Mutual recognition - Decentralised procedures

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Direct interests:					
Employment with a company	NO				
Consultancy for a company	NO				
Strategic advisory role for a company	NO				
Financial interests	NO				
Ownership of a patent	NO				
Indirect interests:					
Principal investigator	NO				
Investigator	NO				
Individual's Institution/Organisation receives a grant or other funding	N0				

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N.B. I am not receiving any compensation

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Eu network

- European Agency (EMA)
- European Commission (EC) European
- Directorate for the Quality of Medicines (EDQM)

- Member States' National Agencies (NCA)
- Coordination Group (CMDh)

National procedure

- Eligible for all active substances outside of the mandatory scope for centralised procedures (including herbals and homeopatics) and for initial applications and additional strenght/ pharmaceutical form (line extension)
- Eligible for all legal basis
- Medicinal product not yet authorised in any European MS
- Limited to one MS only
- Same assessment standards and relevant guidelines as in the European procedures

“European” procedures”

- Mutual Recognition Procedure (MRP)
- Decentralised Procedure (DCP)

- Centralised Procedure (CP)

Dossier

- Same structure for all kinds of procedures (ICH structure) - Same standards of assessment

- Different legal basis according to the product and consequent choice of supporting pre-clinical and clinical data (= NDA/ANDA)

- *Directive 2001/83 (last amendment 2012)*

European Procedures: MRP/DCP

- Eligible for all active substances outside of the mandatory scope for centralised procedures (including herbals and homeopatics, if based on simplified application or traditional use)
- Eligible for all legal basis
- Possibility to apply in 2 to 31 MS

MRP/DCP

- Eligible for initial applications and additional strenght/form (line extension)
- Both eligible for inclusion of additional MSs (repeat use) in subsequent waves
- Both allowed to be run for additional identical dossier in parallel procedures (multiple or duplicate applications)
- Dossiers authorised by MRP/DCP remain harmonised throughout their whole lifecycle

MRP/DCP

- Same legal requirements and dossier structure as nationally autorised and centralised procedures
- Administrative validation at European level, in the respect of national requirements
- Scientific assessment at European level
- Final agreement on acceptability at European level
- Marketing authorisation: national

MRP and DCP

Two routes to receive a MA

1. Mutual recognition procedure (MRP)

   where the medicinal product has already received a Marketing Authorisation in a MS at the time of application

or

2. Decentralised procedure (DCP)

   where the medicinal product has not received a Marketing Authorisation in any MS at the time of application

Mutual recognition procedure

- Medicinal product already authorised in 1 Member State (MS)
- Identical dossier
- Initial MS: Reference MS (RMS)
- Additional MS(s): Concerned MS(s) (CMS)

Mutual recognition procedure

- RMS prepares/updates Assessment Report (AR)
- AR is sent to the list of CMS(s) together with summary of product characteristics (SmPC), package leaflet (PL), labelling
- Approval within 90 days
- Working language: English
- National Marketing Authorisation in CMS(s) within 30 days

MRP: flow chart

- Day 90: end of procedure – start of the national phase in the CMSs (check national translations of product information and granting of a marketing authorisation within 30 days)

or

- Day 90: end of procedure with potentially serious risks for public health unsolved and consequent referral to Coordination Group (CMDh)

Decentralised Procedure

- Medicinal product not yet authorised in any MS at the time of application
- Identical dossier
- Choice of RMS by the applicant
- Additional MS(s): Concerned MS(s)

Decentralised Procedure

- The reference Member State shall prepare a draft assessment report within 120 days after receipt of a valid application
- Within 90 days of receipt of the draft assessment report the MS shall either approve or reject the procedure: same as MRP.
- Working language: English

Decentralised Procedure – flow chart

Step I

- RMS: pre-submission meeting
- Validation phase (day -14/day0) in parallel in both RMS and CMS
- RMS: sends PrAR to all CMS at day 70
- CMS(s): send comments to RMS by day 100
- Day 100-105: consultation among RMS, CMS and applicant
- Day 105: RMS prepares the LoQ for the applicant
- Clock stop: the Applicant prepares the response document – RMS drafts the DAR

Decentralised Procedure – flow chart

Step II

- RMS: at day 120 sends the DAR to the CMS(s)
- CMS(s) : send comments by day 145
- RMS: receives the applicant's responses at day 160 and sends a short report to CMS(s) by day 180
- RMS and CMS: possibility of a Break Out Session at the EMA around day 205
- CMS: final comments at day 195

Decentralised Procedure – flow chart

- Day 210: end of procedure – start of the national phase in RMS and CMSs (check translation of product information and granting of a marketing authorisation within 30 days)

or

- Day 210: end of procedure with potentially serious risks for public health unsolved and either refusal of the DCP (if RMS) or referral to CMDh (if CMS)

Similarities in MRP and DCP

- 90 days phase
- Possibility to submit in 1 to 31 MS
- Both procedures can be used for line extensions of a previous marketing authorisation
- Possibility to have a different trademark in different MS

