Brussels, 27 May 2022

COST 025/22

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “One Health drugs against parasitic vector borne diseases in Europe and beyond” (OneHealthdrugs) CA21111

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action One Health drugs against parasitic vector borne diseases in Europe and beyond approved by the Committee of Senior Officials through written procedure on 27 May 2022.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA21111
ONE HEALTH DRUGS AGAINST PARASITIC VECTOR BORNE DISEASES IN EUROPE AND BEYOND (OneHealthdrugs)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to deliver innovative and prediction tools to identify One Health drugs for human and animal (H&A) neglected infections. The integrated multidisciplinary efforts will reduce the drugs impact on the environment through the coordinated action of researchers and stakeholders (governmental bodies, industries/SME, patients'association). This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
The recent COVID19 pandemic infection has undisclosed long-standing issues in the translation of drugs from animals to humans or vice-versa. Nearly 75% of emerging human infections worldwide originated from animals; existing drugs for human and animal (H&A) vector-borne diseases (VBD) are scarce, with limited efficacy, toxicity, and finite resources. Emerging environmental problems in pharmaceutical use/manufacturing increase attention in the field. The two drug pipelines are developed independently. Hence, cooperation is needed among different expertise to define how it is possible to develop new drugs in a more sustainable approach.

OneHealthdrugs aims at coordinating the discovery of drugs halting H&A VBD keeping with the principles of optimal profile for both organisms, increasing the quality and delivery technologies. The COST Action is the ideal platform aiming at the integration and generation of synergies among drug R&D experts from the chemical/biological/human/veterinary and earth science within academies, SMEs, industries, governments. The platform encompasses pre-clinical drug discovery, animal studies, and drug delivery. Strategies such as bioinformatics, PROTAC, nanotechnology will be enhanced.

OneHealthdrugs will impact in Europe and in disease-endemic countries. The Action will provide a compounds database and a white chart about the discovery of new drugs for H&A infections. Expected benefits include the transfer of academia-industry and Northern-Southern world knowledge. Conferences, training schools for advanced technologies, and STSMs are planned. Novel communication technologies to disseminate the Action results to a broad audience including scientists, stakeholders, and citizens are planned. Young researchers will be trained on advanced techniques.

Areas of Expertise Relevant for the Action	Keywords
● Chemical engineering: Medicinal chemistry, drug synthesis ● Health Sciences: Parasitology ● Biological sciences: Molecular biology and interactions ● Earth and related Environmental sciences: Environment chemistry ● Veterinary science: Veterinary medicine (miscellaneous)	● Drug discovery ● human and animal diseases ● vector borne parasitic diseases ● One Health approach ● Integrated approach

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Coordination and integration of the medicinal chemistry programs by collecting and re-using large compounds databases available from different sources. Associate the libraries with in silico prediction of compounds molecular properties to improve their antiparasitic drugs profile.
● Coordination of the in vitro activity of R&D studies; integration of the activities for reduction/prevention of the drugs impact on the environment. The compounds from different sources (natural, synthetic, from organic waste) will be tested in cell-based assays. Experimental and in silico ecotoxicology studies will be coordinated.
● Coordination of the translation from in vitro-to-in vivo activities to obtain One Health high quality leads and candidates. Introduction of omics technologies (genomic, proteomics and transcriptomics) and imaging for

a limited number of validated leads. Drug delivery of biodegradable nanotechnology and drug targeting tools for pharmacological studies in H&A.
● Coordination of the activities to incorporate procedures and assays of the antiparasitic drugs R&D program in the guideline format. Coordination of meetings and critical analysis on the activities performed and deliverables achieved. The information and deliverables shared with the stakeholder will be translated in an informed whitepaper with guideline content.
● Dissemination and transfer of knowledge, research results, and the proposed solutions to a broad audience (EU agencies, SMEs, industries, general public) via website, scientific papers, conference contributions, newsletters, social media, and integration of existing guidelines. Achievements of new patents on new compound class with H&A action.

