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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

DRAFT

NOTE FOR GUIDANCE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION

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Note:

This draft Nfg has been released for 3-month consultation on 25 July 2002.

Any comments should be sent to the EMEA, EWP Secretariat (fax no +44 20 74 18 86 13), by end of October 2002.

1. BACKGROUND

The first document addressing *'Points to Consider on the Assessment of anti-HIV medicinal products'* was adopted by the CPMP in January 1996, but was soon followed by a revision subsequent to the work of the Surrogate Markers Collaborative group. Further revisions have included elaboration on the regulatory implications of pharmacokinetics, virus resistance, data requirements in patients failing therapy, and the use of boosted protease inhibitor regimens. As this field of drug development now has entered a more mature stage from a regulatory perspective, it was found appropriate to transform the "*Points to Consider*" into a "*Note for Guidance*". Specific regulatory issues that require a rapidly implemented update may be covered by future amendments to this document or by supplementary *'Points to Consider'* document(s).

It is recognised that several issues remain under debate. These include, among others, the optimal timing of initiation of anti-retroviral therapy (ART), the benefits and risks of structured treatment interruptions, and treatment strategies that further improve long-term outcomes. It is also recognised that the resolution of one or more of these issues may influence the appropriate design and patient selection criteria of clinical studies. Thus, along with this document, note must be taken of the current versions of treatment guidelines, such as those of the European AIDS Clinical Society, the British HIV association, the International AIDS Society and the US Panel on Clinical Practices for Treatment of HIV Infection.

2. INTRODUCTION

This document, which should be read in conjunction with Part 4 of Annex I of Directive 2001/83/EC and all other relevant CPMP and ICH guidelines, provides guidance on the clinical development of new medicinal products for the treatment of HIV infection and specifically:

- the requirements for licensing of new medicinal products for the treatment of HIV infections

and

- the wording of the Summary of Products Characteristics

Primary HIV infection, or post-exposure prophylaxis are not covered. Also, due to the as yet limited regulatory experience with immune-based therapies (IBTs), the guideline mainly focuses on the clinical evaluation of direct-acting anti-retroviral substances.

3. GENERAL ASPECTS OF STUDY DESIGN

Due to the inherent high mutation rate in HIV, the combined use of at least three active medicinal products is currently considered essential and any use of sub-optimal therapy should be minimised as far as is possible. Thus, it is recognised that the assessment of the anti-retroviral effect of a novel agent as monotherapy must be limited to proof-of-concept/dose-finding studies of the shortest possible duration.

In order to minimise bias, efficacy studies are expected to be randomised and, whenever possible, double-blind. Even if dose optimisation based on pharmacokinetic data is considered essential in phase III studies, the treating physician and the patient should

preferably be blinded as to treatment assignment.

However, blinding with respect to information that is used in the routine management of patients, such as viral load, CD4+ T-cell count, or drug resistance pattern is not expected.

3.1 PATIENTS TO BE STUDIED

Due to an urgent need for new active substances for heavily pre-treated and treatment refractory patients, the CPMP strongly encourages sponsors to co-operate and to conduct clinical trials in these patients early in the clinical development programme.

Provided that the properties of the experimental agent appear suitable, it is expected that safety and efficacy would be evaluated in patients who are treatment-naïve and in those who are treatment-experienced, including heavily pre-treated patients. The numbers of women and individuals from ethnic minorities should be sufficient to allow generalised conclusions on safety and efficacy. Differences in pharmacogenetics of potential importance for benefit/risk should also be addressed in the planning of the clinical trials programme.

When efficacy and safety have been established in adults, clinical trials in children are expected to be performed. Similarly, safety and efficacy in patients co-infected with hepatitis C (HCV) and B (HBV) virus, should be studied. Until such time as appropriate safety and efficacy data are made available in these groups of patients, the Summary of Product Characteristics would carry statements regarding any such deficiencies.

3.2 MEASURES OF TREATMENT OUTCOME AND SUPPLEMENTARY INVESTIGATIONS

Since the introduction of highly active anti-retroviral treatment (HAART), the use of viral load and CD4+ T-cell counts as surrogate markers for efficacy has been generally accepted in studies with anti-retroviral agents. However, for the evaluation of alternative treatment strategies over the very long term, and for treatment modalities that would not primarily be expected to modify the viral load, such as some IBTs, clinical events remain the most relevant outcome measure.