➢ Same standard of evaluation
➢ Same product information in all MS

- Same final national phase (30 days)

Differences between MRP and DCP

Differences - MRP:

- Medicinal product already authorised
- Need for a preliminary national approval/update
- RMS has to “support” the dossier
- SmPC already approved
- One phase only for assessment
- No possibility to avoid a referral
- The content of the dossier is fixed and there is no possibility to update it without further prolonging the preliminary national phase

Differences between MRP and DCP

Differences - DCP:

- New medicinal product
- RMS assesses the dossier for the first time, “in parallel” with CMSs – dossier updated at the start
- SmPC not yet approved
- Two phases for assessment
- The content of the dossier can be updated during the clock-stop (user testing, GCP, GMP, new studies, other data?)

Differences between MRP and DCP

Differences - DCP:

- No referral in case of withdrawals before day 120 (commercial reasons only)

- Possibility of an earlier closure any time after day 120

- Possibility of a negative opinion from the RMS

MRP/DCP validation phase

- Cover letter and application form + Module 1 (regional to Europe)

- Check of legal basis and administrative details, including national fees

- Possibility of additional national requirements for each MS, on the basis of national legislation

- All documents submitted in English for all MS

MRP validation phase

Synthon ruling by the ECJ (*November 2008*)

- Decision on validation by the RMS to be followed by the CMS(s) – including legal basis
- Conclusions of the RMS as reported in the Assessment Report to be accepted by the CMSs, unless potential serious risks to public health in accordance with the Commission Guideline are highlighted

- *The possibility to comment on MRP and influence its outcome by the CMS(s) has been strongly limited by this sentence*

MRP/DCP – positive outcome

National phase:

- Check of national translations of SmPC, PL and labelling
- Check of administrative details and manufacturing sites
- Drafting of the MA (legally binding document)
- RMS: drafts and publishes the Public Assessment Report on the MR-Product Index (and on the national website)
- All MS: publish SmPC, PL, conditions and summary PAR on their national websites

MRP/DCP – negative outcome

1. Potentially serious risks to public health raised by RMS: refusal of the procedure in all MS (no possibility of appeal)

2. Potentially serious risks to public health raised by a CMS: referral to Coordination Group (both MRP and DCP) and start of the 60 days referral phase

Potential serious risk … = exceptional case

Why exceptional case?

All MS will evaluate an application for a marketing authorisation according to the same standards. These standards are based on Guidelines.

Therefore

Common view on

- the interpretation of Guidelines (e.g. bioequivalence guideline)
- the adherence to - and enforcement of - Guidelines (are they up to the scientific standard?)
- the acceptance to deviate from a Guideline based on a single national scientific advice from the RMS

Definition of potential serious risk to public health

Quality, safety, efficacy as regards to

- patient health or
- public health
- or any risk of undesirable effects on the environment

PLUS:

- adequate proof for bioequivalence
- safe use of medicine :
  - product information is misleading or incorrect for prescriber and patient to ensure the safe use of the medicine

CMDh referral

Trigger:

Disagreement between MS concerned by the application at the end of MRP (Day 90), DCP (Day 210), renewal and type II variation or Worksharing procedure, based on potential serious risk to public health.

The withdrawal of the Application in the disagreeing MS does not prevent a referral to the CMD(h) and CHMP

CMD(h) is not empowered to reject a Referral if a MS concerned by the procedure claims a potential serious risk to public health related to the approval of an application for a marketing authorisation.

CMD(h) & The 60-day Procedure

Outcome of discussions

☑ Agreement reached: The RMS shall record the agreement, close the procedure and inform the applicant accordingly. National phase starts.

☒ Agreement not reached: the European Agency shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34 of Directive 2001/83 and shall be provided with a detailed statement of the matters on which the MS have been unable to reach agreement and the reasons for the disagreement. CHMP referral starts.

EU network: progressing to the future

- Worksharing (variations, paediatric data, ASMF)
- Increased coordination
- Increased transparency
- Strengthened Pharmacovigilance
- Harmonisation among MS as first step to face global harmonisation
- Dialogue with international partners (generics)

