Voluntary Harmonization Process for Multinational Clinical Trials in the EU
Right Direction, But is it Enough?

By Surendra Gokhale, PhD and Marina Gasser-Stracca, PhD

In April 2001, Directive 2001/20/EC (the Clinical Trials Directive) came into force with the objective of harmonizing clinical trial processes and detailing the legal provisions for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) across the EU. The aim was to increase and standardize the protection afforded to clinical trial participants. EU Member States were required to integrate these provisions into national legislation. Since 1 May 2004, all EU clinical trials have been required to be conducted in accordance with GCP principles.

CTA Process in the EU

Before commencing a clinical trial, the sponsor must submit a valid Clinical Trial Application (CTA) seeking authorization to conduct the trial to the Competent Authority in the Member State in which the trial will be conducted, and must receive regulatory approval. Additionally, a single, favorable Ethics Committee opinion is required.\textsuperscript{1,2} Applications to the Competent Authority and Ethics Committee may proceed in parallel or sequentially, depending on the Member State and local guidelines. All Member States implemented the directive’s key features and those of the supporting directives by the end of 2008.

The directive has improved the conduct of clinical trials and the harmonization of core requirements, and has provided greater assurance of patient safety and clinical data quality to support the Marketing Authorization Application. An extensive survey from the European Commission in 2009–10\textsuperscript{3} clearly demonstrated that implementation of the Clinical Trials Directive has been a challenge for all parties involved in conducting clinical trials in Europe, including Ethics Committees, Competent Authorities and medicinal product manufacturers. While the directive has created a general framework for the conduct of clinical trials across Europe,
different interpretations of the legislation by Member States have created nuances in implementation.

Conducting multinational clinical trials has more than doubled the administrative burden for industry without any additional significant safety benefits for the patients involved in the trials. In fact, submission of the CTA containing the same core elements in each participating country, followed by multiple scientific assessments of the same dossier with different timelines and eventually some conflicting decisions, results in significant delays for completing the clinical trials.4

This ultimately results in significant delays in making the innovative medicinal products available to patients. In the last few years, innovative industry has attempted to look into new avenues for completing the necessary clinical programs outside the EU. Thus, the number of clinical trials conducted in the EU has declined over the past several years.5

CTA Process Harmonization Attempts by EU Commission, HMA’s

In an attempt to improve the CTA harmonization across the Member States, the European Commission published Communication 2010/C82/01.22 in March 2010.6 This document provides detailed guidance on the request to the Competent Authorities for authorization of a clinical trial of a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1).

However, this effort did not lead to the expected harmonization and reduction of industry’s overall workload for getting CTAs approved. The Heads of Medicines Agencies’ (HMA) Clinical Trial Facilitation Group (CTFG), which coordinated implementation of the Clinical Trials Directive across the Member States, met to discuss and resolve challenges surrounding CTA management in the individual countries. As a specific step, they introduced the Voluntary Harmonisation Procedure (VHP) in March 2009.

What is the VHP?

The VHP is managed by HMA’s CTFG, and allows a sponsor to obtain a harmonized scientific discussion and a single opinion for any EU multinational CTA. Core documentation is submitted electronically to a single contact address.

The process timelines for different steps of the VHP are given in the VHP guidance and are mostly followed by the participating Member States. Member States have indicated they give priority to VHP applications over nationally submitted applications, although this is not specified in the guidance document.
Based on limited experience with the VHP in 2009 and dialogue with industry, CTFG developed a new version of the VHP in March 2010. The primary changes included a more streamlined assessment, and a wider range of applications were accepted.

In the new VHP process, one of the participating national Competent Authorities takes the lead in the scientific assessment with the participating countries, organizing discussions on an as needed basis and consolidating the outcome, among other actions.

The overall VHP procedure has three phases, from the initial submission to the national health authority approvals. The actual VHP common assessment is a two-step process resulting in a common scientific opinion based on the assessment of all participating countries. This leads to a further national step of submission of the common approved dossier along with the necessary local elements, which are mainly in the local language(s).

Managing Multinational Trials in the EU

Project teams for leading innovative companies with extensive research and development activities in multiple disease areas and projects in different phases of development, together with a strong focus on the development of personalized therapies, are highly motivated to ensure the innovative therapies under development are made available to patients as early as possible. As a result, regulatory professionals are challenged to get CTAs approved in countries based on the availability of patients, qualified investigators and the clinical research facilities as early as possible.

Figure 1: Time from VHP Submission to VHP Approval - Phase I and II in Days

Figure 2: From National CA Submission to National CA approval - Phase III in Days
Based on the authors’ experience over the last five years in conducting more than 50 multinational trials every year, the timeframe for CTA approval is from one to six months after the submission to different participating EU countries. Also, there is a high likelihood that a discrepant opinion from one Member State may lead to changes to the protocol after the trial has been initiated in other countries, resulting in a non-uniform clinical trial design.

