European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
JANUARY 2005 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its January plenary meeting from 17-20 January 2005.

Centralised procedure

Opinions

The CHMP adopted one positive opinion on an initial marketing authorisation application for:

- **Aclasta** (zoledronic acid), from Novartis Europharm Ltd, for the treatment of Pagets disease of the bone. EMEA review began on 17 May 2004 with an active review time of 181 days.

More information about this product can be obtained in the summary of opinion available on the EMEA web site: http://www.emea.eu.int

The Committee also gave two positive opinions on extension of indication for medicinal products that are already authorised in the EU:

- **Pegasys** (peginterferon alfa-2a), Roche Registration Ltd, to extend its use to the treatment of chronic hepatitis B. Pegasys was first authorised in the European Union on 20 June 2002 for the treatment of chronic hepatitis C.

- **Thyrogen** (thyrotrophin alfa), Genzyme B.V., to extend its use to pre-therapeutic stimulation in low-risk post-thyroidectomy patients maintained on hormone suppression therapy for the ablation of thyroid remnant tissue in combination with 100 mCi radioactive iodine. Thyrogen was first authorised in the European Union on 9 March 2000.

The Committee also gave positive opinions on new contra-indications for medicinal products that are already authorised in the EU:

- Sustiva (efavirenz), Bristol-Myers Squibb Pharma EEIG, to contra-indicate the use with voriconazol.
- Stocrin (efavirenz), Merck Sharp & Dohme Ltd, to contra-indicate the use with voriconazol.
- Reyataz (atazanavir), Bristol-Myers Squibb Pharma EEIG, to contra-indicate the use with proton pump inhibitors.

A summary of opinion on Pegasys, Thyrogen, Sustiva and Stocrin is available on the EMEA web site: http://www.emea.eu.int. Regarding Reyataz a Public Statement on this issue was published on the EMEA website in December 2004: http://www.emea.eu.int/pdfs/human/press/pus/20264904en.pdf

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.eu.int http://www.emea.eu.int

The initiative to publish summaries of opinion for certain post-authorisation applications had been announced in the previous CHMP Monthly Report. Further information on these extensions will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

The Committee also adopted a positive opinion on a "line extension" application (Part A) (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Lists of Questions

The Committee adopted three Lists of Questions on initial applications and two Lists of Questions on a "line extension" application (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

An overview of centralised procedures since 1995 is given in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in December 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Application for marketing authorisation for orphan medicinal products

Details of those Orphan medicinal products that have been subject of a centralised application for marketing authorisation since the December 2004 CHMP are provided in **Annex 4**.

Referrals

- As part of the ongoing review of **COX-2 inhibitors**, the Committee heard presentations and held discussions with Pfizer, Merck Sharp & Dohme and Novartis. A separate statement has been issued and is available on the EMEA web site: http://www.emea.eu.int/htms/hotpress/d2354705.htm

- The CHMP concluded a Community-wide review on **Rigevidon** (levonorgestrel and ethinylestradiol), a generic oral contraceptive from Medimpex France SA. The referral was initiated by the Netherlands under Article 29 (2) of the Community code on human medicines (Directive 2001/83/EC as amended) on 29 July 2004 because of concerns whether the normally accepted range for proving bioequivalence is sufficient to demonstrate safety and efficacy of Rigevidon. After reviewing relevant data, the Committee concluded that there was no objection for granting a marketing authorisation for Rigevidon.

- The CHMP began Community referrals under Article 29(2) of the Community code on human medicines (Directive 2001/83/EC as amended) for five generic medicinal products containing **lanzoprazole**. Concerns were raised by Germany and Portugal because of differences in the dosage and indications between the Summaries of Product Characteristics (SPCs) of the reference products and the SPCs of the generic products.

CHMP Working Parties

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Party (SAWP) meeting, which was held on 04-05 January 2005. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the January 2005 CHMP meeting are listed in **Annex 6**.

Please also refer to the section "Organisational matters" for information on Working Parties' organisational related aspects.

Invented Name Review Group (NRG)

The Group discussed the revision of the Invented Name Guideline Rev.4. This Guideline is expected to be adopted and released in March or April 2005.

The next NRG meeting will be held on 14 February 2005.

