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COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

ADEQUACY OF GUIDANCE ON THE ELDERLY REGARDING MEDICINAL PRODUCTS FOR HUMAN USE

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EXECUTIVE SUMMARY

The European Medicines Agency (EMEA) received on August 2006 a request from the European Commission (EC) for the Committee for Human Medicinal Products (CHMP) to provide for an opinion on the adequacy of guidance on the elderly regarding medicinal products for human use, on the basis of Article 5(3) of Regulation (EC) No 724/2004.

This report provides: 1) An overview of how currently CHMP Guidelines (as published on the EMEA external website) address specific requirements for the elderly population, mostly with reference to the International Conference of Harmonisation (ICH) E7 overarching guideline. 2) A preliminary analysis on 10 recently centrally approved medicinal product dossiers, focussing on the actual participation of patients over 65 years in clinical development programmes. The source documents were the CHMP assessment reports and the Day 70-80 Rapporteur and Co-Rapporteur assessment reports. In this phase we did not consider the original dossiers submitted by the Applicants. 3) A preliminary discussion on the current overall adequacy of the ICH E7, focussing on possible areas of further development and or detail.

In keeping with the EC request, a consultation phase with interested parties about the elderly population representativeness in clinical developments of new medicines was started. In this respect, the European Union Geriatric Medicine Society (EUGMS) was met at the EMEA. During this meeting it was agreed that EUGMS would seek a consensus definition of age cut-offs for elderly and very elderly, as well as for 'frailty', to be subsequently integrated in future guidelines.

From this review: 1) Most of the current efficacy guidelines are in compliance with ICH E7. Those that are not, are currently being reviewed (i.e., Alzheimer's disease) or planned for review in 2007/2008. Particularly, we suggest introducing specific requirements for the elderly population in *"Urinary incontinence"* in women (CPMP/EWP/18/01) and *"New anti-fungal agents for invasive fungal infection"* (CPMP/EWP/1343/01). 2) On the basis of the sample of the 10 dossiers we analysed, overall they appear reasonably compliant with both ICH E7 and the disease related efficacy guidelines (as applicable). 3) Concerning the ICH E7, where most issues are already covered in general terms, the requirements for the clinical development programmes should be further specified in terms of elderly and very elderly; and of the distribution of age groups in the targeted patient population which should be taken into account in the clinical studies.

In view of the above, the following recommendations were endorsed by the CHMP:

1. To discuss the opportunity for updating ICH E7, which could lead to a CHMP concept paper.
2. For the professional bodies to define elderly, frailty and adequate age cut-off points.
3. To continue adding a specific section on elderly in the CHMP guidelines and to update these where necessary. Comments from specifically interested parties should be sought during the consultation phase.
4. To emphasise in Scientific Advice and other discussions with the Companies, both at European Union (EU) and National Authority levels, the need to plan to recruit an adequate number of elderly of various ages in the studies, as relevant.
5. To systematically require the appraisal of elderly exposure (as relevant) in the assessment process (centralised procedure, referral and mutual recognition), and to standardise the issue in the CHMP Assessment Report and Summary of Product Characteristics (SPC) (via the update of the existing templates).

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1. INTRODUCTION

1.1 Background

The European population is ageing. The World Health Organisation (WHO) (2001) has recently highlighted that nine of the 10 countries with more than 10 millions habitants which have the largest proportion of people over 60 are in Europe. The older than 75 represent the fastest growing segment of the ageing population and approximately 69 millions of elderly over 80 are still alive worldwide, most of them in developed countries (UN, 2001).

There is an increased interest concerning elderly patients and particularly how their specific biological and medical conditions are taken into account in the development and evaluation of new medicines. The WHO (November 2004), in the study "Priority Medicines for Europe and the World" concluded that "*the elderly are still unjustifiably excluded from clinical trials. Laws and guidelines should be developed which include the obligations towards the participation of the elderly*". In this frame, the European Union Geriatric Medicine Society (EUGMS) has expressed to the European Commission its concern about the lack of clinical trials in the very old and the potential health impact of the transfer of the research results into this population.

1.2 The European Commission Request

The European Medicines Agency (EMEA) received on the 18th of August 2006 a request from the European Commission for the Committee for Human Medicinal Products (CHMP) to provide for an opinion on the adequacy of guidance on the elderly regarding medicinal products for human use, on the basis of Article 5(3) of Regulation (EC) No 724/2004.

In particular the European Commission Enterprise and Industry Directorate General (EC-DG ENT) asked the EMEA:

- To review the scientific guidance relating to the conduct of clinical trials for medicines for human use to assess whether the guidance on the elderly subjects reflects up to date medical knowledge and is comprehensive
- To liaise with the EUGMS to ensure that their concerns are adequately explored.

The EC-DG ENT considered that the CHMP opinion could be delivered by the 31st of December 2006.

1.3 The CHMP action plan

The CHMP, in its September 2006 meeting, discussed and agreed the following action plan:

- Meeting with the EUGMS in October/November 2006 with the objective of identifying priority areas in which guidelines need revision or updating to address the requirements on the inclusion of the elderly and very elderly in clinical trials for drug development
- Provide for a summary overview of current CHMP Guidelines addressing specific requirements for the elderly population. This might result in a proposal for revision of CHMP guidelines (including the ICH based ones) and consideration of the adequacy of the ICH E7 "*Note for guidance on studies in support of special populations: Geriatrics" CPMP/ICH/379/95*
- The need for initiation of additional guidelines in relevant therapeutic areas might also be considered.

1.4 Objectives

The objectives of the present document are:

- To review the existing guidelines' topics characteristic of ageing or known to affect a substantial number of elderly patients
- To review 10 recent assessment reports of new medicinal products within the centralised procedure to assess the availability of the data for the elderly population
- To consider the current adequacy of ICH E7.

2. METHODOLOGY

2.1 In relation to the guidelines

A review of both adopted and draft guidelines and points to consider documents posted on the EMEA external website was conducted. For analysis, we identified those that were relevant for the elderly population.

The documents were evaluated for their compliance to ICH E7 in terms of pharmacokinetics, efficacy and safety and whether or not they asked for specific drug-drug interactions studies. The guidance documents are considered adequate or compliant if they refer to ICH E7 in one of the following ways:

- There is the recommendation to be read in conjunction with ICH E7, or
- They ask for specific requirements included in ICH E7, or
- There is a recommendation to be read in conjunction with methodology guidelines, which require to be read in conjunction with ICH E7.

Further comments on particular guidelines were also done.

Step process:

- To identify general, Efficacy Working Party (EWP), Biologics WP (BWP) and Vaccine WP (VWP) adopted and draft guidelines, as well as "Points to consider" documents relevant to the elderly
- To evaluate whether or not these documents take into account ICH E7 in terms of:
    - Pharmacokinetics (PK)
    - Efficacy (E)
    - Safety (S)
    - Requirement of specific drug-drug interactions studies (DI)
- To draw conclusions on specific points that might be improved.