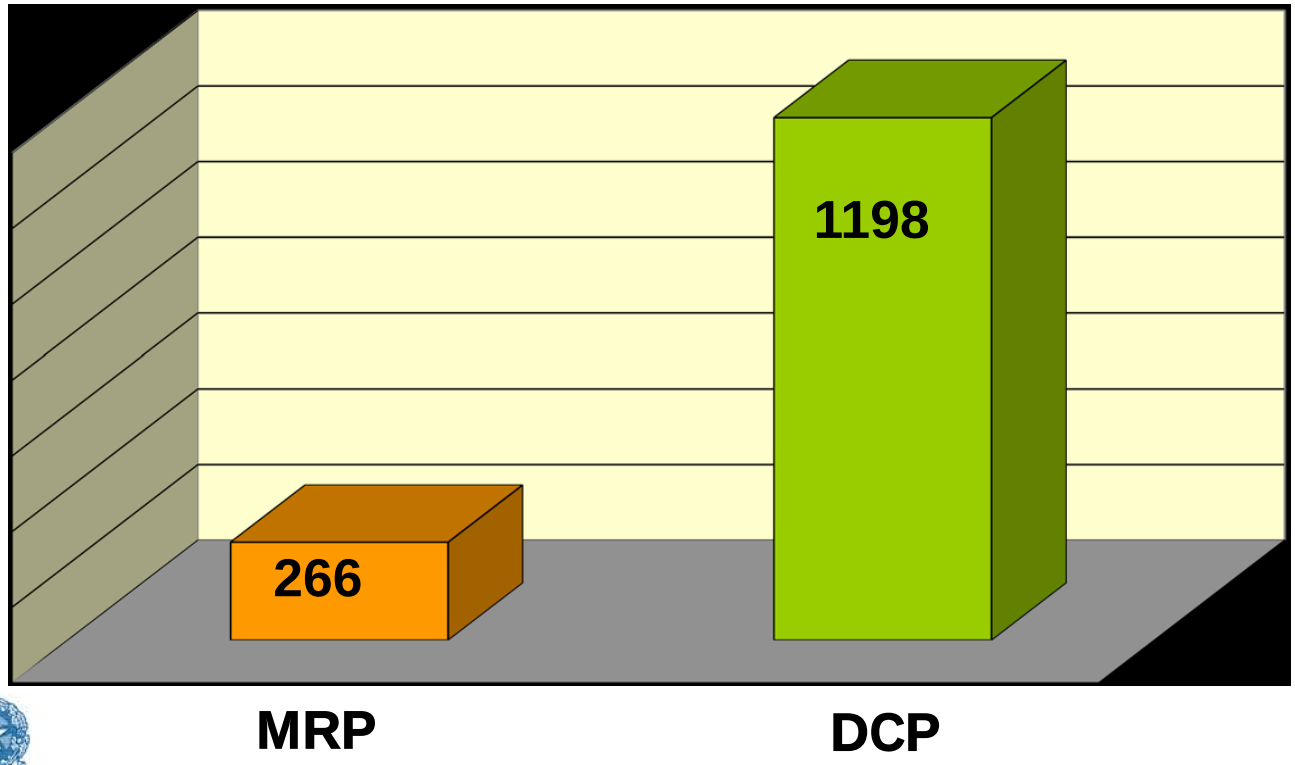
List of products for SPC Harmonisation (Article 30(2)) September 2006

Product Name	Active Substance	MAH
Cozaar	losartan	MSD
Cozaar Comp/Hyzaar/Fontzaar	losartan/hydrochlorothiazide	
Tritace/Cardace	ramipril	Aventis Pharma
Cardace Comp/Tirtazide	ramipril/hydrochlorothiazide	
Risperdal	risperidone	Jansen-Cilag
Efexor	venlafaxine	Wyeth
Zoloft	sertraline	Pfizer
Ciproxin	ciprofloxacin	Bayer
Augmentin	amoxicillin/clavulanic acid	GSK
Gemzar	gemcitabine	Lilly
Zyrtec/Reactine	cetirizine	UCB