Upcoming meetings following the January 2005 CHMP plenary meeting:

- The 9th meeting of the CHMP will be held on 14-17 February 2005.

Organisational matters

The main topics addressed during the January 2005 CHMP related to:

- The set up of a CHMP / EMEA Pharmaceutical Legislation Implementation Task Force. This Task Force will meet on a monthly basis to discuss and review the progress of the procedures and Guidance to be developed in order to enable implementation of the Regulation (EC) No 726/2004 of the European Parliament of the Council. Interested Parties' consultation and a Public Report outlining the progress of the work of this Task Force will be made available in due time.
- A discussion on the revision of the SPC Guideline. Further discussion on this topic will take place at the February 2005 CHMP meeting.
- An extention of the deadline for commenting on the **Concept Papers on biosimilar** medicinal products released in November 2004 by the CHMP (extended for one month from end of January 2005 to the end of February 2005) (please see also **Annex 6**).
- The adoption of the Mandate, Objectives and Rules of Procedure of the Scientific Advice Group on HIV /viral diseases.
- The election of the Chairperson and the Vice–Chairperson of the Quality Working Party (QWP). **Dr Jean-Louis Robert** was elected as Chairperson and **Dr Susanne Keitel** was elected as Vice–Chairperson. There will be a separate election for a Veterinary Vice Chairman which will take place at the February 2005 CVMP meeting.
- The election of the Chairperson and the Vice–Chairperson of the Safety Working Party: **Prof Beatriz Silva Lima** was elected as Chairperson and **Dr Jan Willem Van der Laan** was elected as Vice–Chairperson.

- The adoption, by the CHMP, of the BWP Work Programme 2005. A copy of this document will be published on the EMEA website.
  The election of the Chairperson and Vice-Chairperson of the Biotechnology Working Party (BWP) will take place at the February 2005 CHMP meeting.

- The adoption, by the CHMP, of the Vaccine Working Party Work Programme 2005. A copy of this document will be published on the EMEA website.

- It should be noted that the election of the Chairperson and the Vice–Chairperson of the Efficacy Working Party will take place at the February 2005 CHMP meeting.

- It should also be noted that the election of the Chairperson and Vice-Chairperson of the various other biological CHMP Working Parties/Expert Groups (Blood Products Working Party, Gene Therapy Working Party, Vaccine Working Party, Pharmacogenetics Expert Group, Cell Therapy Working Party, Working Party on Similar Biological (Biosimilar) Medicinal Products), will take place at the March 2005 CHMP meeting.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 17 January 2005. For further details, please see **Annex 7.**

Noël Wathion
Head of Unit
Post-Authorisation Evaluation of Medicines for Human Use, Tel. (+44-20) 74 18 85 92
This CHMP Monthly Report and other documents are available on the Internet at the following address:
http://www.emea.eu.int

EMEA CENTRALISED PROCEDURES

	1995 - 2004	2005	Overall Total
Scientific Advice	**433**	**7**	**440**
Follow-up to Scientific Advice	**71**	**1**	**72**
Protocol Assistance	**59**	**3**	**62**
Follow-up to Protocol Assistance	**12**	**0**	**12**

	1995-2004			2005			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	153	**303**	**456**	1	1	**2**	**458**
Consultation for Medical Device[1]	0	**1**	**1**	0	0	**0**	**1**
Withdrawals	**22**	**62**	**84**	0	**1**	**1**	**85**
Positive opinions[2]	**107**	**197**	304	0	1	**1**	**305**[3]
Negative opinions[4]	**2**	**5**	7	0	**0**	**0**	**7**[5]
Marketing authorisations granted by the Commission	**98**	**190**	288	1	**2**	3	**291**[6]

	1995-2004			2005			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	**863**	**1937**	**2800**	7	29	36	2836
Positive opinions, variations type II	**758**	**886**	**1644**	15	17	**32**	1676
Negative opinions, variations type II	**1**	**6**	**7**	**0**	**0**	**0**	**7**
Extensions (Annex II applications)	**53**	**63**	**116**	**1**	**0**	**1**	**117**