Capacity Building
● To build a sustainable network of European stakeholders from the fields of human and veterinary drug discovery, parasitology, pharmacology, omics and health science and communication all collaborating within and across disciplines towards the common goal of discovering and developing new drugs against VB parasitic diseases.
● To facilitate, through investigations, training schools, workshops, and STSM, an expansion of the currently separated R&D platform for the development of new drugs against H&A. This objective is particularly important for Young Researchers and Innovators and for less research-intensive countries.
● To cooperate with non-European world-leading experts within each scientific field covered, thereby ensuring mutual benefits and the best possible platform for any research and educational activities within the Action.
● To increase the interest of SMEs, industries, local, national governmental institutions in drug discovery research to implement the research activity in the field and ensure a constant feeding of the drug discovery pipeline with new chemical entities with One Health profile, thus supporting the innovation needed in the field.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

The COVID-19 pandemic has increased awareness of the importance of robust investments in pandemic preparedness and response, particularly strengthening the global infectious disease research capacity. It has also increased the attention about the relevance of zoonotic diseases on human and animal health opening the problems of emerging of previously neglected infectious diseases (NID).[1] The devastating effects on sociality and economy showed the need of a multidisciplinary effort under the One Health principles, by taking a more global approach to find new medicine to preserve the human, animal and environment health. The drug research efforts have contributed during times to develop important medicine that saved world people lives, but today has shown its limit in the impact on animals and environmental health. Coordinated actions are needed to comply with the One Health principles.

Vector Borne (VB) parasitic diseases and emerging problems. Recent analysis reports that 75% of all emerging human infectious diseases in the past three decades worldwide originated in animals. Environmental disturbances may affect both human and animal well-being (H&A). Contamination and pollution in Europe and in poor and disadvantaged populations (sub-tropical regions, and, in Europe, Mediterranean countries) may spread new infectious agents.[2-9] VBDs account for 17% of the estimated global burden of all infectious diseases (700000 deaths/year). And billions are at risk. The rapid expansion of global travels and trade; the rapid urbanization in the tropics; the resulting increased interactions of humans with the animal reservoirs of pathogens and vector species in geographically constrained environments; the climate changes; the societal, cultural, and behavioural practices have a growing social and economic impact in endemic Countries and also in Europe. Finally, the limitation of the therapeutic approach is related to low efficacy, high toxicity and rapid growing of drug resistance.[2-9]
Drug resistance. Due to the rapid increasing of antimicrobial drug resistance EMA is proposing a new Veterinary Medicines Regulation (EU) 2019/6 that will come into effect in 2022. One of its main objectives is to strengthen measures to tackle antimicrobial resistance. The Regulation will establish a list of antimicrobial substances, that include also antiparasitic drugs, which are to be reserved for the treatment of certain infections in humans only. The medicine in the list shall not be used at all in animals in the EU. In summary, **three criteria** for drugs classification are identified: 1. High importance to human health. 2. Risk of transfer of resistance from animals to humans. 3. Low importance of the antimicrobial to animal health. This brings concerns about the future antimicrobial therapy in humans and animals.

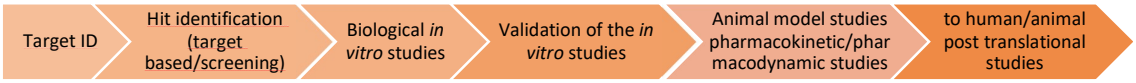
The environmental impact is an additional severe problem in endemic countries and in Europe, affecting the sustainability of the whole drug manufacturing and use. Pharmaceuticals and their residues, including Active Pharmaceutical Ingredients (API), metabolites and transformation products, are emitted into the environment at different stages of their life cycle, from their production to their use to their disposal. A large body of literature reports the presence of pharmaceuticals in environmental compartments (e.g., surface and ground water, soils, biota). They are generally detected at low concentrations (e.g., in the range of sub ng/L to µg/L in the aquatic environment) (www.epa.gov) Example of contamination of the aquatic environment due to drug excretion, and improper drug product

disposal can include single-use administration reagents.[10] Environmental impacts of drug can be catastrophic as exampled by the use of Diclofenac as a veterinary medicine and its involvement in the decline in Vulture populations in India.[11] Management of Health-care waste in compliance with EU standards costs US$ 1-3 per bed per day in France[12] Ivermectine was found in the soil/water and considered a source for drug resistance.[13]

