names they may be misleading because there is little other clear semantic information to go by in a name of this type. The chemical properties of *ion*, in *ionsys* (Jan 2006), and biological meaning of *angio* in *angiox* (Sept 2004) are fairly clear suggesting less cause for ambiguity. However, they are still in contravention.

More of a problem, certainly for the NRG, is where a substantial part of the trademark name is taken up by the INN stem. What of *-gli-* (INN description 'antihyperglycaemics') in *AVAGLIM* (June 2006), which is an antihyperglycaemic, (2006) and *-afil* (INN description 'inhibitors of PDE5 with vasodilator action') in *NOXAFIL* (2005) which is *not* a 'PDE5 inhibitor'. *Noxafil* may conform to the permissible instances of INN usage because not related to INN denotation, in which case *Avaglim* misleads because it so manifestly uses positionally correct INN stems? This looks like having it both ways. If qualitative information is a consideration, then the amount of the drug's names taken up by the stem – 50% visually and phonetically – in acoustically salient positions in invented, thus semantically vacant, words must call into question their unambiguity.

continued on page 6 ▼

continued from page 5 ▲

Another historically older group includes TELMISARTAN, also (telmisartan), (1998) and SOMAVERT (1999), which contain stems *taxo* and *soma*. These both either identical or visually similar to their INNs and they are pharmaco-therapeutically consistent with the INN descriptions. However, these are anachronisms dating from the time before the CHMP's and NRG's schematic, INN focusing, decision tree was grafted on to the fabric of pharmacological expediency. The fact that these problematic Authorisations are from an older period does show that the EMEA are making significant improvements in compliance with WHO recommendations with consequent distinctiveness of registration. However, judged purely on linguistic principles, the boundaries are not completely clear and confusion is still understandable in the uninformed applicant.

At Appella, we ensure names are electronically screened by our proprietary Electric Eel process against % similarity to; 1) negative connotations, 2) existing pharma authorisations in selected territories, 3) all INNs and 4) all INN stems by position. All this is before longlisting to ensure maximum survival rate.

Sources: www.emea.europa.eu

The next edition includes linguistic analysis of EMEA Authorisations

Back to page 1 ▲