

Speaker Abstracts

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GMP and the Challenge Agent: Leishmaniasis

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Background: Leishmaniasis is a globally important but neglected disease, for which no vaccines for human use are currently available. Reflecting the folklore practice in endemic countries of deliberately inoculating lesion scrapings to induce natural immunity ("leishmanization"), almost two million people were inoculated with *Leishmania* parasites during the 20th century. In 1989, the WHO recommended this practice be ceased except as a last resort. In 2000, WHO supported a proof of concept study of leishmanization as a tool for vaccine evaluation, the first modern-day leishmaniasis controlled human infection model (CHIM; Mohebalı et al *Acta Tropica*. 2019. 200:105173). This program was not continued for a combination of scientific and political reasons.

Challenges: Early consultation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) provided the framework for a successful funding application to MRC to support development of a new CHIM involving transmission by sand fly bite. Major discussion points included: provenance of the challenge agent; manufacturing standard (GMP or GMP-like); release and stability assays; mitigation of risks to participants.

Approach: Consideration of all factors indicated that the best option was to source and characterise fresh clinical isolates of *Leishmania major* and to produce a challenge agent under GMP using a contract development & manufacturing organisation (CDMO). The chosen CDMO had no prior experience of working with *Leishmania* but experience with other Category 2 pathogens. Safety documentation was provided and an iterative process of developing SOPs adopted. For two parasite donors, full clinical histories were obtained along with HIV, HTLV1, HBV, HCV and *Mycoplasma pneumoniae* status and donors were followed for 6 months post cure. Parasites were isolated and cultured using GMP grade materials, genotyped, tested for virulence and drug sensitivity in mice and for transmission competence in two sand fly species. Pre-GMP expansion ("research banks") is underway and virulence will be re-confirmed in mice prior to GMP production. A stability plan for the GMP bank has been developed.

Conclusions: Although GMP-like production of this challenge agent might have been possible in an academic setting, the use of an experienced CDMO has had tangible benefits in terms of i) ensuring maximal compliance with our desired product specification, ii) cost, iii) GMP compliance and iv) time to completion.