MRP/DCP statistics – new applications 2012

FINALISED Procedures

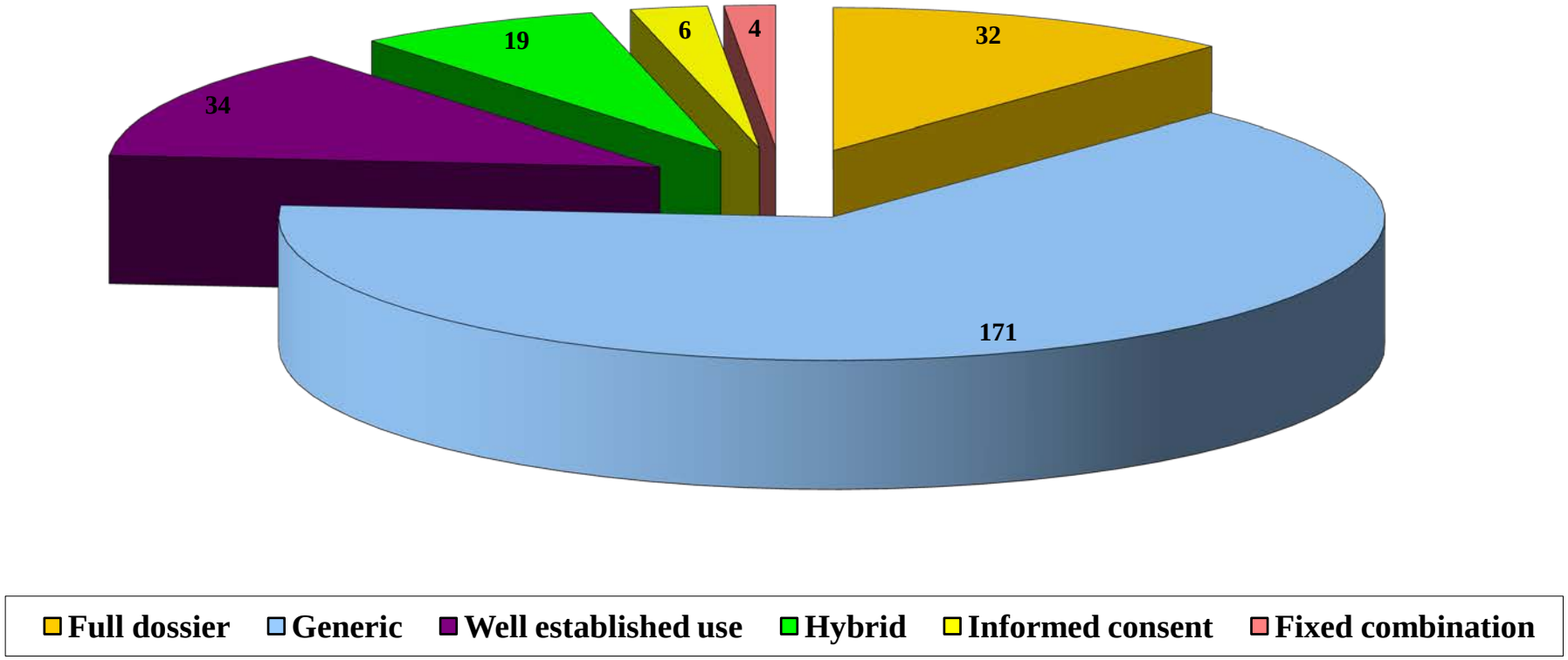
Total: 266 MRP and 1198 DCP (regarding 517 and 2354 products respectively)



MRP/DCP New applications - 2012

FINALISED Procedures - MRP per legal basis

Total: 266 MRP (regarding 517 products)



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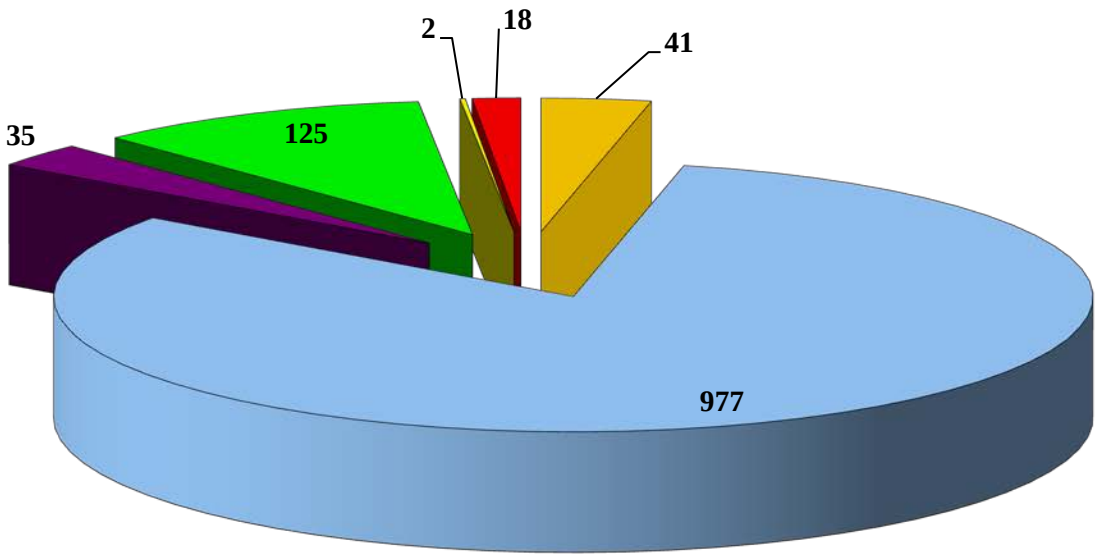
MRP/DCP New applications - 2012

FINALISED Procedures - DCP per legal basis

Total: 1198 DCP (regarding 2354 products)