[1] Consultation in accordance with Council Directive 93/42/EEC concerning medical devices as amended by Directive 2000/70/EC as regards medical devices incorporating stable derivatives of human blood or plasma and Directive 2001/104/EC.
[2] 19 positive opinion corresponding to 19 Orphan Medicinal Products
[3] 305 positive opinions corresponding to 236 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 7 negative opinions corresponding to 6 substances (2 of these negative opinions correspond to 2 Orphan Medicinal Products)
[6] 291 marketing authorisations corresponding to 222 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE DECEMBER 2004 CHMP MONTHLY REPORT

Invented Name	**Cymbalta**
INN	**duloxetine**
Marketing Authorisation Holder	**Eli Lilly Nederland B. V.**
Proposed ATC code	**Application pending**
Indication	**Treatment of major depressive episodes**
CPMP Opinion date	**16/09/2004**
Marketing Authorisation Date	**17/12/2004**

Invented Name	**Xeristar**
INN	**duloxetine**
Marketing Authorisation Holder	**Eli Lilly Nederland B. V.**
Proposed ATC code	**Application pending**
Indication	**Treatment of major depressive episodes**
CPMP Opinion date	**16/09/2004**
Marketing Authorisation Date	**17/12/2004**

Invented Name	**Avastin**
INN	**bevacizumab**
Marketing Authorisation Holder	**Roche Registration Ltd**
Proposed ATC code	**L01XC07**
Indication	**Avastin (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum**
CPMP Opinion date	**21/10/2004**
Marketing Authorisation Date	**12/01/2005**

OUTCOME OF THE JANUARY 2005 CHMP MEETING IN RELATION
TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	Outcome
2 Extensions of indication	2 Positive opinions
11 SPC changes	11 Positive opinions
19 Quality changes	19 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	Outcome	Comments
Foscan (temoporfin) Biolitec Pharma Limited	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Glivec (imatinib mesilate) Novartis Europharm Ltd	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	Outcome	Comments
N/A	N/A	**---**

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION: UPDATE SINCE THE DECEMBER 2004 CHMP MEETING

Active substance	***Sponsor/applicant***	***EU Designation Number & Date of Orphan Designation***	***Designated Orphan Indication***
N-acetylgalactosamine-4-sulfatase (Galsulfase-Biomarin)	BioMarin Europe Ltd	EU/3/01/025 14/02/2001	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome).
Recombinant human acid α-glucosidase (Myozyme)	Genzyme Europe BV	EU/3/01/018 14/02/2001	Treatment of Glycogen Storage Disease type II (Pompe's disease).
Sildenafil citrate (Revatio)	Pfizer Limited	EU/3/03/178 12/12/2003	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

OUTCOME OF THE JANUARY 2005
CHMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharma ceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Glioma		**X**			**X**			
Chemical	Alzheimer's disease	**X**					**X**	**X**	
Chemical	Breast cancer	**X**						**X**	
Chemical	Type 2 Diabetes mellitus			**X**				**X**	
Chemical	Hypoactive sexual desire disorder in females	**X**						**X**	
Chemical	Chronic myeloid leukaemia		**X**				**X**	**X**	**X**
Chemical	HIV	**X**				**X**	**X**	**X**	
Chemical	Wegener's granulomatosis		**X**			**X**	**X**		
Chemical	Glaucoma	**X**					**X**		
Chemical	Type 2 Diabetes mellitus	**X**					**X**	**X**	
Chemical	Diabetic retinopathy	**X**					**X**		

SA: Scientific Advice

PA: Protocol Assistance

In January 2005, the above-mentioned 7 Scientific Advice letters, 1 Follow-up Scientific Advice letters, and 3 Protocol Assistance letters were adopted. The Committee accepted 10 new Scientific Advice requests, 4 new Protocol Assistance requests and 1 Follow-up Protocol Assistance request.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE JANUARY 2005 CHMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CHMP/QWP/10594/2005	Guideline on the pharmaceutical quality of inhalation and nasal products	Released for 6 months consultation

BIOTECH WORKING PARTY

Reference number	Document	Status
EMEA/CHMP/BWP 135148/2004	Environmental Risk Assessments for medicinal products containing, or consisting of, Genetically Modified Organisms (GMOs)	Released for 6 months consultation
CPMP/BWP/125/04	Guideline on Epidemiological Data on Blood Transmissible Infections	Adopted
EMEA/CHMP/BWP/ 188963/2004	Biotech Working Party Work Programme 2005	Adopted