3.2.1 Clinical events

Although the assessment of efficacy according to clinical events would be expected only in specific situations as mentioned above, the occurrence of clinical events according to the 1993 CDC criteria should always be reported in the efficacy analysis of clinical studies.

3.2.2 Viral load

For most efficacy studies, HIV RNA is the appropriate measure of efficacy. Different primary efficacy variables may be defined and include time averaged change from baseline and proportion of subjects that achieve viral suppression below a predefined level, e.g. the limit of detection of the assay. Therefore the use of validated and sensitive assays that meet current standards is essential. In order to define the relationship between viral kinetics and sustained viral response, it is recommended that the dynamics of the early viral response are carefully documented, not only in dose-finding studies, but also in confirmatory (sub-) studies.

Depending on the study population and the geographical location of the study sites, the need for an assay that is able to quantify HIV RNA from various (including rare) subtypes of HIV-1 and HIV-2 should be addressed.

3.2.3 Immune function

Effects on the CD4+ T-cell count should always be documented. The correlation between changes in CD4+ T-cell count and viral load should be explored for populations and individuals as appropriate, and any anomalies should be investigated and discussed. In

heavily pre-treated patients with very low CD4+ T-cell count, improved immune function is of crucial importance. CD4+ T-cell response is, however, often a late event in these patients. This should be considered in the design of studies in heavily pre-treated patients.

If specific claims are to be made for an effect on immune function, such as for IBTs, a much more detailed assessment of the functionality of the immune system is expected. This may include studies of the impact of the therapy on the immune response to conventional vaccines, of effects on specific sub-populations of T-cells such as recent thymic emigrants, and functionality assays. Due to the as yet immature status of this field, regulatory scientific advice is recommended regarding the design of these studies.

3.2.4 Viral resistance

The importance of viral resistance/reduced susceptibility makes the investigation of genotypic and phenotypic resistance an essential element of drug development. The choice of assays and assay conditions should be justified. It is recommended that the resistance pattern should be documented at baseline and at least at the time of virological failure. It is recognised, however, that hidden resistant quasi-species at baseline may influence study outcome. Therefore the likelihood of primary acquisition of resistant virus, or impact of any prior ART, should be taken into account.

Every effort should be made to document the initial response to the next line of therapy after virological failure on the experimental regimen and to examine these responses in relation to viral resistance data.

The development programme should aim to identify appropriate breakpoints to be applied to in-vitro susceptibility test results. Studies investigating the relation between replicative capacity ("viral fitness") and resistance-associated mutations are also encouraged. Post-licensing, epidemiological data as regards resistance development should normally be provided as yearly updates.

3.2.5 Viral subtypes and anti-retroviral activity

The anti-retroviral activity of the novel compound should be studied in relation to viral subtypes and, for example, in the case of entry inhibitors specifically as regards co-receptor usage. Observed differential activity should be mechanistically investigated.

3.2.6 Pharmacogenetics and Immunogenetics

Genetic host factors influence the natural course of HIV disease and apparently contribute to differences in the response to ART. Therefore genetic evaluation might elucidate the reasons for inter-individual differences in pharmacokinetics, idiosyncratic adverse reactions, and overall viral response.

3.2.7 Safety

The long-term safety of ART is of crucial importance. The conduct of long-term post-marketing studies is therefore strongly encouraged, as well as the participation in, or sponsoring of pharmaco-epidemiological studies. These studies may be particularly useful to evaluate the potential effects of various ART regimens on cardiovascular safety, and to address other safety signals of potential long-term clinical importance. Special monitoring of patients with hepatic impairment is also of importance.

It is recommended that special investigations are made regarding lipoatrophy, lipohypertrophy, blood lipid levels, and glucose control. Well designed studies that follow patients for more than one year are needed to document effects on lipodystrophy. In addition, any adverse events that might be predicted by the preclinical findings and any drug class-associated adverse events, such as mitochondrial dysfunction, should be sought and followed

with special care.

Boosted protease inhibitors (PI) regimens may result in higher drug exposures than those previously studied in non-boosted regimens. Consideration should therefore be given to the possible need for additional safety pharmacology and/or toxicology studies. Also, specific studies may be required in cases where non-boosted studies revealed specific safety concerns (e.g. QTc prolongation).

4. HUMAN PHARMACOLOGY

As in-vitro studies of anti-retroviral activity provide essential information for the design of clinical studies, they are mentioned here.

