Initial experiences with the VHP –
A perspective from industry

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Abstract
The Voluntary Harmonisation Procedure (VHP) offers sponsors of multinational clinical trials (MN-CTs) involving three or more EU member states (MS) a harmonised procedure for the regulatory assessment of clinical trial authorisation (CTA) applications. In this article our early experience in the planning and execution of three VHP submissions is discussed. Although the decision to use the VHP for any particular CTA application should be made on a case-by-case basis, our positive experience so far supports future use of the procedure.

Introduction
It is well recognised that national implementation of the EU Clinical Trials Directive (2001/20/EC) has not removed the divergent national regulatory requirements across the EU. This presents significant challenges for sponsors during the start-up of MN-CTs. The assessment of the same CTA application for a given MN-CT might result in varying final decisions, country-specific modifications or approval in one MS and rejection in another. In 2009, the Clinical Trials Facilitation Group (CTFG) introduced the pilot VHP for the assessment of MN-CTs. The CTFG has stated that there is a need to harmonise MN-CT procedures and the decision-making process to ensure the protection of participants as well as the scientific value of trials in the EU.

The initial pilot (Version 1.1) limited the scope to MN-CTs involving an investigational medicinal product (IMP) without a marketing authorisation (MA) in the EU, and which met one of the following criteria: first-in-human (FIH) MN-CT, particularly with an IMP with known or anticipated risks; MN-CTs with an IMP considered to be "critical", for example with a novel mode of action, manufacturing process, indication for orphan disease (based on the judgement of national competent authorities (NCAs) and endorsed by the CTFG); or MN-CTs with very large populations where the sponsor indicated a need for harmonisation.

In March 2010, the CTFG revised the procedure and expanded the scope to all MN-CTs with at least three concerned MS. Version 2 of the VHP also included substantial amendments in the scope of the VHP.

The VHP guidance
The key stages of the initial VHP are summarised in Figure 1 and discussed below. Full details can be found in version 2 of the CTFG’s guideline.

Stage 1: Request for VHP and validation
The initial request for a CTA application to be assessed using the VHP can be made at any time to the VHP-C. The request should highlight important features of the MN-CT and include all documentation detailed in the core CTA application dossier (see Table 1). The CTA application dossier for a VHP is effectively the same as that submitted via standard national procedures. However, VHP documentation need only be submitted in English and does not have to include "national" documents, for example contracts, informed consent forms (ICFs) or clinical trial labels.

Within five working days the VHP-C informs the applicant whether all MS will participate and if there any deficiencies to be addressed. Once the documentation is complete, and any deficiencies addressed, the VHP starts.

Stage 2: VHP assessment steps
The assessment of a VHP submission is a two step process. Step 1 is a 30 calendar day process, which allows NCAs to conduct their assessment of the core CTA application dossier. Not later than Day 30, the VHP-C forwards a consolidated list of grounds for non-acceptance (GNA) to the applicant. If no GNA are raised, then the CTA application can be considered approvable and the applicant can proceed to the ‘national step’ detailed below.

If GNA are issued, the applicant should respond within 10 calendar days, with the VHP file being closed if no response is received from the applicant within the allotted time.

The second stage of the assessment starts following the receipt of the applicant’s responses by the VHP-C. The VHP-C forwards the applicant’s responses to the NCA. Following a seven day period, the VHP-C compiles all the NCAs’ assessments and will inform the applicant that the VHP is considered approvable by Day 50 (ie, within 10 calendar days of the response-to-questions (RTQs) being submitted). If there is no consensus, a teleconference will be organised among the NCAs in order to resolve any outstanding issues, with the decision being communicated to the applicant by Day 60 (ie, within 20 calendar days of the RTQs being submitted). The second stage of the assessment may result in one of three outcomes:
1 Unanimous decision that CTA application is approvable
2 Unanimous decision that CTA application is not approvable
3 CTA application is considered approvable in some MS, with names of MS with unresolved GNA forwarded to applicant.

Keywords
Voluntary Harmonisation Procedure (VHP); Multinational clinical trial (MN-CT); EU member state (MS); Clinical trial authorisation (CTA) application; Clinical Trials Facilitation Group (CTFG); Investigational medicinal product (IMP); VHP-Coordinator (VHP-C); Core CTA application dossier.

References
Stage 3: National steps

Applicants must be aware that a positive “VHP acceptability statement” does not imply that the CTA is authorised in all participating MS. A national CTA application is then required to be submitted in each MS where the VHP was considered approvable. This national CTA application should be submitted within 20 calendar days of the receipt of the VHP acceptability statement. The submission should include the core CTA application dossier submitted as part of the VHP, any other required national documents, and evidence of the VHP acceptability statement. In general, no changes to the core CTA application dossier will be accepted. It is recommended in the cover letter that applicants remind MS that the CTA application has undergone the VHP. The NCAs should issue their decision on the national CTA application within 10 calendar days, and have agreed that there should be no scientific discussion on the core CTA application dossier submitted as part of the VHP.