2.2 In relation to recently approved medicines through the centralised procedure

For analysis, 10 recent dossiers of medicinal products were selected on the basis of their relevance for the elderly population. This sample is not meant to be representative of the overall activity of the EMEA in the recent years, but rather to be used as a first indicator and to illustrate how the requirements for the elderly are implemented. Our objective was to have descriptive statistics for each particular dossier and not to compare percentages of elderly patients exposed to different investigational medicinal products.

The source documents for the analysis of the elderly participation were the CHMP assessment reports and the Day 70-80 Rapporteur and Co-Rapporteur assessment reports. In this stage, we did not consider the original dossiers submitted by the Applicants.

Step process:

- To estimate the proportion of patients aged 65 and above who actually participated in the clinical development programme.
- To describe the number of elderly patients included in each phase clinical trials
- To assess its adequacy to all the requirements of both ICH E7 and the relevant efficacy guideline
- To evaluate the information on the elderly contained in the Summary of Product Characteristics (SPC).

Steps of the analysis for the estimation of the exposure of the elderly population:

- Obtain the total number of patients included in pharmacokinetic, efficacy and safety studies (primary and secondary databases)
- Recognise in phase 1, 2 or 3 studies those which included patients aged 65 or over
- Distinguish the actual number of elderly exposed and non exposed to the treatment for the primary indication, either by
    - Counting them

  or
    - Estimating their number from the mean age of the sample and the standard deviation, assuming that the variable age follows a normal distribution.

3. RESULTS

3. 1 Guidelines adequacy to ICH E7

Table 1: Number of relevant guidelines to the elderly population analysed

• General guidelines		6
• EWP guidelines	*Adopted*	27
	Draft	6
	Points to consider	9
• BPWP guidelines		5
• VWP guidelines		3
Total		56

Most of the current general and efficacy guidelines are in compliance with ICH E7, as well as the draft guidelines and "Points to Consider" documents issued by the EWP.

None of the four BWP guidelines identified as being relevant to the elderly fulfilled ICH E7 requirements. Only *"Points to consider on the development of live attenuated influenza vaccines"* (CPMP/BWP/2289/01 Feb 2003) took into account the elderly population in terms of efficacy and safety.

All the three relevant guidelines from the VWP fulfilled ICH E7 requirements for efficacy and safety.

The details of the above-mentioned results are displayed in Appendix 1.

3. 2 Products' dossiers adequacy to ICH E7

The dossiers analysed were:

1. Cymbalta (duloxetine) for major depression, EMEA/H/C/572
2. Abilify (aripiprazole) for schizophrenia, EMEA/H/C/471
3. Cubicin (daptomycin) for complicated skin and soft tissues infections, EMEA/H/C/637
4. Neupro (rotigotine) for early stage of Parkinson's disease, EMEA/H/C/626
5. Lucentis (ranimizumab) for age-related macular degeneration in patients with subfoveal choroidal neovascularisation, EMEA/H/C/000715
6. Cialis (tadalafil) for erectile dysfunction, EMEA/H/C/436
7. Avastin (bevacizumab) for first line treatment metastatic carcinoma of colon or rectum, EMEA/H/C/582
8. Exubera (insulin inhalation powder) for type 1 and type 2 diabetes mellitus, EMEA/H/C/558
9. Faslodex (fulvestrant) for locally advanced or metastatic breast cancer, EMEA/H/C/540
10. Corlentor (ivabradine) for chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers, EMEA/H/C/598.

3.2.1 ICH E7 requirements

The list below summarises the ICH E7 requirements for which the above-mentioned ten dossiers have been analysed.

Is the indication within the scope of the guideline?
Are at least 100 patients over 65 included?
Does the protocol include > 65 age range?
Does the protocol include > 75 age range?
Do the geriatrics constitute major proportion in the clinical database?
Are there exclusions based on age?
Are there exclusions based on co-morbidity?
Is there an evaluation for age related differences for efficacy?
Is there an evaluation for age related differences for dose response?
Is there an evaluation for age related differences for adverse events?
Is there a characterisation of special PK behaviour?
Is there a PK initial pilot trial young vs. elderly?
Is there a larger single dose PK study young vs. elderly?
Is there a multiple dose PK study young vs. elderly?
Is there an evaluation for demographic factors?
Is there an evaluation for physiological factors?
Is there an extensive renal excretion of active substance?
Is there an extensive hepatic excretion of active substance?
Is there a characterisation of abnormal renal function?
Is there a characterisation of abnormal hepatic function?
Does the drug have a narrow therapeutic range?
Is there a relevant Cyt P450 metabolism?
Are there drug-drug interaction studies?

3.2.2 Overall results

On the basis of this sample, the 10 analysed dossiers appear, overall, reasonably compliant with ICH E7.

The average number of total exposed elderly patients is 451 (range 143; 988). However, the proportion of elderly people among the total number of patients exposed was highly variable, depending on the indication for which the Marketing Authorisation (MA) was sought.

Five of the dossiers included specific studies for the elderly and all of them analysed the results for those aged over 65. Nevertheless, none of them considered an independent analysis for the frail or the very elderly.

3.2.3 Geriatric exposure during the clinical development programmes

For a better comprehension, the proportions of elderly patients enrolled in the clinical studies for each dossier are displayed in conjunction with the discussion.

4. DISCUSSION

4.1 Guidelines

4.1.1 Guidelines recommendations on pharmacokinetic studies applicable to the elderly

The *"Note for guidance on studies in support of special populations: Geriatrics"* (CPMP/ICH/379/95), states that the information regarding age-related differences in the PK of a drug can come, at the sponsor's option, either from a PK screen in conjunction with the main phase 3 studies ***or*** from formal PK studies in the elderly. Where the screen detects large differences, then formal PK studies may be indicated. The formal PK studies can be done in healthy geriatric subjects ***or*** in patient volunteers with the disease to be treated by the drug.

More restrictive in this sense, the guideline on *"Pharmacokinetic Studies in Man"* (EudraLex 3CC3a) also recommends that kinetics should be studied in the extreme ages but in ***patients*** and not in healthy subjects. However, it acknowledges that this requires multiple, long and expensive studies which cannot all be performed before authorisation.

4.1.2 Guidelines recommendations on drug interaction studies applicable to the elderly

The ICH E7 considers that specific drug-drug interaction studies should be planned in the cases where the therapeutic index of the drug or concomitant drugs is narrow. Moreover, *"General considerations for clinical trials"* (CPMP/ICH/291/95) recommends that for drugs which are frequently co-administered, it is usually important that drug-drug interaction testing are performed in non-clinical and, if appropriate, in human studies.

The *"Note for guidance on the investigations of drug interactions"* (CPMP/EWP/560/95, Dec 97) outlines the requirements for interaction studies on new chemical entities (NCE) on the basis of their physico-chemical, pharmacokinetic and pharmacodynamic properties, but not on the basis of their clinical indication or the likelihood of the targeted population of having concomitant treatments.

Nevertheless, this is done intentionally, as mechanistic studies can be done to extrapolate to a variety of situations. Knowledge from adequate absorption/distribution/metabolism/excretion (ADME) studies and mechanistic interaction studies may help in predicting possible problems due to change in C_{max}, AUC or interaction. The fact that specific PK studies would probably be conducted in healthy elderly, and therefore may be less relevant for the targeted population, is also discussed. It is agreed that the place of population PK should be further explored.