4.1 IN VITRO PHARMACODYNAMICS

Comparative in-vitro studies with relevant anti-retroviral compounds must be performed. It is recommended that these studies include assays conducted in (50 %) serum and serum-free media, and that cell lines include peripheral blood mononuclear cells (PBMC). The novel agent should be tested against a wide range of clinical isolates and recombinant viruses that express various resistance-associated mutations.

4.2 PHARMACOKINETICS

In order to reduce the risks associated with sub-optimal therapy in the HIV-infected individual, the initial pharmacokinetic studies should normally be performed in healthy, HIV-negative volunteers. If there are concerns regarding safety, however, it may not be appropriate to perform studies that necessitate multiple dosing in HIV-negative healthy subjects. Some pharmacokinetic data can therefore only be obtained as part of exploratory treatment studies in HIV-infected persons. The pharmacokinetic behaviour may also be altered in HIV-infected patients with advanced disease. A mixed study programme of healthy volunteers and HIV-infected individuals in different stages of the disease is therefore normally needed to properly characterise the pharmacokinetics of the novel compound.

4.2.1 General aspects

The pharmacokinetic properties, including possible time-dependency (*e.g.* auto-induction) must be thoroughly characterised. Possible sources of variability (*e.g.* food interactions, drug-drug interactions, age and gender effects, effects of hepatic and renal impairment, genetic variations in metabolic capacity) should be evaluated. This should normally be done prior to the initiation of confirmatory studies.

For compounds undergoing intracellular activation, *e.g.* nucleoside reverse transcriptase inhibitors (NRTI), sources of variability in the concentrations of the activated compound, such as drug-drug interactions, should be investigated. The intracellular concentrations of compounds affected by transporter proteins such as the PI may be affected by MDR1 polymorphism and drug-drug transporter interactions. Exploratory studies addressing these issues are therefore encouraged. It is also recommended that drug concentrations are determined in viral sanctuaries such as cephalo-spinal fluid and genital secretions.

Data derived from pharmacokinetic studies conducted in HIV-negative volunteers may be used in order to identify dosages and schedules that are likely to be effective and tolerable in HIV-infected individuals. The constraints regarding the prediction of concentration-related activity *in vivo* from in-vitro data are, however, recognised. Ideally, it should be demonstrated that achievable and tolerable concentrations *in vivo* are several-fold higher than protein adjusted IC90 values for the full dose interval.

It is recommended that the relationship between drug exposure and safety and efficacy is

explored also in confirmatory studies, *e.g.* by means of population pharmacokinetics. An understanding of these relations is a prerequisite to be able to assess the relevance of changed drug exposure, *e.g.* due to impaired hepatic function, or changed variability in the population.

4.2.2 Interactions

The routine use of HAART and the pharmacokinetic properties of many of the anti-retroviral and other necessary concomitant drugs provide for a high potential for clinically relevant drug-drug interactions. Interaction studies should be mechanistically based, taking into account also transporter proteins, as well as the evaluation of any consequences for intracellular phosphorylation and/or intra-cellular concentrations as appropriate. If the mechanisms governing, *e.g.* a low oral bioavailability has not been elucidated, however, exploratory interaction studies with commonly co-administered compounds may be needed. An extensive programme of interaction studies is often necessary prior to approval.

Boosted protease inhibitors

Boosted PI regimens refer to the use of a "booster", currently low-dose ritonavir, to enhance the pharmacokinetics of the "boosted" PI and where the anti-retroviral effect is assumed to rely entirely on the boosted PI. Studies should be performed to characterise the pharmacokinetic interaction between the PIs, including potential gender differences in the magnitude of the interaction. Early studies to identify suitable combinations and regimens should normally be performed in healthy volunteers. Several dose combinations should be studied and the concentration of both the boosted and boosting protease inhibitor should be determined.

In current clinical practice, low-dose ritonavir may be used to boost two "active" PIs. Exploratory studies are therefore encouraged to document such combinations.

Boosted PI regimens are associated with an increased potential for undesirable drug-drug interactions, compared with the administration of either PI alone. Thus, additional interaction studies may be necessary.

In principle, it is expected that the benefit/risk of a boosted PI regimen would be documented in confirmatory studies as outlined in section 4.4. See also point 8 "Information on the SPC".

