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Non-clinical animal models used in support of the orphan drug designations in infectious diseases

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Introduction

The aim of this project of the EMA/COMP Non-clinical Models Working Group is to review non-clinical models used to support orphan drug designations (ODDs) in rare infectious diseases. We would like to put these models in the context of the available literature data and assess animal models, as well as rare infectious diseases that are difficult to study in a non-clinical setting. This analysis may lead to a more efficient utilisation of animal models in establishing the pharmacodynamic feasibility of potential therapies for rare infectious diseases in the context of orphan designation, thereby helping and streamlining in critical development decision making regarding use in the clinical setting.

Results

- 26 rare and designated infectious diseases were identified comprising 60 ODD applications.
- Of these ODDs, 24 contained non-clinical data only, making it 40% of applications for rare infectious diseases, for which products were not evaluated in human yet.
- The most prevalent animal species used to test designated products was mouse, followed by non-human primate and rabbit.
- Significant benefit was not required in 38% of the designated conditions. Interestingly, these are mainly viral conditions.
- Non-rare infections that accompany rare diseases (e.g., infections in cystic fibrosis) were not assessed, since the clinical aspects addressed in such applications were considered pertinent to underlying rare disease.

Conclusions

- Non-clinical research in the field of rare infectious diseases is often challenging due to the bio-hazard and human-specific nature of the pathogens.
- Many acceptable and established non-clinical models of infectious diseases exist, which may be used to support the feasibility or medical plausibility of new medicinal products being used in a specific rare infection.
- In the ODD setting it was noted that in 62% of the conditions designated by the COMP there were authorised medicines and therefore the additional criteria of significant benefit had to be established which could be challenging in the setting of non-clinical *in vivo* models.

No.	Medical condition	No. of ODDs	Non-clinical models	Clinically relevant endpoints in models
			Viruses	
1.	**Avian Influenza**	2	mouse	neutralising efficacy
2.	**Cowpox**	1	mouse, squirrel, prairie dog, non-human primate, rabbit	viral load, mortality
3.	**Dengue**	1	mouse	morbidity, mortality, viral load, vascular leak, platelet count, levels of pro-inflammatory cytokines
4.	**Ebola**	6	mouse, non-human primate	survival, symptom scores, viral load
5.	**Hemorrhagic fever**	1	rodent, non-human primate	persistence, clearance, disease outcomes
6.	**Japanese encephalitis**	1	mouse	survival, seroconversion rates
7.	**Monkey pox**	1	mouse, squirrel, prairie dog, non-human primate, rabbit	viral load, mortality
8.	**Polio**	1	mouse	virus titre in brain tissue, survival
9.	**Smallpox**	2	rabbit	survival, respiratory rate, weight loss, development of secondary lesions
10.	**Vaccinia**	2	mouse, squirrel, prairie dog, non-human primate, rabbit	survival, dermal lesion formation, weight, virus-specific antibody titers, cytokine production, viral load
11.	**Variola**	1	mouse, squirrel, prairie dog, non-human primate, rabbit	viral load, poxvirus lesions, mortality
			Bacterias	
12.	**Anthrax**	5	rabbit, non-human primates	survival
13.	**Meningococcus**	1	rat, non-human primate, rabbit	survival, bacterial clearance, TNF-α level, plasma endotoxin levels
14.	**Non-TB mycobacteria**	1	non-human primate, mouse	presence of intracellular mycobacteria in the lungs
15.	**Tuberculosis**	10	mouse, guinea pig	survival, lung / spleen colony forming unit
16.	**Tularaemia**	1	mouse	survival, lung / spleen colony forming unit
17.	**Yersinia pestis**	1	mouse, non-human primate	antibody titres
			Fungi	
18.	**Cryptococcus**	1	mouse	brain fungal burden
19.	**Microsporidia**	1	*in vitro* data only	microsporidia in infected cell cultures, inhibition of microsporidia growth *in vitro*
20.	**Mucormycosis**	2	mouse	survival, fungal burden, infarct score,
21.	**Scedosporidia**	1	mouse	survival
			Parasites	
22.	**Acanthamoeba**	3	chinese hamster, rat	parasite killing kinetics, amoebicidal activity
23.	**Echinococcus**	1	mouse, rat	survival, parasitic burden, number and size of cysts, histology
24.	**Leishmania**	5	mouse, dog, hamster	IgG titres, T cell proliferation, cytokine production, parasite clearance, number of amastigotes in liver cells, lesions
25.	**Malaria (Plasmodium)**	7	mouse, rat, non-human primate	parasite clearance, effective dose, mortality, reoccurrence of parasitemia, percentage of cure
26.	**Trypanosoma**	1	mouse, non-human primate	parasite clearance