Indeed, if no interaction is detected in an appropriately performed *in vitro* study, there is no need to perform an *in vivo* study. Only if an interaction is indicated from *in vitro* data, applicants should

design and perform relevant in vivo studies. However, the claim of *"No clinically relevant interaction with Drug X"* in the SPC requires confirmatory in vivo studies.

In the end, the need of specific PK or drug interaction studies in elderly patients should be based on the knowledge of the product characteristics and the expected clinical use in this population. The appraisal of these integrated aspects (PK, possible interactions and their clinical relevance) should be found in the CHMP assessment report. In this regard, the template could be updated.

4.1.3 Comments on EWP Adopted guidelines

Generally, most of the adopted and draft guidelines, as well as the "Points to Consider" documents, fully comply with ICH E7. However, few of these guidelines contain a section on specific populations/elderly, in which the need for data in this patient group, taking into account the indication, is discussed.

The guidelines which are not formally in compliance with ICH E7 are discussed below.

- *Fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction CPMP/EWP/967/01 (Jun 2003):*
    - This guideline is recommended to be read in conjunction with *"Note for guidance on the investigation on drug interactions"* (CHMP/EWP/560/95). However, a specific section on elderly is lacking.

- *Alzheimer's disease CPMP/EWP/553/95 corrected (Sept 97):*
    - This guideline does not fulfil the formal requirements of ICH E7 in terms of E and PK.
    - Although Alzheimer's disease (AD) is characteristic of ageing, this guideline does not specifically mention ICH E7.
    - Clinical trial's eligibility criteria are based on the diagnosis of the disease regardless of age. However, the chance of having aged patients is very high in the view of the medical condition considered.
    - Efficacy endpoints of AD treatments are not asked to be analysed by age.
    - Efficacy studies are recommended to be hold mainly in mild or moderate forms of the disease as it is difficult to seek improvement in advanced dementia. This may lead to a lack of adequate data to support safety in the very elderly, though separated studies should be conducted in severe forms.
    - Safety relies on *"Note of Guidance on Clinical Investigation of Medicinal Products for Long-Term Use" (EudraLex 3CC6a)*: *"Investigation on Efficacy (…) the extreme age groups (elderly, children) should be appropriately included"*.
    - There is a recommendation to carry out interaction studies between the test drug and the drugs commonly used in the elderly.
    - The *"Recommendation on the need for the revision of the guideline on medicinal products in the treatment of Alzheimer's Disease"* (CHMP/EWP/369929/2005) recommends a review of the existing guideline in terms of an extension of the scope of the document in order to be applicable to other kind of dementia (vascular, Lewy bodies type, mixed), not mentioning any recommendation for the age inclusion criteria. This will be planned for discussion within the next EWP.

- *Urinary incontinence in women CPMP/EWP/18/01/final (Dec 2002)*
    - This guideline does not fulfil the requirements of ICH E7 for E, S and PK.
    - A very unspecific statement says that the guideline should to be read in conjunction with relevant current and future guidelines.

4.1.4 Comments on EWP "Points to consider" documents

- *New Anti-Fungal Agents for Invasive Fungal Infections CPMP/EWP/1343/01 (May 03)*
  - Oropharyngeal and oesophageal candidiasis are within the scope of this document. Although a large number of elderly patients are expected to be affected, there is no specific mention to ICH E7. Moreover this guideline does not fulfil ICH E7 requirements for E, S, or PK.
  - Because of the fact that underlying conditions may affect almost all the patients included in the studies, this document recommends to give special attention to all the possible confounding factors in the inclusion/exclusion criteria section. However, it does not specifically recommend examining the results for the presence of these factors (e.g. age). In this sense, it might be discussed whether the efficacy results of young adults could be extrapolated to the elderly.
  - Although limited safety data might be considered acceptable where the observed safety profile is such that the risk-benefit is considered to be favourable, this should be assessed for the elderly.

- *Irritable bowel syndrome CPMP/EWP/785/97 (Mar 03)*
  - This document does not mention ICH E7 and it does not fulfil its requirements for E, S or PK.
  - Although *"Inclusion and exclusion criteria for Irritable Bowel Syndrome (IBS) studies"* (part III) indicates that the study population should be representative of a broad spectrum of IBS patients, it seems to be related to the patients' care-setting origin (primary, secondary or tertiary care-settings) and not to age or to other demographic characteristics.
  - Sub-group analyses are recommended for gender but not for age.
  - Because of the fact that IBS is not a life-threatening condition and some of the drugs for its treatment may cause adverse reactions among the elderly (e.g. cognitive symptoms), depending on the pharmacology of the product, safety studies, which specifically target the elderly, might be of interest.

4.1.5 Comments on BWP guidelines

The decision to include such guidelines in our analysis relies on the fact that the indications of some of them are conditions expected to affect a meaningful number of elderly. Therefore, the adequacy of the guidance documents to the requirements of ICH E7 should be taken into account by other WP as well.

- *Plasma derived fibrin sealant/haemostatic products CPMP/BPWP/1089/00 (Jul 04)*
  Indications:
  - The application of mechanical pressure is not possible
  - Suturing is difficult
  - Reliable haemostasis is critical
  - Patient's own physiological coagulation is impaired

- *Human normal immunoglobulin for subcutaneous and intramuscular use CPMP/BWP/283/00 (Jul 02)*
  Indications:
  - Myeloma and Chronic Lymphocytic Leukaemia with severe secondary hypogammaglobulinemia and recurrent infections
  - Guillain Barré Syndrome

- *Plasma derived antithrombin products CPMP//BPWP/2220/99 (Jan 02)*
  Indications:
    - Disseminated Intravascular Coagulation, particularly in septic shock

4.1.6 Guidelines currently under revision within the EWP programme

According to the workplan for the Efficacy Working Party 2007-2008, a number of guidelines relevant to the elderly population are currently under revision or are considered for revision. These are summarised in Appendix 2.

In addition to these, we suggest introducing specific paragraphs about elderly patients' participation in clinical trials in the guidelines for the investigation of medicinal products for:

- Urinary incontinence in women (CPMP/EWP/18/01)
- New anti-fungal agents for invasive fungal infection (CPMP/EWP/1343/01)

4.2 Recently approved medicinal products

4.2.1 Cymbalta

Product (INN)/year of start of the procedure	**Cymbalta (duloxetine)/2003**
Indication	Major depression
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	1310
Total number of patients exposed for safety (primary indication)	2774
Number of patients exposed 12 months or longer	445
Mean age of participants	43.6
GERIATRICS EXPOSURE	
Total exposed elderly patients	143 for efficacy 261 for safety
Number of specific trials in the elderly (type)	2 (E, PK)
% efficacy exposure	10.9
% safety exposure	9.4

The centralised procedure for Cymbalta for the treatment of major depression started in 2003. It received a CHMP positive opinion on 16 September 2004 and a MA on 17 December 2004.