4.3 PROOF-OF-CONCEPT AND DOSE-FINDING STUDIES IN HIV INFECTED INDIVIDUALS

The primary aim of these studies is to provide reliable data on short-term anti-retroviral activity of the new compound and, thus, to provide the best possible basis for the designs of confirmatory studies. Due to the risk of resistance development, these studies should be designed to maximise the information gained from any individual study and study participant so that a minimum number of patients are exposed to single agent therapy. These studies should, nevertheless, be designed and powered to minimise the risk that suboptimal doses are further investigated in confirmatory studies. Data derived from these studies may also provide important bridging pharmacokinetics/pharmacodynamics (PK/PD) documentation, *e.g.* if new formulations are to be developed in the future.

Monotherapy studies are needed to characterise the relationship between anti-retroviral activity and dose/concentration, and may be evaluated over a very brief period in treatment-naïve patients, before instituting combination therapy. Alternatively, functional monotherapy may be evaluated over a short period. In this instance, the novel agent is added to regimen(s) on which patients are failing. The studies should be as short as possible and two weeks may be sufficient, at least for some classes of compounds. Class-related differences in the rate of resistance development should be considered in the design of these studies. Patients with high viral loads (>10 000 copies/ml) and/or very low CD4+ T-cell counts are not suitable candidates for these studies.

Interpretation of the data is made easier if patients infected with viral strains that show reduced sensitivity to the experimental agent are excluded, and if enrolment is restricted according to viral load limits. In heavily pre-treated patients, however, the relationship between short-term, anti-retroviral activity *in vivo* and different degrees of reduced susceptibility *in vitro* should normally be explored.

Early and repeated determinations of viral load and drug concentrations are recommended and PK/PD modelling may be a useful tool for dose selection. Appropriate modelling might also provide information on pharmacokinetic markers of importance for efficacy in relation to virus with different degrees of reduced susceptibility *in vitro*. If a range of doses is found to be active and well tolerated, additional short-term, comparative studies of monotherapy may be warranted. These should be randomised studies that compare various doses of the experimental drug with an active comparator.

The possible need for a loading dose and, in case of auto-induction, the need for dose adjustment over time should be considered. If available PK/PD data and/or data related to the pharmacological class indicate that, for instance C_{min} might be critical for anti-retroviral activity, special attention should be paid to the degree of and reasons for inter- and intra-individual variability in C_{min} values.

If pharmacokinetic and pharmacodynamic data altogether indicate that therapeutic drug monitoring would be of importance to optimise benefit/risk, for example, in certain subgroups of patients with increased variability, or in patients infected with virus with reduced susceptibility, this should be considered in the design of confirmatory studies.

As long-term benefit/risk cannot be determined in exploratory studies, the use of more than one dose in confirmatory studies should also be considered.

5. CONFIRMATORY STUDIES

5.1 GENERAL CONSIDERATIONS

The most commonly used designs in confirmatory studies aim at a head-to-head comparison between the novel agent and a relevant licensed medicinal product. This may be accomplished by "add-on" or "substitution studies". In substitution studies one (or rarely more) compound(s) in an established regimen is substituted with the experimental agent, while, in add-on studies, the experimental agent, an active comparator, or placebo is added to an optimised backbone regimen. "Substitution" and "add-on" may be used in order to compare products within a pharmacological class, but also in a comparison between classes. Placebo controlled, add-on studies are typically conducted only in heavily pre-treated patients. Whatever the design and treatment regimen, every effort should be made to conduct these studies under effectively double blind conditions.

Adherence to therapy is of vital importance for treatment outcome and major efforts to encourage and document compliance are important. In non-inferiority trials, subjects who are deemed likely to be poorly compliant should be excluded.

Especially if studies are conducted in heterogeneous populations, stratification (if appropriate using minimisation techniques) should be considered for important prognostic factors such as prior therapy, baseline viral load, genotypic and/or phenotypic sensitivity and CD4+ T-cell count. It is also valuable if the sample size of the studies allows for the conduct of meaningful exploratory subgroup analyses with respect to other factors that potentially affect outcome such as gender and ethnicity.

In order to establish a non-inferiority margin, the activity of the active comparator in the control regimen has to be defined in the population of interest and the acceptance limits have

to be justified directly or indirectly in terms of study data and clinical relevance. Possible differences between reference studies and the actual study have to be taken into account, especially as regards viral load at baseline, prior therapy and disease status.

