

# Managing Clinical Trial Application (CTA) Acceptability to Support Phase I Clinical Studies in the United Kingdom

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## Abstract

**Aim:** The EU Clinical Trials Directive (2001/20/EC) was implemented in the United Kingdom (UK) on 1st May 2004. The directive established the need for regulatory review and approval by the Medicines and Healthcare products Regulatory Agency (MHRA) of the study protocol, investigational medicinal product (IMP) quality, and safety data prior to conduct of a Phase I study. The purpose of this white paper is to assess the impact of this directive on regulatory submissions and to provide insight on how companies can prepare their submissions to ensure the timely and effective conduct of Phase I clinical trials.

**Methods:** All clinical trial applications (N=80) submitted to the MHRA by Celerion or predecessor companies between 1st May 2004 and 1st September 2010 were examined for trends in MHRA comments.

**Results:** The majority of the CTAs contained comments from the MHRA assessors. Remarks were divided into 6 categories: chemistry, manufacturing, storage, non-clinical studies, labeling, and clinical. The three most common comments were related to the design of the protocol: stopping criteria, dose cohort safety assessments, and contraceptive statements. The most common IMP dossier related comments concerned retest/expiry dates, method validation, and batch analyses.

**Conclusion:** MHRA review patterns of CTAs indicate that by paying attention to particular protocol safety parameters and select IMP dossier requirements, the timely review and approval of CTAs can be assured.

## Aims

The EU Clinical Trials Directive (2001/20/EC) was implemented in the UK on the 1st May 2004<sup>1,2</sup>. The directive established the need for regulatory review by the MHRA of the study protocol, investigational medicinal product (IMP) quality, and safety data prior to conduct of a Phase I study. Each study conducted in the European Union (EU) also requires a EudraCT number and EudraCT application form (both can be accessed through a specified webpage)<sup>3</sup>. A complete list of the documents required for review by the MHRA is presented in Figure 1. Despite the new review requirements, the MHRA has set an average review time of 14 calendar days for Phase I healthy volunteer studies even if the regulations allow for 30 calendar days' review time.

In this white paper we assess the impact of this directive on regulatory submissions and provide insight on how companies can prepare their submission data to ensure the timely and effective start-up of Phase I clinical trials.

Figure 1.

### List of documents required by the MHRA for a Phase I healthy volunteer CTA

- Cover Letter
- EudraCT number confirmation
- EudraCT application form (Annex 1)
- Protocol
- Protocol Synopsis
- Investigator Brochure
- Investigational Medicinal Product Dossier (IMPD) (Full, Simplified, SmPC)
- Example of Labeling
- Manufacturers/Import Authorization
- QP Declaration (if product imported from outside EU)
- Delegation Letter
- List of ongoing studies
- List of competent authorities
- Certificate of analysis in exceptional cases\*
- Viral safety studies and data\*
- TSE certificate\*
- GMP status of active biological substance if imported from outside EU\*

\* as required

## Methods

All clinical trial applications submitted by Celerion to the MHRA for Phase I healthy volunteer studies between 1st May 2004 and 1st September 2010 were analyzed. Data from 80 studies whose initial CTA submission was reviewed by the MHRA were examined for trends in reported MHRA comments to the protocol, IMP dossier, and general trial-related activity.

## Results

During the period 1st May 2004 and 1st September 2010, 80 clinical trial applications for Phase I studies were submitted to the MHRA for review. Typically within 2-5 days of CTA submission, the MHRA sends a letter confirming receipt of a complete application which is eligible for review. If the application has deficient/missing information, the MHRA usually informs the applicants by email.

The MHRA regularly publishes performance metrics on the timelines for clinical trial review. Current metrics quote that the review timelines of Phase I trials in healthy volunteers is 11-13 days<sup>4</sup> whereas the European standard can be up to 60 days.

The calculated Celerion review timelines are slightly longer since these data include the time required for confirmation of CTA receipt by the MHRA. The median average time from submission to MHRA to receipt of approval letter is 14 days.

Due to adequate regulatory preparations and proper judgment, all studies submitted by Celerion have been approved by the MHRA within the forecast time frame (data on file).

A potential bias in the Celerion analysis is possible: prior to 2007, comments from the MHRA were appended to the end of the approval letter and referred to as "Remarks". These remarks could be in the form of assumptions or requests for further information.

In 2007, following legal advice, the MHRA changed its process. In the current process if these remarks are minor or assumptions, they continue to be included in the approval letter. However, if the MHRA requires further information then a 'Grounds for Non-Acceptance' (GNA) letter is issued. This should not be viewed as the rejection of a study, rather a request for more information. If further information is requested, companies have 14 days (unless permission is sought from the MHRA to increase this timeline) to respond or their trial would be deemed not-approved.

Table 1.

MHRA Review of Phase I Healthy Volunteer CTAs					
Year	Number of Phase I CTAs	Approved at Initial Application	GNA	Non-responses	Rejections
2005	298	284	14	1	0
2006	267	247	20	0	1
2007	274	215	59	6	2
2008	255	NA	NA	NA	NA
2009	235	NA	NA	NA	NA

NA: Detailed information not available

Categorization of the Celerion data according to the content of the MHRA communication (e.g. comment on chemistry) rather than the means of communication is expected to remove the bias.