VBD affecting both human and animals and drugs in use. Leishmaniasis is relevant in Europe, due to the high prevalence of canine leishmaniasis that act as reservoir and its expansion in recent years.[8] Therapy includes antimonials, amphotericin, miltefosine, pentamidine. Resistance has emerged for antimonials and the optimal therapy relies on the expensive liposomal amphotericin (AmBisome®). **Chagas disease**, historically confined to Latin America, is becoming a global health threat, affecting to 4.2 % of over 3.5 million immigrants settled in Europe and 300000 infected people are estimated in the USA.[9] Drugs in use are nifurtimox and benznidazole. **Human African trypanosomiasis (HAT)** is spread in Africa. Treatment options are pentamidine, suramin, melarsoprol, eflornithine monotherapy, and nifurtimox–eflornithine combination therapy (NECT). Recently, fexinidazole for oral use has been approved in 2019 (in Democratic Republic of Congo).[14] The Animal African Trypanosomiasis (AAT) has a huge impact on cattle (and other livestock) health thus heavily impacting country's economies and development (an estimated 46 million of cattle at risk of trypanosomiasis).[15] Drugs available are: diminazene aceturate, phenanthridine, ethidium bromide and isometamidium (ISM), (used mainly as prophylactic). **Schistosomiasis.** WHO estimates show that at least 290 million people required preventive treatment for schistosomiasis in 2018[16] and there are numerous animal species as reservoirs.[17] The main therapeutic agent is still Praziquantel, also employed in animals. **Other infections with emerging relevance are Babesia infections**. (Babesia divergens from cattle, B.venatorum) transmitted by ticks, and common in livestock and pets. Bovine babesiosis, is the economically most important arthropod-transmitted pathogen of cattle causing mortalities, abortions and decreased meat production.[18] Human cases in Europe and around the world have been found.[19-20] Chemotherapy relies on atovaquone, marketed over 35 years ago, clindamycin, azithromycin but show drug resistance.[21]

Drug discovery for neglected infectious diseases. The NID drug discovery process is driven by medical need and in many cases ideal and acceptable target product profiles (TPP) have been elaborated by the non-governmental development organisations (NGDO) such as the Drugs for Neglected Diseases Initiative (DNDi) and the WHO.[22] TPP's further focus R&D expenditure and streamline development processes crucial for maximising chances of success in achieving the selected drugs. However, there is a persistent gap in innovation and investment by large pharmaceutical companies due to the low potential of financial return.[23] In the large majority of the cases, the drug discovery processes for human and animal infections are performed independently by pharma, academic groups and research institutions or through Public Private partnerships (PPP)s.[24,25]

The strategies of DRUG RESEARCH consist in a multidisciplinary approach that span the chemistry and biology disciplines and should be integrated with environmental impact of all products life cycle (see below). Different approaches are adopted in each specific phase of the life cycle. Examples are given, below.



TARGET-BASED APPROACH. The targets for infectious diseases should be essential and selective for the parasite compared to the H&A host considering structure, function and localization at the cellular/body level. Among the intracellular enzymes purine salvage pathway and the S-