For superiority studies, the most suitable primary analysis is normally that in an ITT population defined as all treated patients and with all indeterminate outcomes and withdrawals designated as failures. Other approaches to analyses in the ITT population may include last observation carried forward (LOCF). Outcomes in patients who meet the criteria for the "per protocol" population are also important when evaluating consistency between populations and analyses. Especially in studies conducted in populations where a high withdrawal rate is expected and in the case of non-inferiority trials, further "sensitivity analyses" should be considered and defined in the protocol. If the study cannot be conducted under double-blind conditions, very conservative analyses should be employed in order to minimise the impact of possible bias related to withdrawal from therapy.

5.2 STUDIES IN ART NAÏVE PATIENTS

Patients included in clinical trials should fulfil criteria that indicate a need to commence ART, as defined by recognised clinical guidelines. Similarly, it is advisable that the comparative regimen is chosen from among those that are "strongly recommended" for the initial therapy of established HIV infection. These studies are normally designed as substitution studies and the comparative agent should be chosen so as to facilitate double-blinding, taking into account pharmacokinetic interactions, pill burden (compliance), adverse effects, etc.

Although it may be possible to show superior anti-retroviral effects already after a few months of therapy, at least one year is needed to exclude clinically relevant inferiority for compounds assumed to be equally effective. It remains mandatory, however, that these studies are designed to provide long-term safety data (96 weeks) preferably under double blind conditions.

The percentage of patients with HIV viral load below the limit of quantification (currently <50 copies/ml) at 48 weeks or later is an appropriate primary endpoint in these studies. Viral responses according to alternative criteria and time-averaged differences may be secondary measures of efficacy.

Virological failure, whether primary or secondary, should be defined in the protocol in accordance with clinical guidelines. It is recognised that the current interest in early effects on viral load may result in revised recommendations for this definition and that opinions may differ among investigators and patients. Therefore, it is of importance to establish justifiable criteria in the protocol that are adhered to throughout the study. Every effort should be made to identify the reason(s) for virological failure in individual patients.

The benefit/risk of high intensity, multiple-class, induction regimens followed by simplified maintenance therapy, *e.g.* in patients with high viral load (*e.g.* > 50 000 copies/ml) has not been established yet, but studies exploring this concept are encouraged. For simplified maintenance regimens, see 5.3.1

5.3 STUDIES IN ART EXPERIENCED PATIENTS

5.3.1 Patients not failing their current regimen

Most studies in ART experienced patients are conducted in patients with evidence of virological failure on their current regimen. Studies of maintenance therapy with simplified and/or possibly better tolerated regimens in patients showing adequate virological control after induction therapy is, however, an area of current clinical interest. The most commonly used study design involves the substitution of one or more drugs within an existing regimen with the novel agent.

These studies should normally be double-blinded with respect to treatment assignment, but may be open label as regards common elements in the two regimens. If the conduct under double blind conditions, nevertheless, results in an unavoidable and hard to accept pill burden (double dummy, etc.), it is debatable whether the merits of blinding outweighs the likely loss in compliance. If an open label design is chosen, it is of special importance that conservative efficacy analyses not favouring the experimental arm are applied. All criteria for withdrawal, for example, have to be strictly defined and justified in the protocol. Withdrawal from the control arm in accordance with pre-specified criteria may then be regarded as treatment failure, while in case of withdrawal due to "patient wish", etc. LOCF may be used for imputation of missing data with respect to viral load. In the experimental arm, however, all withdrawals may be regarded as failures in conservative sensitivity analyses.

Time to virological failure as defined in current management guidelines is an acceptable primary endpoint. As all patients should show adequate viral response at baseline, more than 48 weeks of follow-up are needed to properly assess long-term efficacy. If improved safety is the rationale behind the experimental regimen, an adequate measure of safety should be defined in the protocol as a co-primary end point.

5.3.2 Patients failing their current regimen but with various remaining treatment options

The decision when and how to change an apparently failing regimen is not straightforward and it is recommended that eligibility is defined in accordance with up-to-date guidelines on patient management. By definition, these patients are naïve to at least one class of licensed anti-HIV agents. Treatment history in combination with resistance testing should be used to characterise the individual patient's suitability for inclusion in the studies.

There are alternative design options, but all eligible patients should be well suited for treatment with the selected comparator regimen(s) according to current patient management recommendations. If the novel agent belongs to a licensed class of compounds, the simplest design is to select patients naïve to this class for a randomised comparison with an agent of the same class on top of an optimised background regimen ("add-on") or within a justified standard regimen ("substitution"). This approach is also applicable in the case of experimental drugs belonging to a novel class of compounds for a head-to-head comparison with an established agent from a class to which the patients are treatment naïve. As with studies conducted in treatment naïve patients it is of importance to select a comparator agent that facilitates blinding.