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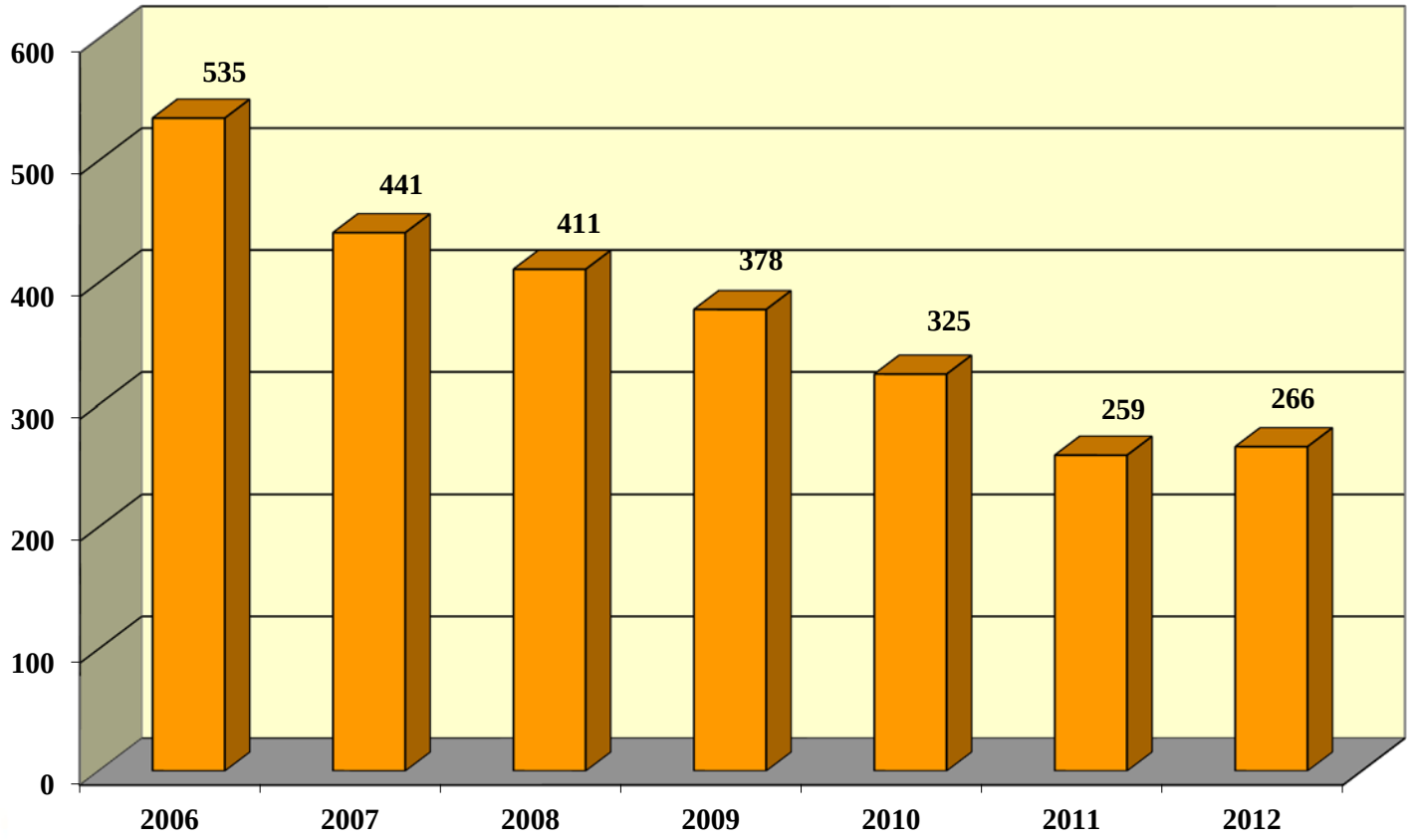
MRP/DCP New applications 2006-2012