SAFETY WORKING PARTY

Reference number	Document	Status
CHMP/SWP/4447/00	Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use	Released for 3 months consultation
CHMP/SWP/151915/2004	Concept Paper on the Development of a CHMP Guideline on the In-vitro investigation of Mitochondrial Toxicity of Anti-HIV Medicinal Products	Adopted
CHMP/SWP/199726/20	Reflection paper on the Assessment of the Genotoxic Potential of Antisense Oligodeoxynucleotides	Adopted

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/EWP/021/97 rev. 1	Guideline on Hormone Replacement Therapy	Released for 6 months consultation
CHMP/EWP/4279/02	Guideline on clinical investigation of medicinal products for the treatment of obsessive compulsive	Adopted

	disorder	
CPMP/EWP/4284/02	Guideline on the clinical investigation of medicinal products indicated for generalised anxiety disorder	Adopted
CHMP/EWP/4280/02	Guideline on clinical investigation of medicinal products indicated for the treatment of panic disorder	Adopted

VACCINE WORKING PARTY

Reference number	Document	Status
CHMP/VEG/194335/2004	Vaccine Working Party Work Programme 2005	Adopted
CPMP/VEG/134716/2004	Guideline on Adjuvants in vaccines for Human use	Adopted

AD HOC WORKING GROUP ON (PRE)-CLINICAL COMPARABILITY OF BIOTECHNOLOGY PRODUCTS

The following four Concept Papers were released in November 2004 for 2-months consultation. Please note that the deadline for comments is now extended from end January 2005 to end February 2005.

Reference number	Document	Status
CHMP/Comparability Working Party/146701/04	Concept Paper on the Development of a CHMP Annex to the guideline development of biosimilar medicinal products containing biotechnology derived proteins as active -(non) clinical issues recombinant -Human granulocyte colony-stimulating factor (Filgastrim) containing products	The deadline for the comments is extended from end January 2005 to end February 2005
CHMP/Comparability Working Party/146710/04	Concept Paper on the Development of a CHMP Annex to the guideline on comparability of biological medicinal products containing biotechnology derived proteins as active -(non) clinical issues-recombinant Human Insulin Containing products	The deadline for the comments is extended from end January 2005 to end February 2005
CHMP/Comparability Working Party/146489/04	Concept Paper on the Development of a CHMP Annex to the guideline development of biosimilar medicinal products containing biotechnology derived proteins as active -(non) clinical issues-Somatropin containing products	The deadline for the comments is extended from end January 2005 to end February 2005
CHMP/Comparability Working Party/146664/04	Concept Paper on the Development of a CHMP Annex to the guideline development of biosimilar medicinal products containing biotechnology derived proteins as active -(non) clinical issues-Erythropetin containing products	The deadline for the comments is extended from end January 2005 to end February 2005

Report from the meeting held on 17 January 2005

General Issues

Joint MRFG/QRD Working group on Patient information

The MRFG Sub-group on Patient information held its second meeting in the morning following the MRFG plenary session to continue the discussions on the new legal requirements for patient information leaflets and the need for guidance on User testing and Usability.

The proposal for an internal workshop on patient information leaflets, to take place in March 2005, was agreed.

Procedure for Automatic Validation of MR Procedures for New Applications

An updated version of the document has been adopted by the group and will be published on the website.

Co-ordination Group - CMD(h) meeting dates for 2006, 2007 and 2008

The MRFG has agreed to have two-days meetings for the future CMD(h) to take place on the Monday and Tuesday of the CHMP week. The calendar for the meetings will be published on the website.

Summary of MRFG Activities in 2004

The MRFG has decided to publish on the website a summary of the main activities carried out by the MRFG and its sub-groups in 2004.

MRP statistics for New Member States in 2004

Due to the enlargement of the European Union on 1 May 2004 to 10 new Member States, the MRFG has decided to publish on the website statistics regarding the number of MRP and repeat-use MRP for marketing authorisation applications submitted in new Member States (as CMS or RMS) in 2004.

MRP statistics 2004

Statistics regarding new applications in the MRP in the year 2004 according to the 5-level classification will be available on the website by the end of January 2004.

Meeting schedule

The next MRFG meeting will be held on 14 February 2005.