The treatment goal in clinical practice is to achieve a viral load below the limit of quantification (currently HIV-RNA < 50 copies/ml) and the proportion of patients that achieve this degree of viral suppression should always be reported. In the selection of primary efficacy measure, however, the predicted anti-retroviral activity of the comparative regimen should be taken into account. "Adequate control" and "virological failure" criteria should, thus, be defined in relation to the expected activity of the comparative regimen and updated clinical treatment guidelines. The primary endpoint may be the percentage of patients with adequate control at, *e.g.* 48 weeks, but time-averaged difference may be an acceptable alternative. For superiority trials, the primary efficacy analysis may be performed at 24 weeks, but the trial duration should be at least 48 weeks, with or without institution of a "roll-over" protocol to follow. If a non-inferiority margin can be scientifically justified and non-inferiority is a reasonable clinical objective, such studies are acceptable in this population, but a longer duration of these trials is needed to obtain mature efficacy data.

5.3.3 Heavily pre-treated patients failing their current regimen but with remaining therapeutic options

These patients should have failed therapeutic regimens that have included at least one compound in all licensed classes of anti-retroviral agents. Treatment history and resistance testing should in addition make it unlikely that durable virological suppression is achievable with currently available treatment options. Based on documented low-degree clinical cross-resistance, there should, however, remain likely active drugs in at least two classes. Prior to the inclusion in clinical trials, these characteristics should be verified and documented.

The most straightforward design of these studies is add-on to optimised background versus an active comparator or placebo. If placebo is chosen, this should be justified by reference to patient characteristics and absence of active alternatives. If at all possible, the studies should be conducted double blind. A proof-of-concept/dose-finding phase of functional mono therapy may precede the optimised therapy phase (see 4.3). Studies with more than one experimental agent may be appropriate and in these cases factorial designs should be considered.

As for studies in other previously treated patients, the predicted activity of the comparator arm may be used for guidance as to the proper duration of the trial. A reduction in viral load of at least 0.5 log is considered clinically meaningful and may be used to define superior virological response. If the comparator regimen is likely to be only modestly active, 16 weeks under double blind and controlled conditions are considered sufficient. For the assessment of durability of viral response and effects on CD4+ T-cell count, follow-up data are expected, however. Response rate at, *e.g.* 16 weeks, time-averaged difference, or time to virological failure as defined in the protocol, are suitable primary efficacy variables.

For modestly active comparator regimens, it is hardly possible to define a non-inferiority margin. Therefore even studies conducted with the primary objective to improve tolerability have to be designed as superiority trials as regards anti-retroviral activity.

6. STUDIES IN SPECIAL PATIENT POPULATIONS

6.1 STUDIES IN HEAVILY PRE-TREATED PATIENTS FAILING THEIR CURRENT REGIMEN AND WITH NO OR VERY LIMITED REMAINING THERAPEUTIC OPTIONS

These patients should have failed on products from all licensed classes of anti-retroviral agents. Based on treatment histories and resistance testing, there should be no available treatments options of likely clinical benefit. For clinical trials in such patients with "refractory" disease, it should be taken into account that:

a) There will be no accepted comparative regimen.

b) Currently, it is thought that at least two active compounds are needed to achieve a significant and stable anti-retroviral response.

c) Short-term virological activity may be shown with a single active agent, but the duration of any response is likely to be short.

d) Patients are often unwilling to accept treatment that may have a very low or very unpredictable likelihood of success and which may serve to increase multi-drug resistance.

e) The dropout rate is likely to be high since patients may be unwilling to be kept in a stringent clinical trial setting and failures often occur because of poor tolerability.

Controlled clinical trials are hard to conduct under these circumstances, and co-operation between companies is necessary in order to rapidly provide these patients with effective and

tolerable treatment. If companies in a co-development programme, for example, are aiming to specifically document the efficacy and safety of novel compounds in patients with refractory disease, regulatory scientific advice is recommended.

6.2 STUDIES IN CHILDREN

The development of a suitable pharmaceutical formulation for children is normally expected to take place early. Provided that reliable pharmacokinetic data allow for proper dose recommendations for different age groups, extrapolation to children from efficacy data obtained in adults may be accepted. However, at least non-comparative data on the safety and efficacy of the proposed dose regimens over appropriate time-spans should be provided. Trials should take into account maternal treatment histories and viral susceptibility patterns. Due to high viral loads in the youngest children, viral response data in these patients are of particular interest.