adenosylmethionine synthetase (METK) enzyme[26], folate related proteins are largely studied. Energy metabolism is essential for survival. Membrane transporters targeted or mechanistically involved in the drug actions are for example purine salvage transporters in kinetoplastids including *T.brucei* adenosine transporter 1 (TbAT1), *T.brucei* aquaporine[2] (TbAQP2), working as efflux transporters. In Leishmania, pyrimidine salvage and pyrimidine uptake into cells depends upon specific transporters. It is essential to establish if transporters in various Leishmania species are similar to those present in other Trypanosoms such as *T. evansi*, causing AAT2.[27] This is the most widely distributed in AAT, mainly causing disease in horses, camels, and water buffaloes, other than cattle, cats, dogs and others. Recently a step towards the degradome technology is proposed.[28,29] The transmission process in VBD infections happens through vectors such as mosquitoes, flees, mites, ticks. Intervention transmission is a robust way to block the infection spread.[29] In that respect, the vector itself is considered as a parasite (ectoparasite) and drugs affecting the vector were identified specifically such as isoxazolines.[30-32] Repurposing was largely considered but now a renowned strategy is necessary.[33,34]

Direct screening of many COMPOUND LIBRARIES available to the public or for private use only, is largely used against target proteins. MEDIUM OR HIGHTHROUPUT PHENOTYPIC SCREENING (HTS or HCS-high content screening) are directly used to screen compound libraries on parasites. New bioassays are developed in the research of anti-Leishmania agents using more sophisticated assays that may overcome the limit of promastigote *vs* amstigote assay,[35] anti-*T.brucei* and other parasites.[36,37]

Novel source of hits and leads from organic waste material from human activity industries. Among these sources, the non-psychoactive *Cannabis sativa* L. (hemp) product market capacity shows a historic jump off as high as 10 times in less than a decade. In the industrial process after the extraction and purification of cannabidiol (CBD) from hemp female inflorescences the remaining hemp from industrial extraction process may be employed for further exploitation in the medicinal field, thus favouring the full recycling of industrial waste material. Flavonoids, and other agents with potential antiparasitic activity may be extracted. Agriculture is estimated to generate about 700 million tons of waste annually in the EU. Novel valorisation technologies are developing continuously to recover and recycle valuable compounds and nutrients from waste materials.[38] Insect organic waste (frass) are also recently identified. This is a new field that helps in the circular economy and can contribute to the identification of novel substances.

Recently OMIC TECHNOLOGIES have been applied[39-40] with libraries screening purposes, for the identification of new targets, mechanism of action and drug resistance. These technologies have also been applied in the environmental science to characterize the dramatic effects of drugs in the fish and other animals[41]. IMAGING techniques allow the molecular characterization of the compounds mechanisms thus favouring their application in target engagement studies to validate intracellular compound allocation.[42] In the recent years, RTD European platforms have been funded and they offer service with the most advanced technologies[42] for free, upon application (ESFR,[43] EMBL[44], EUROPEAN screening platform[45] and European Lead Factory (ELF).[46]

Animal studies and use of NANO SYSTEMS FOR PHARMACOKINETIC AND PHARMACODYNAMIC improvement. Significant progress is the use of nanocarriers for enhanced oral bioavailability of antiparasitic drugs have been achieved[47,48], mixed formulation of conventional and PEGylated liposomes for a broader and more effective drug targeting of the infection sites in canine visceral leishmaniasis[49] nano systems to overcome resistance associated with current treatments for HAT48 and Leishmaniasis.[49] Other promising approaches consist in the combination therapy at the nanoscale, as a mean to maintain *in vivo* the synergistic ratio of the drug combination and the co-incorporation of both immunomodulatory and chemotherapeutic agents.[3] Recent advances in the design of nanoparticles for effective *in vivo* siRNA, mRNA and DNA delivery[50,51] also open new perspectives for more specific antiparasitic treatments.

The main aim and objective of the Action **OneHealth*drugs*** is to coordinate the ongoing R&D activity on novel drugs against NID taking into consideration the global social and economic context of the diseases. This will happen through the networking in the same platform of the researchers and stakeholders in the field of the human and animal NID. The ideal goal of the COST Action is to enrich the pipeline with high quality, effective, reduced cost drugs, with improved tolerability on one hand and having minimal environmental impact by incorporating the principles of the One Health in every step of the research process. This approach encompasses the values to the goals of Universal health Coverage and the Sustainable Development Goals (SDGs)[2] to fight both humans and animals present infections and be prepared for the future ones.

