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Comparisons between US and UK Regulatory Environments for Conducting Phase I Clinical Research

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PURPOSE

In a global development environment, with converging regulatory processes and guidance, companies are faced with the question of where to conduct their early clinical development programs.

A significant proportion of pharmaceutical and biotech companies are located within the US, which, together with a substantive early phase clinical research infrastructure and a recognised Investigational New Drug (IND) regulatory process ensure its position as one of the leading global regions for performing early phase clinical research. Europe is also a highly active environment for the conduct of early clinical research with approximately 450 Phase I trials carried out in 2014, 40% of which were performed within the UK[1].

The UK has a highly respected and influential regulatory environment due to its world-leading Health Authority, the MHRA, and the availability of diverse and extensive experience in the field of early phase research from a wide variety of organisations. This claim is further substantiated by an increase in the volume of Clinical Trial Authorisation (CTA) applications by 11% in 2015 compared to only a 7% global increase[2].

The objective of this poster is to provide comparative information on the CTA and IND applications, highlighting factors that may influence companies in deciding where to conduct Phase I clinical research.

METHOD

Information from relevant EU and US legislation and guidance in addition to applicable material published by National Competent Authorities MHRA and FDA have been collated to compare and contrast CTA and IND submission processes. Data have also been gathered from existing Quotient Clinical Sponsors via a questionnaire to solicit their opinions and experiences with CTA submissions in the UK. US based Sponsors accounted for 75% of completed questionnaires, with the remaining 25% from within the EU.

RESULTS

A comparison of CTA and IND regulatory processes indicated several similarities (Table 1). Key differences were highlighted as the pre-submission requirements in the US prior to the first-in-human (FIH) trial, and subsequent IND longevity, as opposed to study-by-study submission cycles in the UK.

RESULTS *cont.*

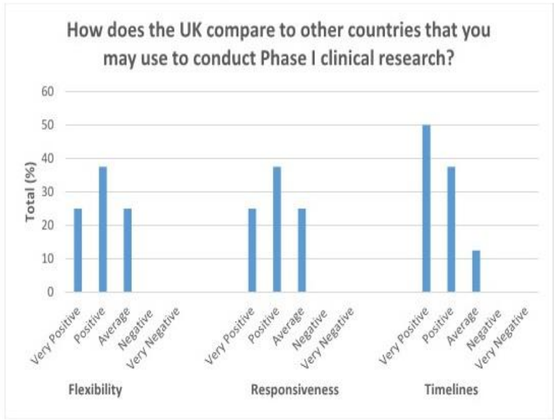
Overall approval timelines have the potential to be shorter in the UK (14 days) compared to the minimum US cycle (30 days), accepting positive affirmation is required in the UK whereas a company can proceed if no objections are raised in the US. During 2016 Q1 and Q2, average review times for Phase I trials at the MHRA were 12.1-14.1 days[3], although Quotient Clinical saw an average review time of 9.8 days. Amendment requirements and experiences are comparable to those of the initial submission in both regions. In the US, additional annual reports must be filed but this is not a UK requirement.

Table 1: Comparisons between UK and US regulatory processes for Phase 1 clinical trials

Regulatory Process	CTA (UK)	IND (US)
Pre-submission requirements	No specific requirements	Extended pre-IND meeting process
Purpose	One CTA for one clinical trial	One IND for one molecule, product or indication. Multiple trials through one IND
Review timelines	14 days for Healthy Volunteer studies 14 days for Sponsor to respond to a NGNA if raised Final decision from MHRA within maximum 60 days of initial validation	30 days for initial submission review (after this, updates can be made without waiting for review) If clinical hold imposed FDA have 30 days to provide response to Sponsor comments[4]
Amendments	Substantial (SA) or non-substantial (NSA) amendments. MHRA have up to 35 days to review an SA, NSAs are not submitted.	Protocol or information. Both types require submission but communication of approval from FDA not required.
Maintenance	Not required	Annual reports within 60 days of effective date anniversary[6]
Chemical and Pharmaceutical Quality information	Information and data limited[5] Declarations on EU GMP compliance, assuring product quality and importation requirements. Retest dates and shelf life	More detailed information but less data requirements

Data generated from existing Quotient Clinical customers highlighted key drivers for selecting the UK as a location for conducting Phase I clinical research (Figure 1). Sponsors rated the UK as 'very positive' with respect to timelines for review and approval of CTA applications. Favourable feedback was also received with regard to the responsiveness of the MHRA to interactive dialogue throughout the submission process and also their flexibility in being open to innovative, science-based approaches to adaptive CMC and protocol designs. Supplementary feedback received on reasons for selecting the UK included pragmatism and efficiency of MHRA assessors. Quotient Clinical examples of pragmatism and flexibility by MHRA assessors include:

Figure 1: Sponsor perspectives on the UK regulatory environment



- Design space CMC development projects
- Within-protocol decision making through adaptive protocol design
- Incorporation of Healthy Volunteers, Patients or other specialist populations to accelerate the Proof of Concept development phase
- The flexibility to use multiple routes of study drug administration

CONCLUSION

The similarities between CTA and IND processes provide a level of familiarity for companies determining Phase I research placement. Commonality in GCP, GMP and ICH standards ensure transferability of data in downstream submissions. This includes the requirement to submit information in the ICH CTD (Common Technical Document) format, with MHRA making electronic (eCTD or other accepted electronic submission) CTD submissions mandatory in February 2016 and FDA due to follow suit by 2018.

Companies often feel that opening an IND offers regulatory efficiencies by being able to update continuously during the development life-cycle. However as indicated, the by-study submission cycle within the UK can be faster for Phase I studies. Equally, opening an IND is often seen as a key investor milestone however, this can still be achieved regardless of where the FIH study is submitted/performed.

Differences in the CTA procedure such as requirements surrounding quality documentation coupled with favourable timelines and responsiveness of the MHRA, may be viewed as advantageous with regard to speed and flexibility for conducting early phase research in the UK. This makes the UK an attractive location in which to conduct early phase clinical trials given the industry need to increase R&D productivity. Whilst the European regulatory environment is facing change in the coming years with the implementation of the new EU Clinical Trial Regulation, it is not expected to impact these UK benefits to any great extent.

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