[redacted]

Medicines & Healthcare products Regulatory Agency

[redacted]
Cell Therapy Limited, trading as Celixir
Celixir House Stratford Business & Technology Park
Innovation Way
Stratford-Upon-Avon, CV37 7GZ

By special delivery and email

MHRA

HQA, 10th floor
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London
E14 4PU
United Kingdom

www.gov.uk/mhra

Our Ref: INSPECTION REPORT GCP 46397/18142462-0001

Date: 17 July 2024

INFRINGEMENT NOTICE
Served pursuant to regulation 48 of the
Medicines for Human Use (Clinical Trials) Regulations 2004

Dear Sir,

The Secretary of State for Health and Social Care (the "Enforcement Authority") is serving this Infringement Notice on Cell Therapy Ltd (trading as Celixir) ("Celixir") under regulation 48[1] of the Medicines for Human Use (Clinical Trials) Regulations 2004 (the "Regulations") and references to a regulation in this notice are to those Regulations, unless otherwise specified.

A Good Clinical Practice ("GCP") inspection carried out on 22 July 2020 (Clinical Investigator site) and on 28-29 September 2020 (Sponsor site) identified 9 critical and 3 major findings and it is the view of the Enforcement Authority that Celixir, the trial sponsor, failed to ensure the conduct of the trial in accordance with the conditions and principles of good clinical practice and therefore risked seriously jeopardising the rights, safety and well-being of trial participants.

The inspection revealed the following breaches of the Regulations, in a number of defined areas:

- Trial Oversight *Failure to comply with Regulation 28(1) and (2)*
- Investigational Medicinal Product (IMP) *Failure to comply with 29(b)(iii).*
- Trial Master File (TMF) *Failure to comply with Reg 31A(1)-(3) and (5)*
- Clinical Trial Authorisation (CTA) *Failure to comply with Regulation 12(1) and 29(b)(i)*

Summary of regulatory breaches

Trial Oversight
Failure to comply with Regulation 28(1) and (2)

The sponsor had an inadequate quality system with insufficient procedures to secure the quality of every aspect of the trial and to cover how they would perform their sponsor responsibilities and trial activities to ensure these were performed in compliance with GCP regulations and guidelines.

[1] Regulation 48 applies to regulations 3A, 12(1), 22(b), 27, 28(1) to (3), 29, 29A, 30(2), 31A and 32-35 of the Medicines for Human Use (Clinical Trials) Regulations 2004.

There was a lack of evidence that sponsor staff had the appropriate clinical trial experience to be able to adequately oversee the conduct of a clinical trial and perform their responsibilities as sponsor to ensure the rights, safety and well-being of trial participants were protected and that all aspects of GCP were complied with. Examples of lack of formal processes included documentation of substantiality review of proposed protocol amendments. Inadequate documentation of the creation, review and submission of all regulatory documents to ensure these were created, reviewed and approved in compliance with GCP. No procedures for management of serious breaches (e.g. urgent safety measures) or for the use and oversight of vendors or consultants to ensure they undertook their delegated tasks in compliance with GCP.

Investigational Medicinal Product (IMP)
Failure to comply with Regulation 29(b)(iii).[2]

Batch certificates for the IMP signed by the Qualified Person ("QP") supplied to the trial in April 2019 indicated a 12 Month shelf life which was used for labelling of the IMP. The Investigational Medicinal Product Dossier (IMPD) in the Clinical Trial Authorisation submission contained the stability period. The 12-month shelf life was beyond that specified in MHRA approvals which were 3 months (IMPD version 2) at the time of labelling, and 9 months (IMPD version 3) at the time of shipping of the IMP. While it is noted that a substantial amendment to update the IMPD to version 4 was submitted in January 2020 which extended the stability period to 12 months this had not been finalised at the time the IMP was manufactured labelled and QP certified and, even if the substantial amendment had been accepted, the shelf life could not be extended beyond that stipulated in IMPD version 3 as it was based on an IMP manufactured under a different IMPD version. Therefore, the expiry dates were beyond those approved by the MHRA.