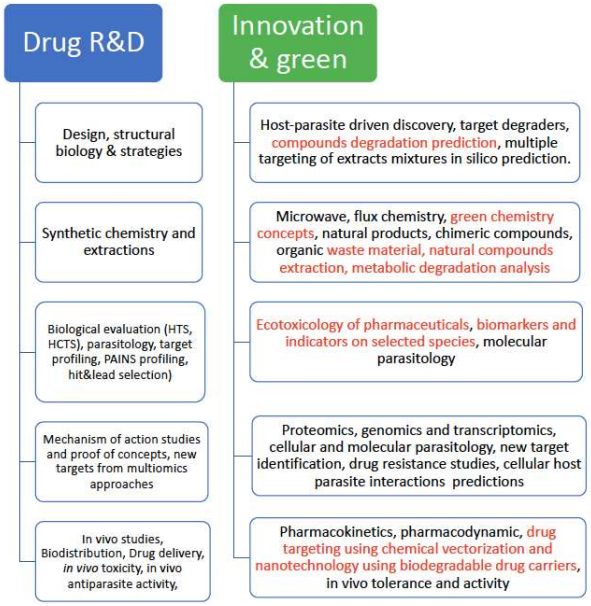
1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

OneHealth*drugs* will face different challenges:
Challenge 1. Existing drugs for human and animal neglected infections against VBD are scarce, with limited efficacy and toxicity. *Therefore, a collective effort for innovative compounds and prediction tools should be identified to improve the therapeutic properties of the antiparasitic drugs and identify new drugs.*
Challenge 2. The impact of pharmaceutics and their R&D process on the environment is high and it is responsible of huge loss due to contaminated water that affects human and animal health, generate drug resistance problems. *Integrated multidisciplinary efforts (design, synthesis/extraction, in vitro and in vivo biological/animal studies, delivery) should be developed to reduce the drugs impact on the environment at every step of the drug research and development process. This requires the coordinated action of researchers and stakeholders (governmental bodies, patients' organizations, industries and SME*.
Challenge 3. Not enough control and informed procedures are available to link the environmental impact to drug production and use. Specific guidelines do not exist to address the problem during the whole process from conception to manufacturing and use. *Concepts and strategic support in a guideline/white paper format should be given to the stakeholder in the field for a standard approach to develop safer drugs for humans and animals.*
Challenge 4. Researchers approaches, industrial entities working in the field of VBD, lack communication and interactions in relation to environmental sustainability and innovation. OneHealth*drugs will represent the ideal platform for networking and communication, to establish interaction and contribute to the training of young researchers.*
Challenge 5. The transfer of knowledge at European level on H&A drugs R&D is not achieved yet, despite the available initiatives. *This COST Action will promote the transfer of knowledge among the different stakeholders also through neighbouring and international partners to train young researchers in the field of the R&D of VBD antiparasitic drugs*.

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

OneHealth*drugs* addresses the open challenge through the joint efforts of the qualified experts from the medicinal chemistry, parasitology, veterinary, human health, ecotoxicology fields will de-risk the outcome of the drug discovery process and finely tailor the leads and candidate for human or animal use by avoiding or preventing drug resistance, reducing inefficacy risks, reducing economic impacts and strengthen a robust pipeline progression with a few candidates that follow the one health profile. This Action aims to advance the state-of-the-art through a well-organized workflow coordinating the drug R&D process with innovation and low environmental impact of the procedures and new drugs identified. The procedures reported in Figure 1 includes a non-exhaustive list of activities in relation to compound libraries sharing, in silico drug design studies. Compounds degradation prediction. Identification of new hits from organic sources of waste material from the human technologies. Green chemistry principles and metabolic degradation analysis. HTS(HCTS) technologies application. Use of degradome pathways and PROTAC technology. Biodegradable use of delivery and targeting systems in bioavailability studies using advanced technologies in animal studies. Omics technologies applied to mechanism of action and ecotoxicology. Environmental impact studies by including suitable assays into the selection process: ecotoxicology assay predictive tools for studying the impact effects and analytical tools development and applications. Biomarkers, organisms and indicators.