The provision of adequate data in children is especially important should large inter-individual pharmacokinetic variability be observed in the paediatric population. Also, additional drug-drug interaction studies may be considered necessary, at least as post-marketing commitments, and population pharmacokinetic studies should be considered. Long term post-marketing and pharmaco-epidemiological studies are encouraged.

6.3 STUDIES IN PREGNANT WOMEN

The need to further optimise anti-retroviral therapy in pregnant women is fully recognised, balancing the risk of sub-optimal therapy, viral resistance and vertical viral transmission against foetal toxicity and long-term consequences for the child. Prospective and well-designed studies are therefore needed. Based on mature and promising clinical and preclinical data, studies of a "new" compound may, thus, be warranted and are encouraged.

As the use of new compounds during pregnancy is partly inevitable, the applicants should commit to provide reliable follow-up data of children exposed *in-utero* to anti-retroviral compounds. This should include long-term follow-up as far as possible as regards potential delayed development and carcinogenic effects. As appropriate, this may also include the active support of Anti-retroviral Pregnancy Registries.

6.4 STUDIES IN CO-INFECTED PATIENTS

Patients who are co-infected with HIV and HCV and/or HBV constitute an important, and in some study sites, large proportion of HIV-infected individuals. Therefore safety and efficacy against HIV should be documented in these patients by allowing enrolment into at least some of the clinical trials. Sufficient numbers should be exposed to the experimental agent so as to document safety of ART over medium to long-term follow-up periods. If these data indicate acceptable hepatic safety, and taking into account potential pharmacokinetic interactions, studies in which ART is combined with anti-hepatitis therapy are encouraged.

When the novel anti-retroviral agent also shows activity against HBV or other viruses that may co-exist in HIV-infected individuals, it is important that any activity on these other viruses is documented during ART. Whether or not the applicant intends to formally study the experimental agent in separate studies in patients who are infected with these other viruses, it is vital to determine whether the dose regimen that is to be used for ART may be effective against these viruses. Viral loads of co-infecting viruses should therefore be monitored so as to assess any potential for the selection of drug-resistant mutants. These data cannot be used to assess the efficacy and safety of the novel compound against these co-infecting viruses, but the information is of importance in order to provide prescribers with guidance as to the safe use of the drug in co-infected patients.

7. LICENSING CRITERIA

This section is meant to provide guidance as regards licensing criteria. With respect to "exceptional circumstances" the exceptional nature makes it hard to provide more than very general guidance, with the possible exception of "heavily pre-treated patients".

7.1 FULL APPROVAL

For <u>ART naïve patients,</u> extensive efficacy and safety data, normally derived from studies encompassing different regimens, should be provided.

If superior anti-retroviral efficacy has been demonstrated, one-year safety data are normally considered acceptable if there are no specific concerns and if the number of patients treated for one year is sufficient for a reliable comparative safety analysis. A commitment to provide 2-year safety data post-approval, derived from extension phases of pivotal studies is expected.

Otherwise, study data confirming acceptable benefit/risk after about 24 months of therapy should be available at the time of full licensing. The database should make possible a qualified comparative safety analysis.

At the time of licensing, comprehensive data on secondary virological failure, resistance patterns and response to next-line therapies may not be available. These issues should be covered by post approval commitments.

An indication for use in <u>ART experienced</u> patients with various remaining treatment options should be supported by efficacy and safety data derived from studies of at least 12 months duration. Post approval commitments may encompass safety follow-up, resistance profiles, response to next-line therapies, etc., as appropriate.

An indication for use in <u>heavily pre-treated</u> patients is unlikely to be the sole indication pursued in the case of a full licensing. If applicable, however, a case by case evaluation will be made based on available efficacy and safety data.

Whether it is possible or not to obtain a <u>non-restricted</u> indication without conclusive study data in relation to all groups of patients detailed above has to be judged on a case by case basis. If safety and efficacy are well documented in treatment naïve and heavily pre-treated patients and the clinical activity of the compound has been documented in relation to a broad range of clinical viral isolates, a non-restricted indication appears possible. Each case must be supported by a comprehensive justification from the Applicant.