Mutual Recognition Monitoring

The MRFG noted that 116 new mutual recognition procedures were finalised during the month of December 2004, as well as 292 type IA variations, 174 type IB variations and 87 type II variations. 6 arbitrations related to a new application have been referred to the CHMP.

The status as of 31st December of procedures and for the whole year under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Arbitrations referred to CHMP
2004	760	285	3240	1998	1083	9 N.A

The global status since 1st January 1995 is as follows (further detailed statistics can be found at the MRFG website):

Years	Procedures from New applications finalised	Procedures from Type I variations finalised	Procedures from Type IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Arbitrations referred to CPMP
1995	10	16			17	1 N.A.
1996	84	49			73	1 N.A. and 1 variation
1997	146	101			163	1 N.A. and 1 variation
1998	182	339			222	1 N.A. and 4 variations
1999	228	671			301	2 N.A. and 2 variations
2000	306	1007			320	3 N.A. and 2 variations
2001	443	1487			474	1 N.A. and 3 variations
2002	420	2104			527	2 N.A. and 7 variations
2003	529	2473	230	94	754	5 N.A. and 3 variations
2004	760	43	3240	1998	1083	9 N.A.
1995-2004	3108	8290	3470	2092	3934	26 N.A. and 23 variations

93 new procedures (regarding 243 products) started in December 2004. The categories of these procedures are as follows:

7 new active substances (first authorisation in the European Community after RMS approval), including 3 repeat use.

19 known active substances (already authorised in at least one member state), including 1 multiple application and 10 repeat use.

61 abridged applications including 27 multiple applications and 4 repeat use.

6 line extension applications including 2 multiple applications and 1 repeat use.
The new procedures started related to 20 full dossiers, 46 generics, 6 bibliographic applications, 4 informed consent and 17 for different use, route or dose.

The procedures consisted of 89 chemical substances, 2 biological-others, 1 biological-blood product and 1 biological-vaccine[1].

90 of these procedures were prescription-only medicinal products in the reference Member State and 3 procedures were classified as a Non-prescription (including OTC) medicinal product[2].

1. As considered by RMS.
2. In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Number of countries involved in the new applications procedures started in December 2004

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	1
AT (1)	1
AT (1)	1
AT (1)	1
AT (1)	1
AT (1)	1
AT (1)	1
CZ (1)	2
CZ (1)	6
DE (1)	18
DE (4)	8
DE (4)	10
DE (1)	20
DK (4)	8
DK (1)	12
DK (4)	1
DK (1)	7
DK (1)	2
DK (2)	1
DK (3)	15
DK (4)	1
DK (4)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	1
DK (6)	2

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (6)	1
DK (6)	1
ES (1)	7
FI (1)	10
FI (3)	17
FI (5)	5
FI (5)	1
FR (1)	10
FR (1)	9
FR (1)	7
FR (2)	13
FR (1)	10
NL (1)	3
NL (1)	8
NL (2)	7
NL (1)	12
NL (1)	8
NL (3)	14
NL (3)	14
NL (3)	6
NL (1)	7
NL (2)	7
NO (3)	1
NO (2)	1
SE (6)	3
SE (5)	1
SE (1)	5
SE (1)	8
SE (1)	4
SE (1)	26
SE (4)	18
SE (1)	7
SE (1)	12
SE (3)	8
SE (4)	4
SE (2)	2
SE (1)	1
UK (1)	22
UK (1)	8
UK (1)	15
UK (1)	6
UK (2)	4
UK (4)	16
UK (1)	10
UK (3)	3
UK (1)	1
UK (2)	8
UK (1)	8
UK (1)	1
UK (1)	1
UK (1)	1
UK (1)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (1)	1
UK (1)	1
UK (1)	2
UK (1)	4
UK (4)	9
UK (2)	8

All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading MRFG Guidance.

Information on the above mentioned issues can be obtained from the chair of the MRFG on behalf of the Luxembourg Presidency:

Mrs. Truus Janse-de Hoog
College ter Beoordeling van Geneesmiddelen
Kalvermarkt 53
NL – 2500 Den Haag
The Netherlands

Phone: + 31 70 356 74 08
Fax: + 31 70 356 75 15
e-mail: gm.janse@cbg-meb.nl

Or you could visit the MRFG web site at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:
http://heads.medagencies.org/