Buy-in From the Project Teams for the VHP Option

Due to some of the challenges outlined earlier, regulatory managers were successful in convincing some project teams to try the VHP in late 2009, although the industry experience was very limited at that time and there were many uncertainties with the process. The main argument influencing the project teams was the option to obtain consolidated health authority questions and a common scientific opinion with the chance to get approval for a uniform trial design in all participating Member States.

In the first four VHP procedures attempted for the multinational trials, overall experience was positive, which resulted in more project teams agreeing to use the VHP for multinational EU clinical trials. Over the last 18 months, the VHP procedure has been used for 18 trials. This number is significant, considering the approximately 144 VHP applications managed by the CTFG overall from March 2009 to February 2012.

VHP Performance Data Observations

Based on the experience of initiated and ongoing VHP procedures, as well as nine that have been completed, the following conclusions can be drawn:

- average time used for a VHP: Phase I (Validation)—7 days; Phase II—55–65 days; Phase III—12–32 days (Figure 1 and Figure 2)
- overall time from initial submission to approval: 70–82 days authority time + 20–40 days internal time (Figure 3)
- countries not participating at all: Poland, Italy
- countries not participating in specific trails: Bulgaria, Greece, Netherlands
- formal national approval (Phase III) was delayed as EC approval is needed before the health authority approval is confirmed: Spain, Netherlands

Conclusions

Based on the trials ranging from Phase I to Phase III involving four to 11 countries, we have developed an overview indicating pros and cons of the VHP system (Figure 4). This information is being used with the project teams for future planning.
Overall, VHP appears to be a step in the right direction to manage some of the challenges faced by the existing national CTA submission process. However, for every VHP procedure initiated, there are always one or two countries that do not participate. As a result, a parallel national CTA procedure needs to be initiated in these countries.

Current contacts for the VHP procedures are very open to quick information exchange or answering queries from companies. In addition to the existing guidance, some additional elements, e.g., information on Central Ethics Committees, are needed for the initial VHP application.

All requirements need to be transparent for planning purposes. Our limited experience with managing substantial amendments for trials approved via the VHP was less positive, as participating countries could not agree on a common approach for the amendments. Some further guidance will be needed from CTFG on the management of the amendments.

Currently, amendments can be submitted nationally. However, if this is done once, all advantages of the VHP procedure are lost and all further steps need to be handled nationally for individual countries. Companies should negotiate amendment submissions via the VHP as the preferred approach with the VHP coordinator.

The VHP offers a short- to medium-term alternative to the purely national system of the management of clinical trials in the EU. However, it applies only to health authority submissions, not to Ethics Committees or Institutional Review Board submissions.

Also, the VHP is not anchored in any EU directive or regulation, and countries can opt out of the procedure if they wish. This results in uncertainties for overall clinical development.

The currently planned revision of the Clinical Trial Directive needs to take the above experience into account in order to provide a simplified, efficient and more predictable regulatory framework for clinical trials. Innovative industry needs a streamlined EU procedure consisting of unambiguous and detailed, but uniform, requirements; a central submission portal for data-sharing among Member States; and a single EU scientific and technical assessment of the dossier resulting in a uniform approval respecting the approval timeline of 60 days which was the Clinical Trial Directive’s initial goal.

Yes, the VHP has been an improvement, but industry needs more efforts from the regulators to create a more efficient way of managing the CTA process and bringing innovative therapies to patients.

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### Figure 4: Pros & Cons

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<th>Pros</th>
<th>Cons</th>
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<tr>
<td>• Utilises same core documentation as required for Core CTA e.g. Protocol, IB, IMPD</td>
<td>• VHP still a voluntary program [used so far in 144 out of over 2000 multinational trials]</td>
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<td>• Streamlined process for common scientific review</td>
<td>• Only ten days to respond to List of Questions</td>
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<td>• One harmonized List of Questions [some national differences are vetted internally]</td>
<td>• All national documents to be included in the local CTA have to be available locally by day 30 of VHP assessment (possible approval day)</td>
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<td>• Higher likelihood of getting uniform protocol approved.</td>
<td>• VHP applies only to HA submission process and EC submissions are still purely national</td>
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<td>• HA approval using VHP is not faster compared to few national CTA approvals timelines in the individual countries</td>
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<td>• SMT and the affiliates can work on the local documents during the ongoing VHP OR Phase II assessment</td>
<td>• Individual countries can still decide on their own not be part of the VHP process</td>
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<tr>
<td>• Timelines given in the VHP guidance document were strictly adhered</td>
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<td></td>
<td>• Always predictability of the actions</td>
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<td>• Team can optimize resources and plan availability of experts</td>
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References


Authors

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