Depression is a common disorder in the over 65, with severe depression affecting 1–3% of the population and milder forms affecting 10–15% (WHO, 1999). It may sometimes be a difficult diagnosis, as depression in late life can be caused by concomitant administration of drugs and physical illnesses, such as hypothyroidism. Moreover, the incidence of major depression is significantly increased after stroke, after bereavement and in those with organic diseases or dementia, such as Parkinson's disease, Alzheimer's disease, Vascular Dementia or Dementia with Lewy Bodies.

According to the initial submission 143 and 261 elderly patients were exposed during the clinical development for efficacy and safety, respectively. ICH E7 requires al least 100, as a *"minimum (…) to allow detection of clinical important differences"*. There was one single dose (40 mg) PK study specifically in the elderly. Although the mean age of participants was 43.6 years, approximately 10.9% of the patients exposed for efficacy and 9.4% of those exposed for safety were aged 65 or over.

The age differences were evaluated for efficacy, safety and dose-response, and there was a characterisation of the abnormal hepatic and renal function.

Although the *"Note for guidance on clinical investigation of medicinal products in the treatment of depression"* (EMEA/EWP/518/97rev1) only requires specific trials in the elderly for new products with a new mechanism of action, the CHMP requested specific data on the elderly. The Marketing Authorisation Holder (MAH) presented a specific phase 3 study in the elderly including 207 patients aged 65 or older (study HMBV) as a follow-up measure. While the study was not powered to assess efficacy in patients over 75, 64 of the participants were in this age group. Taking into account this follow-up measure results, a total of 350 elderly patients were exposed to Cymbalta for efficacy.

More than 100 patients (445) were exposed to duloxetine for at least 12 months, as required by the *"Note for Guidance for the Clinical Investigation of Medicinal Products for Long-term Use"* (EudraLex 3CC6a).

The elderly population is taken into account in the SPC (Posology, Special warnings and PK properties).

4.2.2 Abilify

Product (INN)/year of start of the procedure	**Abilify (aripiprazole)/2001**
Indication	Schizophrenia
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	1704
Total number of patients exposed for safety (all aripiprazole dataset)	4199
Number of patients exposed 12 months or longer	805
Mean age of participants	43
GERIATRICS EXPOSURE	
Total exposed elderly patients	148
Number of specific trials in the elderly (type)	2 (E)
% efficacy exposure	8.6
% safety exposure	3.5

The centralised procedure for Abilify for the treatment of schizophrenia started in 2001. It received a CHMP positive opinion on 26 February 2004 and a MA on 04 June 2004.

Although schizophrenia is a disease of young adults, psychosis and behavioural disturbances are the most commonly associated problems to dementia. The prevalence of dementia after 65 years was estimated as being between 4 and 7% in 10 epidemiological studies. It doubles every 5 years such that rates rise from 1% at ages 65–74 to 7% at ages 75–84 to finally 25% after the age of 85 (WHO, 1999).

One hundred forty-eight (148) elderly patients were exposed during the clinical development. There were two efficacy studies for elderly patients:

- Study 31-98-203: 29 elderly patients with dementia, all of them receiving aripiprazole
- Study 138-006: 203 elderly patients with psychosis in Alzheimer's dementia, of whom 104 received aripiprazole

Study 31-98-203 was also used to evaluate the influence of age on aripiprazole pharmacokinetics.

Psychosis and behavioural disturbances are not within the scope of the *"Note for guidance for the clinical investigation of medicinal products in the treatment of schizophrenia"* (CPMP/EWP/559/95), and therefore the elderly might be considered being out of the target population. However, because of the fact that no product has been approved through the centralised procedure for psychosis in dementia, off-label use of antipsychotics in the elderly has to be taken into perspective.

Though the total number of elderly included in the clinical development was greater than 100, only 8.6% of the patients exposed for efficacy and 3.52% of those exposed for safety were aged 65 or over. The co-rapporteur pointed out that the limited sample size for patients who were ≥ 65 years of age (< 1% of the short-term placebo controls study population) precluded meaningful interpretation of their adverse events (AEs) relatively to the patients in other age groups. In the long-term controlled studies in schizophrenia, no patient was > 65 years of age and only 3 patients were exactly 65 at the study entry.

Therefore, in May 2005, the MAH submitted as follow-up measure requested by the CHMP a report of three studies involving 293 elderly institutionalised patients with Alzheimer's disease and psychosis (CN 138004, CN 138005 and an extension of CN 138006). Taking into account this follow-up measure results, a total of 441 elderly patients were exposed to Abilify for efficacy.

The SPC mentions the elderly for Special posology and PK properties (no need for dose adjustment). There was an overall compliance with the relevant efficacy guideline and more than 100 patients (805) were exposed to aripiprazole for at least 12 months, as required by *the "Note for Guidance for the Clinical Investigation of Medicinal Products for Long-term Use"* (EudraLex 3CC6a).

4.2.3 Cubicin

Product (INN)/year of start of the procedure	**Cubicin (daptomycin)/2004**
Indication	Complicated skin and soft tissues infections
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	1440
Total number of patients exposed for safety	1474
Number of patients exposed 12 months or longer	0
Mean age of participants	51.7
GERIATRICS EXPOSURE	
Total exposed elderly patients	431
Number of specific trials in the elderly (type)	1 (PK)
% efficacy exposure	29.9
% safety exposure	29.2

The centralised procedure for Cubicin for the treatment of complicated skin and soft tissue infections started in 2004. It received a CHMP positive opinion on 17 November 2005 and a MA on 19 January 2006.

Four hundred thirty-one (431) elderly patients were exposed during the clinical development. There was one single dose (4 mg) PK study specifically on the elderly (DAP-GER-01-11) which evaluated the PK responses of 10 men and 2 women aged 75 to 82.

The mean age of study participants was 51.7 years. Approximately 30% of the patients exposed for efficacy and 29.2% of those exposed for safety were over 65. More than 12% of the patients exposed to daptomycin in the 2 pivotal phase 3 studies were aged 75 or over.

A relatively large percentage of elderly exposure was expected, as the main studies were carried out in hospitals and the diagnosis for inclusion were conditions likely to affect aged patients (e.g. wound infections, major abscesses, infected ulcers, severe carbunculosis, infections involving deeper soft tissue, fascia or muscle, pre-existing skin lesion or some underlying condition that might adversely affect either the delivery of drug to the affected area, the immunologic response, or healing).

Although the age differences (< 65 vs. > 65) were evaluated for efficacy, safety and dose-response, and there was a characterisation of the abnormal hepatic and renal function, there was not a specific efficacy or safety analysis for the very elderly or for the frail.

The elderly population is taken into account in the SPC (Posology, Special warnings and PK properties), and there was an overall compliance with the relevant efficacy guideline.

4.2.4 Neupro

Product (INN)/year of start of the procedure	**Neupro (rotigotine)/2004**
Indication	Early stage of Parkinson's disease
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	1017
Total number of patients exposed for safety (primary indication)	1087
Number of patients exposed 12 months or longer	302
Mean age of participants	61.5
GERIATRICS EXPOSURE	
Total exposed elderly patients	290
Number of specific trials in the elderly (type)	0
% efficacy exposure	28.5
% safety exposure	26.7

The centralised procedure for Neupro for the treatment of early stage of Parkinson's disease started in 2004. It received a CHMP positive opinion on 14 December 2005 and a MA on 15 February 2006.