The MHRA has published metrics that reflect this change in process (Table 1). The results show that in 2005, 95% of applications were initially approved compared to 47% in 2008. During that time period, the number of GNA letters increased substantially during the 2007/8 time period. There was also a 21% drop in applications between 2005 and 2010. This drop in numbers is explained by the MHRA as being due to increasingly complex protocols, which combine previously separate studies. The MHRA has confirmed that they have reviewed and approved multiple 'umbrella' protocols that also included a patient cohort in a healthy volunteer study.

A review of the MHRA correspondence from the 80 CTA submitted by Celerion (from 1st May 2004 to 1st September 2010) revealed that a significant number of remarks/comments/assumptions from the assessors.

The comments and remarks were placed into 6 broad categories: chemistry, manufacturing, storage, non-clinical studies, labeling and clinical. A total of 185 comments were received. Figure 2 shows the percentage breakdown of comments.

### Chemistry

The most common IMP dossier (Chemistry) related comments concerned retest/ expiry dates, method validation, and batch analyses. Figure 3 shows the breakdown of comments relating to the IMP dossier.

Figure 2.

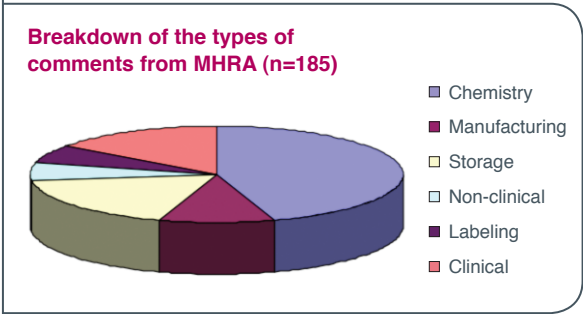
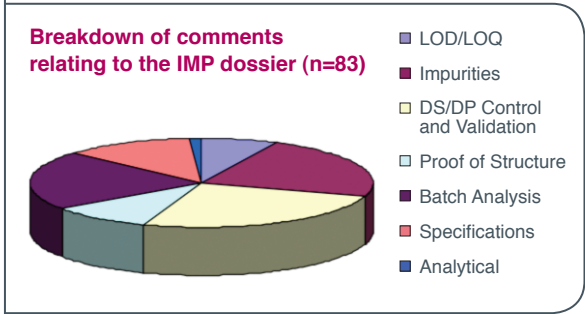


Figure 3.

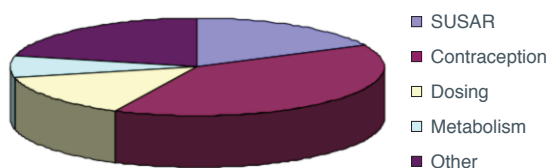


## Clinical

The three most common comments that were related to the design of the protocol were related to stopping criteria, dose cohort safety assessments, and contraceptive statements. Of note there were additional hurdles applied relating to dosing and safety reporting shortly after the TeGenero incident in 2006. Figure 4 show the breakdown of the types of comments relating to the clinical documentation.

Figure 4.

### Breakdown of the types of comments relating to the protocol (n=28)



## Conclusions

Prior to May 2004, Phase I studies conducted at single investigator sites required Ethics Committee/IRB and Principal Investigator approval only. The Clinical Trials Directive (2001/20/EC) prescribed a structure for the regulatory review and approval of Phase I clinical trial submissions for Phase I studies. Since implementation there have been a number of reviews and changes

to the process in the UK. Despite these changes, the MHRA claims much shorter approval times than those observed in other EU countries (less than 14 days compared to up to 60 days). The Celerion experience shows that whilst the UK regulators may adopt a conservative approach to clinical studies from some perspectives, the comments by the regulators are reasonable as long as the CTA submission is robust.

The MHRA has recently shared information on the breakdown of the types of requests for information outlined in the GNA letters. Around 50% of comments are scientific whilst the remaining 50% are administrative.

The agency advises that administrative issues (such as missing documents) are completely avoidable and lead to delays to study start. By examining the data from clinical trial applications, regulators' comments can be analyzed and proactively implemented to ensure timely and effective Phase I trial study start up.

The three most common comments were related to the design of the protocol: stopping criteria, dose cohort safety assessments, and contraceptive statements. The most common IMP dossier related comments concerned retest/expiry dates, method validation, and batch analyses.

MHRA review patterns of CTAs indicate that by paying attention to particular protocol safety parameters and select IMP dossier requirements, the timely review and approval of CTAs can be assured.

## References

- Clinical Trials Directive: Directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- UK Statutory Instrument 2004 No. 1031: The Medicines for Human Use (Clinical Trials) Regulations 2004
- EudraCT website: <https://eudract.emea.europa.eu/>
- MHRA website: <http://www.mhra.gov.uk/index.htm>
- Preliminary results were reported in an Abstract at the ASCPT Meeting 2006, Baltimore, MD.