FINALISED Procedures – MRP



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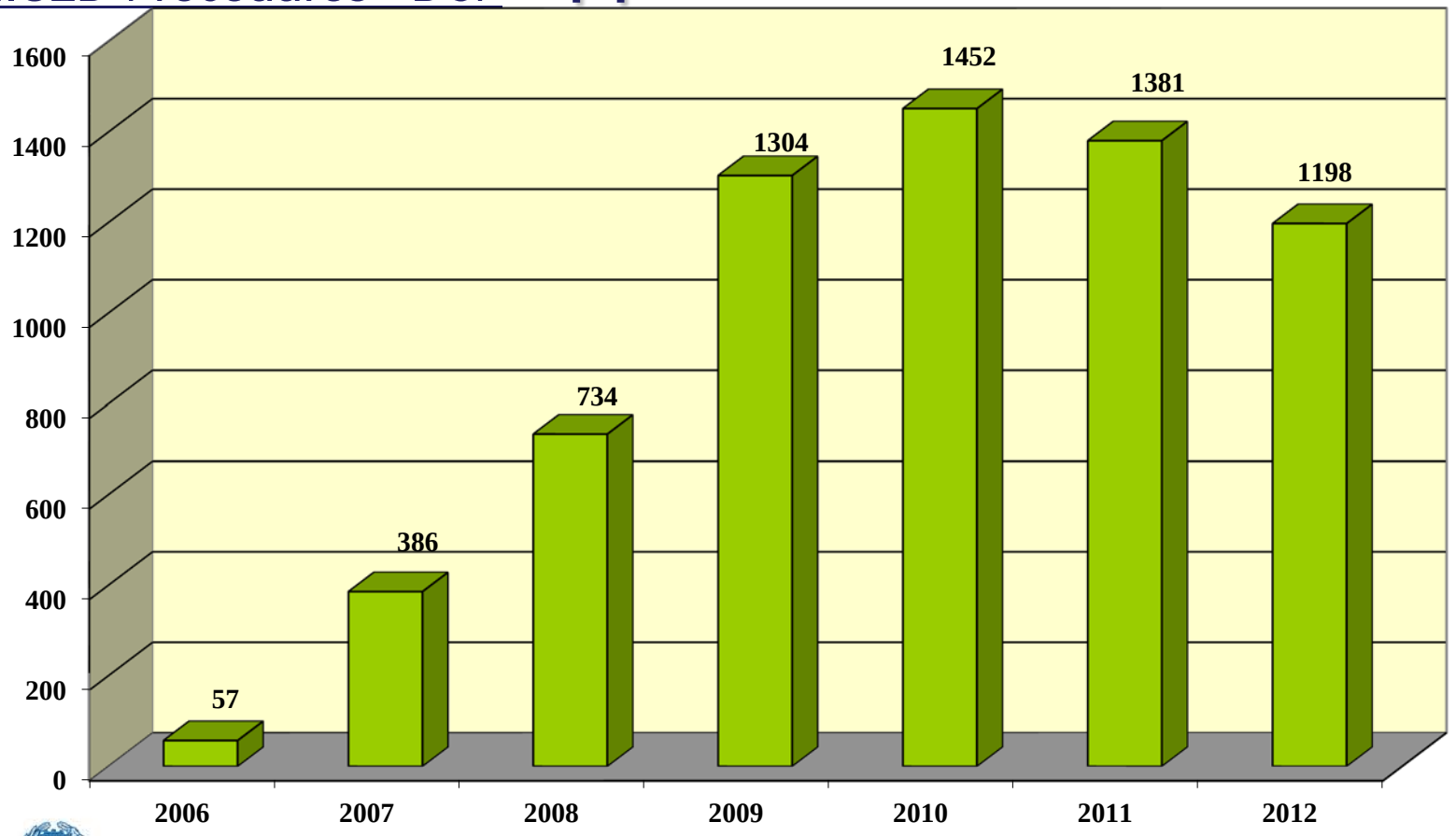
MRP/DCP New applications

FINALISED Procedures –DCP



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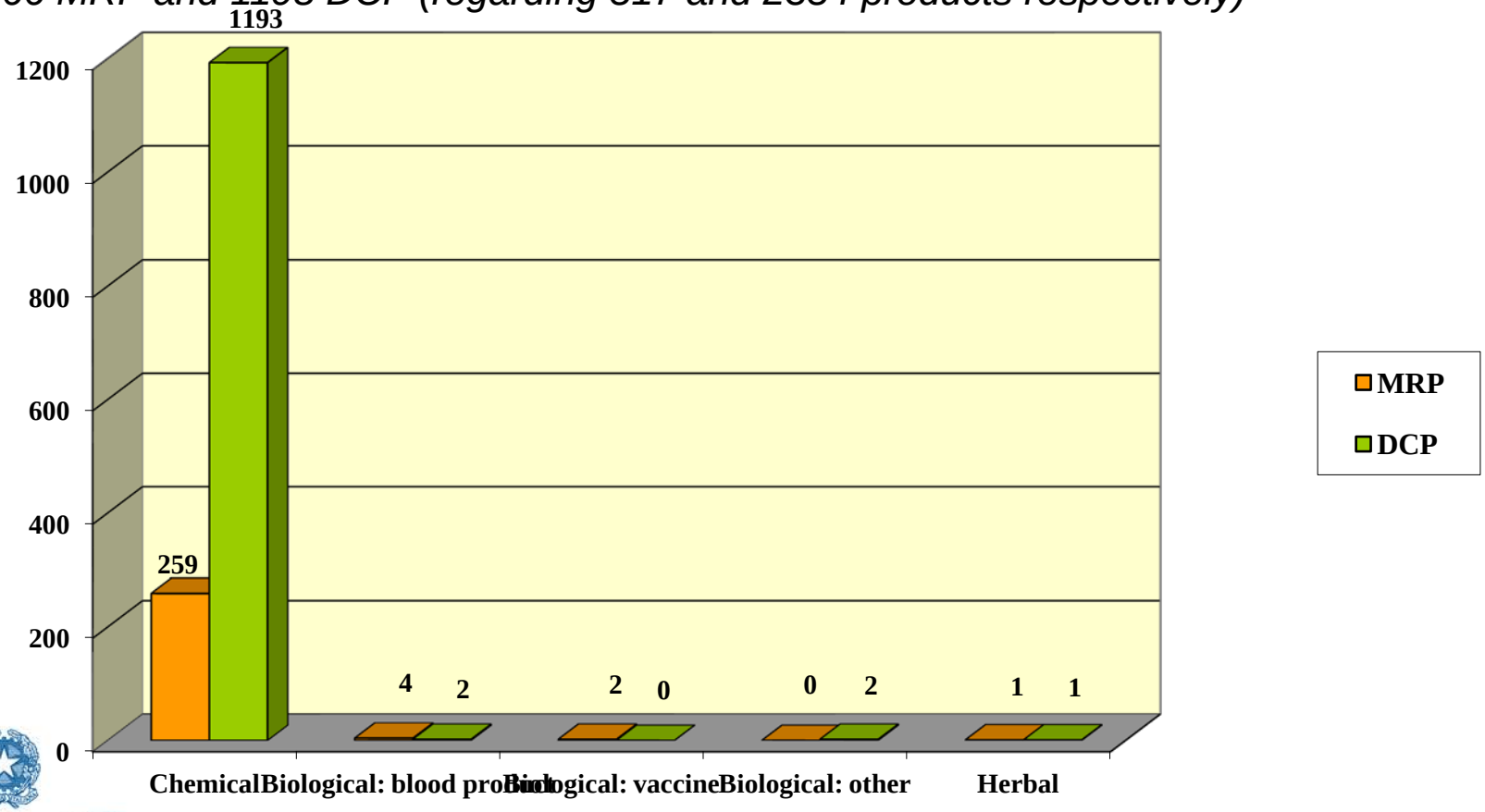
MRP/DCP New applications - 2012