In 1991, in Europe, the overall prevalence per 100 population of parkinsonism and Parkinson's disease for the age groups 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85 to 89 years was respectively, 0.9, 1.5, 3.7, 5.0, and 5.1 (Europarkinson Collaborative Study, 1997). More recently, the Neurologic Disease Research Group in the Elderly (2000) measured an overall prevalence of Parkinson's disease in persons 65 years of age and older of 1.8, with an increase from 0.6 for those age 65 to 69 years to 2.6 for those 85 to 89 years.

Two hundred ninety (290) elderly patients were exposed during the clinical development programme. There was no specific trial for the elderly.

Approximately 30% of the patients exposed for efficacy and 26.7% of those exposed for safety were aged 65 or over. Parkinson's disease is a condition characteristic of ageing. However, the indication, for which the MA was sought (early stage of the disease), might have reduced the mean age of the participants. Indeed, only 73 patients (of whom 27 received the drug) of the two main pivotal studies were older than 75. The approximate mean age of the patients in the three efficacy studies was 61.5 years (Standard Deviation =10).

Age differences were evaluated for efficacy, safety and dose- response. Abnormal hepatic and renal functions were characterised. However, there were no specific analyses for the very elderly or for the frail.

The elderly population is taken into account in the SPC (Posology and PK properties). There was an overall compliance with the relevant efficacy guideline, and more than 100 patients (302) were exposed to rotigotine for at least 12 months.

4.2.5 Lucentis

Product (INN)/year of start of the procedure	**Lucentis (ranibizumab)/2006**
Indication	Age-related macular degeneration
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	979
Total number of patients exposed for safety (primary indication)	1096
Number of patients exposed 12 months or longer	916
Mean age of participants	78 (median)
GERIATRICS EXPOSURE	
Total exposed elderly patients	914
Number of specific trials in the elderly (type)	0
% efficacy exposure	93.4
% safety exposure	83.4

The centralised procedure for Lucentis for the treatment of age-related macular degeneration (AMD) in patients with subfoveal choroidal neovascularisation, started in 2006. It obtained a CHMP positive opinion on 16 November 2006 and a MA on 22 January 2007.

AMD is a disease occurring in older patients. Population based epidemiological studies have shown that AMD is rare before 55 years of age. It affects roughly 10% of the population aged 75 and above.

Nine hundred fourteen (914) patients aged 65 or over were exposed during the clinical development. There were no specific trials in the elderly. However, taking into account the age onset of AMD, a large proportion of elderly among the patients exposed was expected (93.4% for efficacy and 83.4% for safety). Indeed the median and range age observed in the studied population was 78 years and 65-87 years (5^{th} and 95^{th} percentiles), respectively. Subgroup analyses of the primary efficacy endpoint were performed by age (74 or younger vs. 75 or older).

The SPC does not contain any relevant additional information on the elderly, as it is assumed to be the targeted population.

4.2.6 Cialis

Product (INN)/year of start of the procedure	**Cialis (tadalafil)/2001**
Indication	Erectile dysfunction
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	949
Total number of patients exposed for safety (primary indication)	2991
Number of patients exposed 12 months or longer	231
Mean age of participants	58
GERIATRICS EXPOSURE	
Total exposed elderly patients	277
Number of specific trials in the elderly (type)	1 (PK)
% efficacy exposure	27.9
% safety exposure	Not available

The centralised procedure for Cialis for the treatment of erectile dysfunction started in 2001. It obtained a CHMP positive opinion on 25 July 2002 and a MA on 12 November 2002.

The Men's Health Survey (1998) assessed erectile dysfunction in 3607 men of all ages from five European countries and Canada. This study reported that the prevalence of complete erectile dysfunction triples from 5% in the 40 years old men to 15% in the 70 years old.

Two hundred seventy-seven (277) elderly patients were exposed during the clinical development. There was one single dose (10 mg) PK study specifically in the elderly.

A total of 231 patients were exposed to 20 mg of tadalafil for 12 months or longer. Overall, 312 patients were exposed for the same period to either 10 or 20 mg, which are the doses recommended in the SPC.

Approximately 28% of the patients exposed for efficacy were aged over 65. Based on the information contained on the day 70-80 assessments reports, and due to the particularities of the primary safety database, it was not possible to give a reliable estimation of the proportion of elderly patients exposed for safety.

Efficacy in patients aged over 65 was evaluated, which showed a significantly improved erectile function in a similar magnitude than in younger patients. The CHMP observed during the procedure that there was no specific analysis for the older than 75. However, taking into account the restrictions in the SPC for patients with renal impairment and other disease conditions, available data did not suggest the need for specific warnings based solely on age.

The elderly population is mentioned in the SPC in the Posology, Undesirable effects and PK properties sections.

4.2.7 Avastin

Product (INN)/year of start of the procedure	**Avastin (bevacizumab)/2003**
Indication	Colon or rectum metastatic carcinoma
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	1284
Total number of patients exposed for safety (primary indication)	591
Number of patients exposed 12 months or longer	205
Mean age of participants	60 (median)
GERIATRICS EXPOSURE	
Total exposed elderly patients	363
Number of specific trials in the elderly (type)	0
% efficacy exposure	28.3
% safety exposure	32.9

The centralised procedure for Avastin for first line treatment of metastatic carcinoma of colon and rectum started in 2003. It received a CHMP positive opinion on 21 October 2004 and a MA on 12 January 2005.

Colorectal cancer is the third most common malignant neoplasm worldwide, with a total of 495,000 deaths in 1996. The average age of detection is 63.8 years (WHO, 1999).

Three hundred sixty-three (363) elderly patients were exposed during the clinical development. There were no specific studies in the elderly. The approximate median age of the patients included in the efficacy studies within the clinical development was 60.

More than 28% of the patients exposed for efficacy and 32.9% of those exposed for safety were over 65. Patients older than 75 were separately analysed for safety and were found to be at higher risk of developing hypertension and diarrhoea than younger patients.

The SPC considers the elderly population in the following sections: Posology and Method of administration, Undesirable effects and Possible side effects.

4.2.8 Exubera

Product (INN)/year of start of the procedure	**Exubera (insulin inhalation powder)/2004**
Indication	Type 1 and 2 diabetes mellitus
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	2319
Total number of patients exposed for safety (primary indication)	3426
Number of patients exposed 12 months or longer	745
Mean age of participants	56
GERIATRICS EXPOSURE	
Total exposed elderly patients	342
Number of specific trials in the elderly (type)	1 (PK)
% efficacy exposure	14.8
% safety exposure	10

The centralised procedure for Exubera for the treatment of type 1 and 2 diabetes mellitus (DM) started in 2004. It obtained a CHMP positive opinion on 13 October 2005 and a MA on 24 January 2006.

The DEODE meta-analysis (2003) assembled data from 13 European countries. It estimated that the prevalence of total diabetes in the elderly population (per 100) was 15.5 and 16.1 in men and women aged 60-69 and 23.4 and 27.3 in men and women aged 70-79.