7.2 APPROVAL UNDER EXCEPTIONAL CIRCUMSTANCES

Pursuant to Annex I of CD 2001/83/EC, approval may be considered under exceptional circumstances. This may apply for well-defined groups of patients with a clearly unmet medical need (as justified by the Applicant). Non-comprehensive efficacy and safety data may under these circumstances be sufficient to support marketing authorisation.

In general terms, the CPMP recognises the urgent need to develop effective and safe medicinal products for the treatment of heavily pre-treated patients, children, pregnant women, patients with CNS disease, etc. Some guidance as regards data that should be obtained in heavily pre-treated patients can be found in this document (5.3.3). Otherwise it is postulated that an added value in clinically relevant terms has been demonstrated and an application will be assessed taking into account

- the indicated benefit/risk in this well defined population

- the unmet clinical need

put in relation to

- the lack of comprehensive clinical data

- available preclinical safety data

- the safety profile of the pharmacological class.

In the case of licensing under exceptional circumstances, specific obligations must be fulfilled by the Applicant. The fulfilment of these obligations will be assessed in the annual re-assessment of the benefit-risk profile of the medicinal product.

8.   INFORMATION IN THE SUMMARY OF PRODUCT CHARACTERISTICS

At the time of licensing of a new anti-retroviral product, whether under exceptional circumstances or not, the benefit/risk has normally not been demonstrated in the full spectrum of HIV infection. This should be reflected in section 4.1, with a reference to 5.1. For example, "X is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected, anti-retroviral experienced, adults (see section 5.1)".

If the experience is restricted to a subgroup of patients, e.g. patients with a viral load below 10,000 copies/ml, this should also be clearly stated.

When the documentation covers the full spectrum of HIV infection, a general indication should be used "X is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents, and/or children above X years of age" (as appropriate) (see section 5.1)

If comprehensive clinical efficacy data have not been provided at the time of authorisation, *i.e.* the approval is under exceptional circumstances, the limitations of the data should be clearly outlined in section 5.1.

For a medicinal product indicated for use in ART experienced or heavily pre-treated patients the following should also be stated: "In deciding on a new regimen for patients who have failed an anti-retroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different drugs. Where available, resistance testing may be appropriate".

Sections 4.5, 5.1 and 5.2 should not mirror the cumulative growth of experience, but should focus on the most relevant information, *i.e.* information becoming less relevant should be deleted when new data are incorporated. In general, the information should be as concise as possible. Tables may be useful. Data on resistance patterns and cross-resistance to other medicinal products should be provided. Resistance data should be up-dated on a yearly basis if not otherwise justified.

For <u>boosted protease inhibitors</u> the following is recommended:

4.2 Posology and method of administration

Specific recommendations for a boosted PI regimen should be included only when sufficient safety and efficacy data are available allowing a relevant comparative clinical benefit/risk assessment. A reference to section 5.1 should be given.

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic information may be put forward for boosted PI combinations, even if safety and efficacy data are sparse. These limitations, however, should be clearly delineated in the text.

5.1 Pharmacodynamic properties

If limited, but still relevant efficacy and safety data support a specific combination, this

information may be included in this section. Relevant *in vitro* and *in vivo* activity data for the boosted combination and resistance information related to patients failing the boosted regimen may be included in this section.

5.2 Pharmacokinetic properties

In cases where information on efficacy and safety is put forward in 5.1, relevant PK data (including measures of variability) should also be given in section 5.2

9.   GLOSSARY AND ABBREVIATIONS

Advanced disease (= AIDS)	Patients diagnosed with any condition meeting the 1993 CDC definition of AIDS (excluding CD4+ T-cell count <200), whether treated with ART or not
AIDS	Acquired immune-deficiency syndrome
ART	Anti-retroviral therapy
ART experienced	Patients treated with ART for more than a very short period of time
Functional monotherapy	Addition of a single anti-retroviral agent to a failing regimen
Heavily pre-treated	Prior therapy encompassing all licensed classes of ART
Highly active anti-retroviral therapy (HAART)	ART currently consisting of at least 3 different compounds (typically from 2 different substance classes)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IBT	Immune based therapies
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PBMC	Peripheral blood mononuclear cells
Primary failure	Adequate suppression of viral load not achieved with HAART
PI	Protease inhibitor
Secondary failure	Rising viral load during HAART after a period of adequate suppression
Treatment naïve	HIV infected patients previously not treated with ART and being infected with wild type HIV-1 or HIV-2