In the case where one or more MS has unresolved GNA at the end of the VHP, these open points can be resolved via a standard national CTA application process if the applicant wishes. In these circumstances, standard national timelines apply rather than the abbreviated timetable following a positive VHP acceptability statement.

It is of note that if the applicant subsequently decides to file the CTA application in an MS that was not part of the original VHP assessment then the NCA of this MS may decide to accept the decisions taken in the VHP, without changes to the core CTA application dossier.

Substantial amendments using the VHP

The process for submitting substantial amendments using the VHP is also described in version 2 of the CTFG guideline and so will not be discussed in detail here. Importantly, only substantial amendments of a trial that was initially assessed using the VHP can utilise the VHP. Submission of substantial amendments using the VHP is similar to the initial application and submissions can be made at any time. Validation again takes five working days, with the result of the assessment being communicated within 35 calendar days. The applicant is not able to address GNA during this process, but if any are raised the applicant can resubmit the amendment, with the subsequent submission having a shortened 20 calendar days for approval. Once the amendment is considered acceptable, national amendment submissions should be made within 10 calendar days, with approval being issued within seven calendar days.

Practical experience with the VHP

Amgen's current experience is limited to three VHPs (see Table 2). The second and third procedures (VHP2 and VHP3) involved the same IMP, meaning that VHP3 included a simplified IMPD cross-referring to the full IMPD approved in VHP2.

Where necessary (due to countries not participating in the VHP) national CTA applications were submitted in parallel to the VHP. It should be noted that the decision to participate or not in the VHP is made by the NCAs; companies should plan for all relevant MS to participate in the VHP for any individual study.

At the time of authoring this article, Amgen has no experience of submitting substantial amendments via a VHP.

Planning for a VHP

In general, the decision to use the VHP for a specific CTA application should be made in consultation with relevant functions such as clinical development, study management and local affiliates, and involves an assessment of the pros and cons. As these three procedures would represent our first experience of VHP, Phase II studies with a relatively small number of participating countries were chosen.

It is important that all functions understand the differences in the VHP timelines compared with the usual national CTA application procedures. These differences can potentially have significant impact. The sequence of submission of some documents is different; national documents can be submitted only at the national phase. This may allow earlier submission of the core dossier compared with national procedures, for example site lists do not have to be final at this stage. Given the possibility that a VHP decision can come at Day 30, Day 50 or Day 60, the 20-day clock for national submissions can be triggered at three time points. Coordination of national document availability in each country is essential. In our three procedures, a Day 50 decision was assumed to be the base case for planning purposes.

Teams should also consider the relationship between Ethics Committee (EC) review and regulatory review in each country, and address any questions with the NCA and/or VHP-C at this stage. It should be clear to teams that EC review and decision-making is outside the scope of the VHP pilot and in some countries the NCA will not be able to issue an approval if there is a rejection from the EC. Following a positive VHP decision it is also important to remember that there
### Table 1: Core CTA dossier for initial VHP submission

<table>
<thead>
<tr>
<th></th>
<th>VHP 1</th>
<th>VHP 2</th>
<th>VHP 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Covering letter including the EudraCT number and a short description of the key features of the CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>List of the NCAs the applicant intends to submit a CTA in the national phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Core CTA EudraCT form (common information for all MS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Study protocol including synopsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Investigator’s brochure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Investigational medicinal product dossier (IMPD), as defined in EudraLex – Volume 10 (including viral safety and IMPD on the placebo, if applicable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>IMP additional information (if not included in IMPD):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Manufacturing authorisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- GMP compliance certificate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Importation authorisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Certificate of analysis, if applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Authorisation for special characteristics of products, eg, GMO or radio-elements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NIMP dossier according to Annex I of the VHP Guidance, if applicable*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Copy/summary of any scientific advice from any competent authority or EMA and PIP summary, if applicable.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The European Commission has issued draft guidance for consultation on the requirements for non-investigational medicinal products (NIMP), with comments being available for consultation on the European Commission website.*

### Table 2: Characteristics of studies submitted using the VHP

<table>
<thead>
<tr>
<th></th>
<th>VHP 1</th>
<th>VHP 2</th>
<th>VHP 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product type</td>
<td>Peptide (marketed)</td>
<td>Monoclonal antibody</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Development phase</td>
<td>Phase II</td>
<td>Phase II</td>
<td>Phase II</td>
</tr>
<tr>
<td>Number of countries</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>participating in VHP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Countries involved in VHP</td>
<td>UK, France, Germany, the Netherlands, Spain, Hungary</td>
<td>France, Belgium, the Netherlands, Spain</td>
<td>France, Belgium, the Netherlands, Spain</td>
</tr>
</tbody>
</table>

### Table 3: Metrics for each stage of the VHP

<table>
<thead>
<tr>
<th>Stage</th>
<th>Timeline in guideline</th>
<th>VHP 1</th>
<th>VHP 2</th>
<th>VHP 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>5 working days</td>
<td>7 working days</td>
<td>5 working days</td>
<td>5 working days</td>
</tr>
<tr>
<td>Assessment stage 1</td>
<td>30</td>
<td>30</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Applicant RTQ</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Assessment stage 2</td>
<td>10/20*</td>
<td>11</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Applicant national CTA</td>
<td>20</td>
<td>2-17</td>
<td>11-20</td>
<td>9-20</td>
</tr>
<tr>
<td>National approval</td>
<td>10</td>
<td>4-10**</td>
<td>1-12**</td>
<td>2-12**</td>
</tr>
</tbody>
</table>

*Timeline for Assessment Stage 2 depends on whether consensus is reached amongst participating NCAs.