Three hundred forty-two (342) elderly patients were exposed during the clinical development. The estimated mean age of the participants was 56 years. Approximately 15% of type 1 and type 2 DM patients exposed for efficacy were over 65. This age group represented 10% of the patients exposed for safety. Regarding studies on type 2 DM, the elderly represented 16.6% of the exposure in phase 3. Only 37 subjects in phase 2 /3 studies were over 75 years. There was one single dose (4 mg) PK study specifically in the elderly.

The relevant efficacy guideline (CPMP/EWP/1080/00 May 02) recommends including a reasonable number of patients older than 75 in order to get unrestricted indication. The CHMP assessment report highlighted that the experience with Exubera in patients of this age was limited. This age limitation is acknowledged in the SPC. The MAH committed to include information on these patients in the Periodic Safety Update Reports.

More than 100 (745) patients were exposed to Exubera for at least 12 months, as required by the "*Note for Guidance for the Clinical Investigation of Medicinal Products for Long-term Use*" (EudraLex 3CC6a).

4.2.9 Faslodex

Product (INN)/year of start of the procedure	**Faslodex (fulvestrant)/2003**
Indication	Locally advanced or metastatic breast cancer
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	680
Total number of patients exposed for safety (primary indication)	1149
Number of patients exposed 12 months or longer	131
Mean age of participants	64 (median)
GERIATRICS EXPOSURE	
Total exposed elderly patients	298 for efficacy 465 for safety
Number of specific trials in the elderly (type)	0
% efficacy exposure	43.8
% safety exposure	40.5

The centralised procedure for Faslodex for the treatment of locally advanced or metastatic breast cancer started in 2003. It obtained a CHMP positive opinion on 20 November 2003 and a MA on 10 March 2004.

The incidence of breast cancer in Europe in the period 93-97 was 73.5 new cases per 100,000 inhabitants, with an increased ratio in relation to the period 73-77 of 1.42 in those aged 65-79 (*Althuis et al. Int J Epid 2005*).

Two hundred ninety-eight (298) and 465 patients aged 65 or over were exposed during the clinical development for efficacy and safety respectively, which represents 43.8 % and 40.5 % of the total exposure. The median age of patients included in the clinical development was 64 years.

However, the age-related differences were only evaluated for dose-response and not for efficacy or safety. Moreover, there were no specific trials in the elderly and potential participants were excluded on the basis of serious concurrent medical illnesses.

The SPC only mentions the elderly in the Posology section. No dose adjustment is needed.

4.2.10 Corlentor

Product (INN)/year of start of the procedure	**Corlentor (ivabradine)/2004**
Indication	Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers
TOTAL EXPOSURE	
Total number of patients exposed for efficacy	2805
Total number of patients exposed for safety (primary indication)	2907
Number of patients exposed 12 months or longer	216
Mean age of participants	60
GERIATRICS EXPOSURE	
Total exposed elderly patients	949 for efficacy 988 for safety
Number of specific trials in the elderly (type)	0
% efficacy exposure	33.8
% safety exposure	33.9

The centralised procedure for Corlentor for the treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers, started in 2004. It obtained a CHMP positive opinion on 27 July 2005 and a MA on 25 October 2005.

During the clinical development, 949 elderly patients were exposed for efficacy and 988 for safety. Patients aged 65 or over represented approximately 34% of the population exposed to ivabradine.

Although the estimated mean age of the participants in the clinical development was 60 years, only a limited number of patients older than 75 (n = 68) were included in the studies. Moreover, further analyses were requested from the MA holder during the scientific evaluation, where it was shown that PK was comparable for ≥ 65, ≥ 70 and > 75 year old patients group.

More than 100 (216) patients were exposed to ivabradine for at least 12 months, as required by the *"Note for Guidance for the Clinical Investigation of Medicinal Products for Long-term Use"* (EudraLex 3CC6a).

Efficacy and safety data were available in a limited number of patients aged 75 years or more, which is reflected in the SPC. Additional information on the elderly is included in Posology, Methods of administration and PK properties.

4.3 Preliminary considerations on the current adequacy of ICH E7 over the elderly population

ICH E7 recommends including in clinical trials a meaningful number of elderly patients (100 aged 65 years or older) for this "*would usually allow the detection of clinically important differences*" in relation to younger patients. Some issues should be considered in this respect:

- ***Age cut-offs***

ICH E7 arbitrary defines its scope as patients aged 65 years (standard retirement age) or older. At the present and hopefully in the next coming decades, people in their 60s or even in their 70s are becoming healthier. Nevertheless, the physiological changes of ageing (weight, body composition, decreased glomerular filtration rate, etc.) and the increased risk of neurodegenerative diseases, diabetes, cardiovascular events etc., make this age group different from the standard adults. The representativeness of the samples from this population has to be improved in concomitance to these demographic trends. 1) The current threshold for elderhood (the age of 65) needs to be reconsidered and 2) the interval from elderly to very elderly has to be defined, in order that both groups could be properly evaluated. A consensus will be sought, via the EUGMS.

- ***A difficult-to-reach population***

A consistent group of very elderly patients constitutes a difficult-to-reach population. At the final stages of life, expanding the life expectancy or achieving a cure may be a secondary goal. The quality of life is most of the times the major concern of patients, their families and their physicians. For these reasons, it may be unlikely to obtain from a significant number of these patients the informed consent to participate in clinical research programmes, especially in those for which the decrease of mortality is the primary endpoint. Moreover, this subgroup is a heterogeneous one. Concomitant illnesses and treatments make each patient unique, and therefore the sample representativeness less consistent.

- ***Frailty***

The frail constitute a subgroup within the elderly, which ICH E7 has to be aware of. However, frailty has not been univocally defined to date, although chronic conditions, co-morbidity and physical dependency take part in this scenario. A reliable estimation of their number would be useful. A consensus will be sought, via the EUGMS.

- ***Galenic formulations***

Both the physiological changes of ageing and the presence of concomitant illnesses in the elderly lead to variable pharmacokinetic and pharmacodynamic responses to substances. Moreover, other factors characteristic of this population such as poly-medication, disability, dependence on carers or social isolation may affect compliance. In this respect similar issues are applicable to children. The Paediatric Working Party and the Quality Working Party have recently published the *"Reflection Paper: Formulations of Choice for the Paediatric Population"* (CHMP/PEG/194810/2005). The objective of this document is to assist in the development of galenic formulations that facilitate the dose adjustment and enable both the patients and the carers to reduce the risk of medication errors and to improve compliance. A similar approach could be implemented for the elderly.

5. CONCLUSIONS

Summary of observations

Most of the current efficacy guidelines are in compliance with ICH E7. Those that are not, are currently being reviewed or planned for review in 2007/2008. Nevertheless, we suggest introducing specific requirements for the elderly population in the guidelines on Urinary Incontinence in women (CPMP/EWP/18/01) and on New Anti-fungal Agents for Invasive Fungal Infection (CPMP/EWP/1343/01).