FINALISED Procedures – MRP/DCP per type of product*

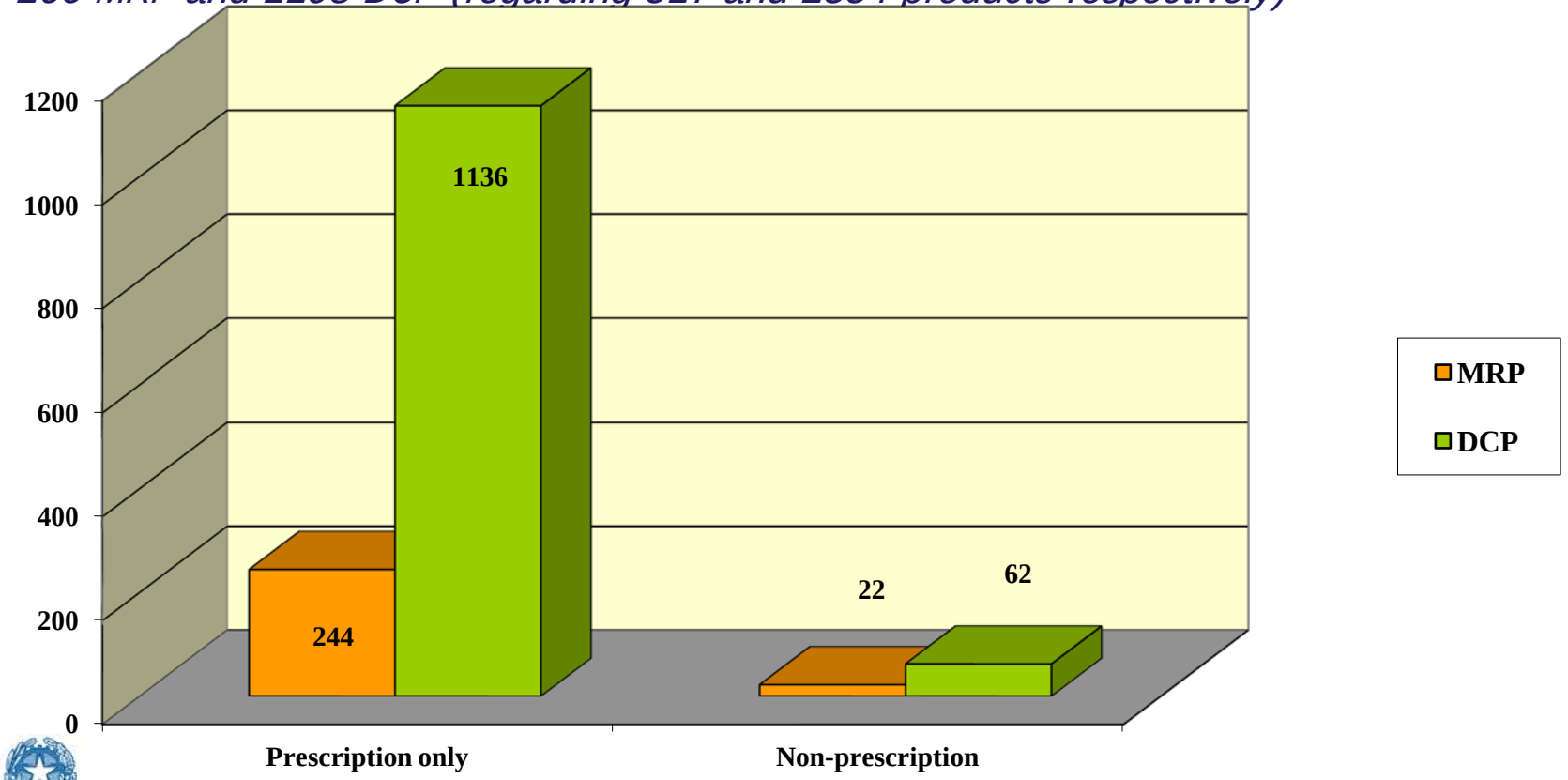
Total: 266 MRP and 1198 DCP (regarding 517 and 2354 products respectively)