Regulation 13 concerns the supply of IMP for clinical trials. Although MHRA it is outside the scope of this Notice, it is noted the batch certificates for QP certification signed by the QP referenced the incorrect legislation and was also contrary to the quality agreement between Celixir and Cell Therapy Hellas. Therefore, the IMP was not QP certified in compliance with the appropriate legislation.

There were discrepancies within the certificates of analysis for the initial IMP batches and no instructions provided to the investigator site pharmacy to quarantine until the relevant clinical trial documentation was accepted and the clinical trial authorisation was in place.

Trial Master File (TMF)
Failure to comply with Regulation 31A(1)-(3) and (5)

There were significant deficiencies with the TMF that impeded the ability to reconstruct the trial conduct. Celixir had no formal TMF for the sponsor documentation and had no process or documentation to define the TMF in terms of the systems it comprised. The UK TMF Management Plan was not in place at the start of essential documents being generated and many essential documents related to the clinical trial were missing from the eTMF that was managed by the contract research organisation**.**

Clinical Trial Authorisation (CTA)
Failing to comply with Regulation 12(1) and 29(b)(i)

The MHRA granted a CTA for a Phase two trial. The previous clinical information was based on results from a clinical trial conducted in Greece in 2012 and the sponsor subsequently submitted a substantial amendment and removed any reference to this trial. The MHRA issued a notice of non-acceptance of the amendment in 2020, however, the trial commenced, and a single patient was dosed[3] contrary to the understanding of the licensing authority that this would not occur. The IMP had also technically expired at the time of dosing based on the approved IMPD3. Documents in the initial CTA and substantial amendments submitted previously all indicated that there was previous experience of this IMP. The

[2] The role of a QP as set out in the Human Medicines Regulations 2012 (specifically regulations 41(2) and 41(8)) are outside the scope of this Notice.

[3] It was subsequently confirmed that the patient in question had been administered a placebo.

original protocol and investigator brochure was not complied with and there was no valid approved clinical trial authorisation for the IMP dosed.

Celixir are required to put in place preventative measures to ensure that these breaches do not recur, and that any future clinical trial activity in the UK in which Celixir sponsor or are otherwise involved in is conducted in a manner fully compliant with the Regulations.

To date we have no information that the patient, who was dosed has been informed, and you are required to provide to the MHRA any documents to enable us to confirm that we have correctly identified and contacted the patient[3].

In particular, Celixir must implement effective mechanisms:

- To check that a regulatory authorisation is in place prior to commencement of any future trial sponsored by Celixir and conducted in the UK in accordance with Regulation 12.
- To ensure that investigational medicinal products are supplied to a participant in relation to a clinical trial conducted in the UK are in line with the documentation which is specified in Regulation 29(b)(iii) (and as required by Regulation 13).
- To ensure for any trial conducted in the UK and sponsored by Celixir that the principles of GCP are complied with, in particular Schedule 1, part 2 of the Regulations.

A written response is required within 21 days of the date of this Notice. The response should confirm that the measures set out above will be implemented, providing a reasonable timeframe for doing so. Celixir are reminded that each of the breaches identified in this Notice constitutes a criminal offence punishable by a fine and/or up to 2 years imprisonment (see regulations 49 and 52). Unless the measures set out in this notice are taken within the time periods specified in this notice, further action may be taken in respect of the contraventions.

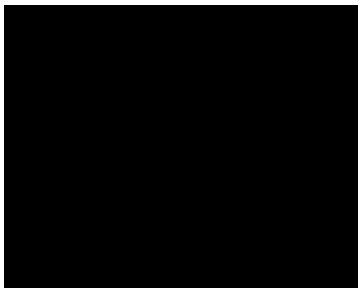
If Celixir fail to confirm this within 21 days, further action against you, including criminal prosecution, will be considered.

Celixir should also note this Notice, plus any responses, will be provided to the Health Research Authority (for distribution to the relevant ethics committee). It may also be published on the MHRA website.

This Notice is without prejudice to any other action that may be taken by the Licensing Authority.

Please mark all correspondence for the attention of Dr Chris Jones, IAG Chair, at the email address shown below.

Yours sincerely,



Dr Chris Jones
A person authorised to sign on behalf of The Secretary of State for Health and Social Care
Email: IAG2Secretariat@mhra.gov.uk