On the basis of the sample of the 10 MA dossiers analysed, overall it appears a reasonable fulfilment of ICH E7 requirements and of the specific guidelines. All reviewed dossiers include more than 100 patients aged over 65 in the clinical development (though further analysis would be needed to see whether sufficient patients in the higher age range were included). When the proportion of patients over 65 was rather low, either specific studies (PK or efficacy trials) or independent analysis for dose-response, safety and efficacy were performed for this age group. If not, an acknowledgement was included in the SPC or the MA holder was required to provide further data in the Periodic Safety Update Reports.

At the same time as the European Commission request, the EMEA has started a consultation phase with parties interested on the representation of the elderly population in clinical developments of new medical products. In this respect, it was agreed that the European Union Geriatric Medicine Society (EUGMS) would issue a consensus definition of age cut-offs and frailty. Another main issue was raised concerning the possible role of regulators, professional bodies and prescribers, and also learned societies, on how to tackle *off-label* use of medicines in the elderly (e.g. antipsychotics for psychotic symptoms or behavioural disturbances associated to dementia). We planned to pursue this phase during the next two years.

The number of elderly patients in the clinical development programmes and the need for data in this population depend on the indication. For instance, schizophrenia *per se* is not typically a disorder of the elderly. On another hand, macular degeneration is common in the elderly whereas Parkinson's disease spreads across the end of adulthood and elderhood. This was reflected in the development programmes of the various products and is also discussed in the relevant guidelines. One area to be discussed more in depth is whether data are needed for efficacy, for safety or both. In other words, for any disease, in which extent existing efficacy data may be extrapolated from the younger age group to the older one, whether specific safety concerns apply to elderly patients, etc.

Final recommendations

Despite the fact that ICH E7 covers most of the possible issues in general terms, areas of improvements were identified:

1. To increase the number of elderly patients participating in the clinical development programmes, requiring a proportion of the efficacy and safety database, in relation to the indication, and mirroring the target population.
2. To consider the minimum requirements for two different age classes: elderly and very elderly.
3. In relation to the PK specific considerations, an adequate representation of elderly in the efficacy and safety database would integrate and complete the PK requirements (via population PK).

Nevertheless, these requirements may lead to multiple, long and expensive studies, which may not all be feasible before authorisation. In such cases, the MAH could be asked to produce observational data, including the follow-up of a sample of frail elderly, in the frame of post-authorisation commitments within the Risk Management Plan. The current *"Guideline on Risk Management Systems for Medicinal Products for Human Use"* (CHMP/96268/2005) specifically takes into account a number of requirements to mirror as much as possible the characteristics of the targeted population of the pre-authorisation studies.

Though most of the CHMP guidance documents address the need for data in the elderly and it appears from the 10 dossiers we reviewed that overall data in the elderly are available, the following recommendations are made:

1. To discuss the opportunity for updating ICH E7, as indicated above, which could lead to a CHMP concept paper.
2. For the professional bodies to define elderly, frailty and adequate age cut-off points.
3. To continue adding a specific section on elderly in the CHMP guidelines and to update these where necessary. Comments from specifically interested parties should be sought during the consultation phase.
4. To emphasise in Scientific Advice and other discussions with the Companies, both at EU and National Authority levels, the need to plan to recruit an adequate number of elderly of various ages in the studies, as relevant.
5. To systematically require the appraisal of elderly exposure (as relevant) in the assessment process (centralised procedure, referral and mutual recognition), and to standardise the issue in the CHMP assessment report and SPC (via the update of the existing templates).

APPENDIX 1

The following tables display the results of the analysis of the guidelines, E meaning adequacy to ICH E7 in terms of efficacy, S safety, PK pharmacokinetics and DI, the existence of specific studies evaluating drug-drug interactions.

General guidelines

Table 1: Adequacy of general guidelines to ICH E7

GUIDELINE		***ADEQUACY ICH-E7***			
1	Pharmacokinetic studies in man EudraLex 3CC3a (Oct 88)	-	-	PK	-
2	Note for guidance on the investigations of drug interactions CPMP/EWP/560/95 (Dec 97)	-	-	-	-
3	Note for guidance on statistical principles for Clinical Trials CPMP/ICH/363/96	-	S	-	DI
4	Note for guidance on general considerations for Clinical Trials CPMP/ICH/291/95	-	S	PK	DI
5	Note for guidance on Structure and Content of Clinical Studies reports CPMP/ICH/137/95	E	S	-	-
6.1	CTD Efficacy, Module 2.5: Clinical overview CPMP/ICH/2887/99 Rev1	E	S	PK	-
6.2	CTD Efficacy, Module 2.7: Clinical summaries CPMP/ICH/2887/99 Rev1	E	S	PK	-

EWP guidelines

Table 2: Adequacy of efficacy approved guidelines to ICH E7

GUIDELINE		***ADEQUACY ICH-E7***			
Cardiovascular diseases					
1	Acute cardiac failure CPMP/EWP/2986/03 (JUL 04)	-	S	-	DI
2	Cardiac failure CPMP/EWP/235/95 (Dec 99)	-	-	PK	DI
3	Hypertension CPMP/EWP/238/95 rev.2 (Jun 04)	E	S	PK	DI
4	Anti-angina products for stable angina pectoris CPMP/EWP/234/95/rev.1 (Jun 06)	E	S	PK	DI
5	Antiarrhythmics CPMP/EWP/237/95/final (Nov 95)	E	S	PK	DI
6	Fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction CPMP/EWP/967/01 (Jun 03)	E	S	-	-
7	Peripheral arterial occlusive disease CPMP/EWP/714/98/rev.1 (Apr 02)	-	S	PK	DI

Table 2: Adequacy of efficacy approved guidelines to ICH E7					
GUIDELINE		***ADEQUACY ICH-E7***			
8	Venous thromboembolic disease CPMP/EWP/563/98 (Dec 99)	E	S	PK	DI
9	Venous thromboembolic risk in non-surgical patients CPMP/EWP/6235/04 (Jun 06)	E	S	-	DI
10	Prophylaxis of Intra and Post-operative venous thromboembolic risk CPMP/EWP/707/98 (Jun 00)	E	S	PK	DI
Infections					
1	Bacterial Infections CPMP/EWP/558/95/rev.1 (Apr 04)	E	S	-	DI
2	Sepsis CPMP/EWP/4713/03 (Jun 06)	E	S	PK	DI
Nervous system					
1	Depression CPMP/EWP/518/97/rev.1 (Apr 02)	E	S	PK	DI
2	Schizophrenia CPMP/EWP/559/95 (Feb 98)	E	S	PK	DI
3	Schizophrenia (depot preparations) CPMP/EWP/49/01 (Feb 03)	-	S	-	DI
4	Nociceptive pain CPMP/EWP/612/00 (Nov 02)	E	S	PK	DI
5	Generalised anxiety disorder CPMP/EWP/4284/02 (Jan 06)	E	S	PK	DI
6	Parkinson's Disease CHMP/EWP/563/95 (Dec 98)	E	S	PK	DI
7	Alzheimer's Disease CPMP/EWP/553/95 corrected (Sept 97)	-	S	-	DI
Metabolic disorders					
1	DM CPMP/EWP/1080/00 (May 02)	E	S	PK	DI
2	Lipid disorders CPMP/EWP/3020/03 (July 04)	E	S	PK	DI
Other					
1	Postmenopausal osteoporosis in women CPMP/EWP/552/95/rev.1 (Jan 01)	E	S	PK	-
2	Urinary incontinence in women CPMP/EWP/18/01/final (Dec 02)	-	-	-	-
3	Anticancer medicinal products in Man CPMP/EWP/205/95/rev.3/Corr. (Dec 05)	E	S	PK	DI
4	Locally applied, locally acting products containing known constituents CPMP/EWP/239/95 final (Nov 95)	-	-	-	-
5	Fixed combination of medicinal products CPMP/EWP/240/95 (Apr 96)	-	-	PK	
6	Acute respiratory distress CPMP/EWP/504/97 rev.1 (Sept 06)	E	S	PK	DI
7	Note for guidance on the clinical investigation of medicinal products in the treatment of asthma CPMP/EWP/2922/01 (Nov 02)	E	S	PK	DI