**Excludes countries where EC approval is required before NCA approval can be issued.*
are some countries where an EC approval is needed before the NCA can issue national regulatory approval; this can impact the timing of the final NCA decision.

An additional practical consideration when planning the submission is that a single IMPD per IMP is submitted to the VHP-C. This means that a full IMPD should be submitted if the VHP group of countries contains any MS which has not previously authorised a CT with the IMP concerned, even if the majority of MS involved would have accepted a simplified IMPD.

Experience during stages 1–3

Stage 1: Request for VHP and validation

The VHP-C reviews the request and dossier for compliance with published requirements as well as gaining agreement from each NCA to take part in the VHP. Some national documents (such as labels) may be requested at this stage by NCAs in order to facilitate a seamless transition to the later national phase, but they are not absolutely required.

Stage 2: VHP assessment steps

Having validated the submission, the VHP-C shares the CTA application with the relevant NCAs for individual review. In all three VHP a GNA was received at Day 30, via the VHP-C who had consolidated the questions from individual agencies into two lists. The first list contained questions that were considered GNA and were not attributable to individual agencies, although it was clear if more than one agency had asked the same question. In contrast, the second list contained questions that were attributable to specific agencies, and although described as ‘not relevant for approval’, still required a response from the sponsor. Some agencies also provided additional comments to facilitate the subsequent national step, such as a reminder regarding the electronic CTA submission process in Spain. In all three cases the response to questions was considered acceptable by the NCA and this led to the VHP acceptability statement being provided by the VHP-C on or slightly before Day 50.

Stage 3: National steps

Having received the VHP acceptability statement, the national submissions were made in all countries within the allotted 20 calendar days. Key to achieving this was the interaction between the central and local company teams discussed in the planning stage above. Importantly, there was no additional scientific discussion of the documents agreed during the VHP.

As EC approval is outside of the scope of the VHP this can still influence the ability of the sponsor to initiate the clinical trial, and could in some countries lead to an NCA administrative rejection where EC approval is mandatory in order for NCA approval to be issued.

Our experience in adding additional countries to a CT authorised following a VHP is limited. In the one case where a request was made for an MS to accept the VHP this was not agreed; and the submission was made (and approved) using the national process. As the decision to accept the outcome of the VHP by additional countries is voluntary, and assessed on a case by case basis, it is not clear what the usual outcome would be from our limited experience.

Timelines

The timelines for each VHP broadly followed those published in the VHP guidance, or were ahead of schedule (see Table 3). In general, the national approvals were issued in a timely manner, sometimes even within one day of submission. However, in MS where the regulatory approval is not issued until after the corresponding EC approval, the national approval may take longer than the published 10 days.

Our experience suggests that the process from original regulatory submission to actual study start in the first European country may not be substantially impacted by following VHP compared with national procedures. Some countries are historically known to have rapid national procedures and others take longer. From our experience we believe VHP has a neutral effect on study timelines, if start-up in all countries is considered rather than start-up in the fastest countries (see Table 3).

Discussion

In general, our experience of the VHP has been positive and we have found the process to operate in accordance with version 2 of the CFTG’s guideline. Efficiencies have been realised, particularly with respect to the resolution of GNA from multiple MS at a single well defined time in the procedure. It is not possible to say whether fewer questions were received than if separate national procedures had been followed. However, the CFTG has indicated that some consolidation of questions can occur prior to sponsors receiving questions. We have found the impact on study start-up timelines to be neutral.

We anticipate that greater efficiencies and scientific benefits may be obtained when seeking authorisation of large studies involving more countries than in the three case studies described, such as for large Phase III studies.

In general, the national approvals were issued in a timely manner, sometimes even within one day of submission.

In conclusion, the VHP has facilitated a harmonised regulatory decision across MS participating in MN-CTs. Although companies should evaluate the VHP on a case by case basis, further use of the VHP pilot is to be encouraged.

Disclaimer and acknowledgements

The views expressed in this article are the personal views of the authors and do not necessarily represent the views of Agena Limited. The authors would like to thank their internal and external colleagues who were involved in the submissions described in this article.

References


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3 ‘One voice for clinical trials in Europe, an interview with Dr Hartmut Krafft’, Regulatory Rapporteur, July–August 2010.