MRP/DCP New applications - 2012

FINALISED Procedures – MRP/DCP per prescription status *(as approved by the RMS)*

Total: 266 MRP and 1198 DCP (regarding 517 and 2354 products respectively)



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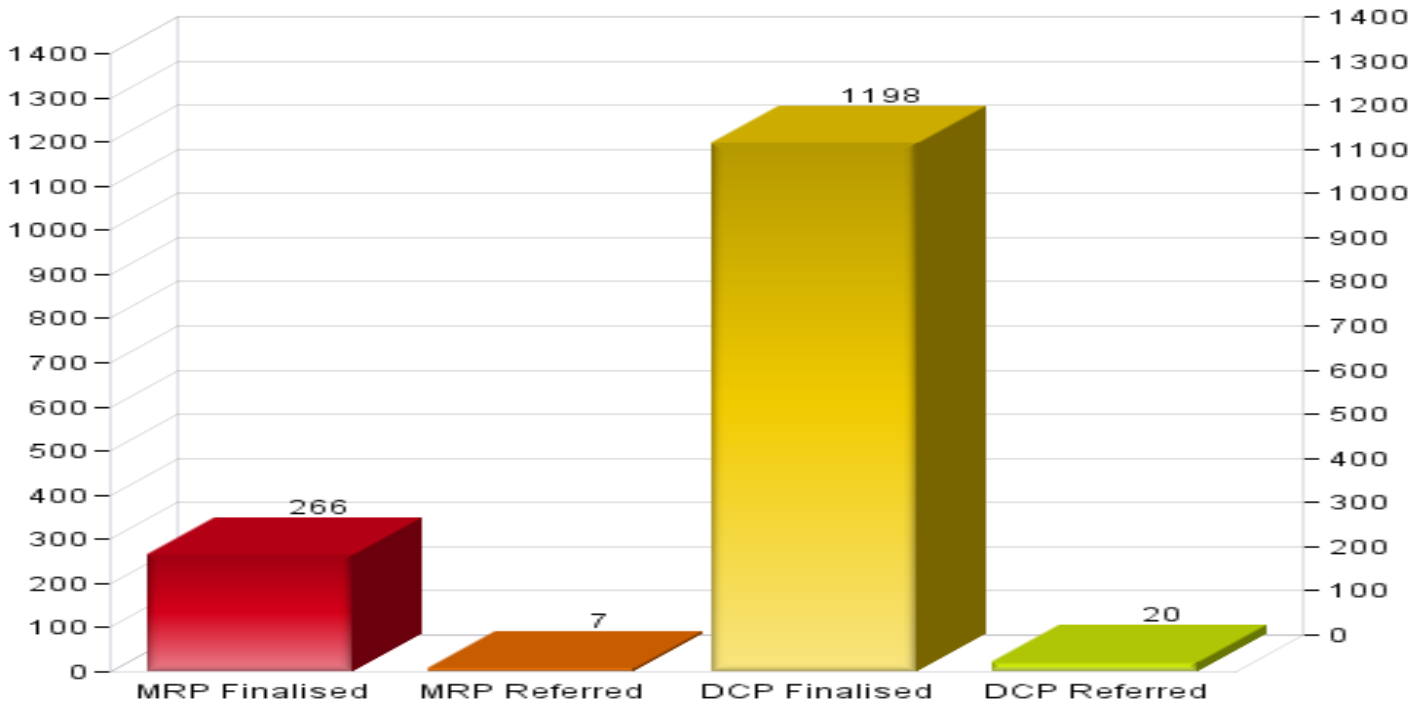
CMDh 60-day Referral Procedures - 2012

Per Type of Procedures (MRP/DCP)
Overview Finalised vs. Referred to CMDh in 2011

** The numbers include **2** procedures (DCP) referred to the CMDh on identical grounds*



2.6% **1.7%**

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DCP: New active substances authorised 2013

- A/California/07/2009(H1N1)v, A/California/7/2004(H3N2)-like virus, B/Brisbane/60/2008, B/Hong Kong/330/2001-like virus
- Olodaterol
- Ceftobiprolmedocaril

Legislation and guidance

- Directive 2001/83 and amendments

  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF
- EC Guideline on the definition of potential serious risk to public health

  http://ec.europa.eu/health/files/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf
- Notice to applicants (vol. 2)

  http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm
- BPG/SOP, Q&A and specific guidance: CMDh website

  http://www.hma.eu/cmdh.html
- EU network of NCAs:

  http://www.hma.eu/index.html

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