Table 3: Adequacy of efficacy draft guidelines to ICH E7					
GUIDELINE		***ADEQUACY ICH-E7***			
1	Migraine CPMP/EWP/252/03 rev.1 (RC Jan 2006)	E	S	PK	DI
2	Drug used for weight control CPMP/EWP/281/96 (RC Jun 2006)	E	-	PK	DI
3	Neuropathic pain CPMP/EWP/252/03 rev.1 (RC Jan 2006)	E	S	PK	DI
4	Primary osteoporosis CPMP/EWP/552/95 rev.2 (RC Dec 2005)	E	S	PK	DI
5	Nausea and vomiting associated with Cancer Chemotherapy CHMP/EWP/4937/03 (RC Feb 2005)	E	S	PK	DI
6	Multiple Sclerosis CHMP/EWP/561/98 Rev 1 (Sep 05)	-	S	PK	DI

Table 4: Adequacy of efficacy "Points to consider" documents to ICH E7					
GUIDELINE		***ADEQUACY ICH-E7***			
1	Products other than NSAIDS in Rheumatoid Arthritis CPMP/EWP/556/95 (Dec 03)	-	S	-	DI
2	New Anti-Fungal Agents for Invasive Fungal Infections CPMP/EWP/1343/01 (May 03)	-	-	-	DI
3	Irritable Bowel Syndrome CPMP/EWP/785/97 (Mar 03)	-	-	-	-
4	Acute Stroke CPMP/EWP/560/98 (Sep 01)	E	S	PK	DI
5	Amyotrophic Lateral Sclerosis CPMP/EWP/565/98 (Oct 00)	-	S	PK	DI
6	Pharmacokinetics and Pharmacodynamics in the development of Antibacterial Medicinal Products CPMP/EWP/2655/99 (Jul 00)	-	-	PK	-
7	Acute Coronary syndrome without persistent ST-segment elevation CPMP/EWP/570/98 (Feb 00)	E	S	PK	DI
8	Chronic Obstructive Pulmonary Disease (COPD) CPMP/EWP/562/95 (May 99)	E	S	PK	DI
9	Osteoarthritis CPMP/EWP/784/97 (Jul 98)	E	S	-	-

BWP guidelines

Table 5: Adequacy of BWP guidelines to ICH E7					
GUIDELINE		***ADEQUACY ICH-E7***			
1	Plasma derived fibrin sealant/haemostatic products CPMP/BPWP/1089/00 (July 04)	-	-	-	-
2	Human normal immunoglobulin for subcutaneous and intramuscular use CPMP/BWP/283/00 (Jul 02)	-	-	-	
3	Plasma derived antithrombin products CPMP//BPWP/2220/99 (Jan 02)	-	-	-	-
4	Human normal immunoglobulin for intravenous administration CPMP/388/95 rev.1 (June 00)	-	-	-	-
5	Points to consider on the development of live attenuated influenza vaccines CPMP/BWP/2289/01 (Feb 2003)	E	S	-	-

VWP guidelines

Table 6: Adequacy of VWP guidelines to ICH E7					
GUIDELINE		***ADEQUACY ICH-E7***			
1	Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation CPMP/VEG/4717/03 (Apr 04)	E	S	-	-
2	Note for guidance on the Clinical Evaluation of Vaccines CPMP/VEG/164653/05 (RC May 05)	E	S	-	-
3	Note for guidance on clinical evaluation of new vaccines CPMP/EWP/463/97 (May 99)	E	S	-	-

APPENDIX 2

The following tables display EWP currently under revision or within the 2007-2008 workplan.

Table 1: EWP guidelines under revision

GUIDELINE		***ACTION***
1	Guideline on the clinical investigation of Antiemetic medicinal products for Oncology (CPMP/EWP/4937/03)	Released for consultation in February 2005. Finalisation expected in 3/4Q 2006
2	Appendix to the guideline on the evaluation of Anticancer Medicinal Products in man (CPMP/EWP/205/95 Rev 3)	Released for consultation in July 2006. Finalisation expected 3Q 2007
3	Guideline on Antiarrhythmics (CPMP/EWP/237/95)	Concept paper adopted on Sep 2006. Draft revised guideline to be released for consultation in 2/3 Q 2007.
4	Guideline on Postmenopausal Osteoporosis in Women (CPMP/EWP/552/95 Rev 1)	Revision adopted in Nov 2006 Publication soon
5	Guideline on the clinical investigation of medicinal products for the treatment of Multiple Sclerosis (CPMP/EWP/561/98)	Revision adopted in Nov 2006 Publication soon
6	Guideline on Clinical Investigation of Medicinal Products in the treatment of Alzheimer's Disease (CPMP/EWP/553/95)	Concept paper adopted in 4Q 2005. Draft guideline is expected to be released for consultation in 1Q 2007
7	Guideline on Clinical Investigation of Medicinal Products in the treatment of Parkinson's Disease (CPMP/EWP/563/95)	Concept paper adopted in 4Q 2005. Draft guideline is expected to be released for consultation in 1Q 2007.
8	Points to consider on clinical investigation of Medicinal Products in the Prophylaxis of Intra and Post-operative venous thromboembolic risk (CPMP/EWP/707/98)	Draft guideline to be released for consultation in 4Q 2006 Finalisation expected in 3/4Q 2007

Table 2: EWP guidelines considered for revision

GUIDELINE		***ACTION***
1	Points to consider on Clinical Investigation of Medicinal Products used in the treatment of Osteoarthritis (CPMP/EWP/784/97)	Revision to be considered in 2007
2	Points to consider on Clinical investigation of Medicinal Products for the treatment of Amyotrophic Lateral Sclerosis (CPMP/EWP/565/98)	Revision to be considered in 2007
3	Guideline on Clinical Investigation of medicinal products in the treatment of Diabetes Mellitus (CPMP/EWP/1080/00)	Revision to be considered in 4Q 2007
4	Guideline on fixed combination of medicinal products (CPMP/EWP/240/95)	Revision to be considered in 2007