1.2.2. OBJECTIVES

1.2.2.1 Research Coordination Objectives

Objective 1. Coordination and integration of the medicinal chemistry programs by collecting and re-using large compounds databases available from different sources. Associate the libraries with in silico prediction of compounds behaviours (e.g. molecular and chemioinformatic properties, metabolic and chemical degradation, ADME-tox properties of metabolites) to improve the properties of the antiparasitic drugs. Actions: Increase the number of compounds to screen in a coordinated approach (from virtual or phenotypic approaches). Coordination of the compounds' libraries available and usable for screening and repurposing studies by the participants. The compounds libraries that are IP free (with no intellectual protection), discovered previously or/and during the 4 years of the Action, will be made available to all participants. Compounds degradation prediction. Collection of the information in an open access database repository dedicated to OneHealth*drug*, such as FAIRDOM database (FAIRDOM is open source database[52]). **KPI**: the Action will adopt 3 metrics to measure objective 1.1 activities to be updated, at least every 6 months 1.2 Number of compounds identified belonging to different libraries >10000. 1.3 Number of in silico studies including metabolic (enzyme assisted) and chemical degradation.

Objective 2. **Coordination of the *in vitro* activity of the R&D process and integration of the necessary actions for the reduction/prevention of the drugs impact on the environment.** Actions: Expertise the different sources of compounds (natural source, synthetic chemistry, organic waste

matter). Biological evaluation on the target and profile of the compounds in cellular assays that integrate the activities necessary for the reduction/prevention of the drugs impact on the environment. Coordinate ecotoxicology studies on selected models. HTS/MPS screening by evaluating natural source, compounds libraries, and innovative sources such as organic material of the human industrial activities. This includes hemp extraction residual waste, exhausted agricultural material, extraction from frass of insects and insects themselves, other similar waste products. Green chemistry principles approach for the compounds production, such as microwave extractions, flux chemistry. Use of predictive tools for reaction optimization and for synthesis implementation. (Figure 1). Ecotoxicology of drugs and degradation prediction, analysis with innovative methods and analytical tools. **KPI**: the Action will adopt 3 metrics to measure objective 3 to be reviewed once a year. 3.1 Number of hits identified from the different sources compared to the compounds' library screened (many thousands available from different sources). 3.2 Number of projects developing research with organic waste material 3.3 Number of new projects planned within the One Health concept.

Objective 3. **Coordination of the translation from *in vitro*-to-*in vivo* activities to obtain high quality leads and candidates**. Actions: Introduction of omics technologies (genomic, proteomics and transcriptomics) and imaging for a limited number of validated leads. Drug delivery of biodegradable nanotechnology and drug targeting tools applications for both H&A R&D, pharmacology (pharmacokinetics and pharmacodynamics) on animal models by changing drug regimen and study of the effects of the different drug bioavailability tools. This can be acquired through European RTD organization and allow the achievement of high-quality leads with associated biological properties tailored for the H&A VB parasitic infections drug research program. **KPI**: 3 metrics adopted to measure objective 3 to be reviewed once a year. 3.1 Number of successful examples of biodegradable nanotechnology formulation on dose regimen for each infection. 3.2 Number of projects developed in collaboration with the RTD platform and other stakeholders. 3.3 Number of animal studies including the degradable formulation and targeting vectorization.

Objective 4. **Coordination of the activities to incorporate procedures and assays of the antiparasitic drugs R&D program in the guideline format.** Actions: Coordination of meetings and critical analysis on the activities performed and deliverables achieved. Coordination of the information and deliverables with the stakeholder. Translation of the task achieved at the end of the Action in an informed whitepaper with guideline-like content. **KPI**: the Action will adopt 2 metrics to measure objective 4 to be reviewed once a year. 4.1 Number of deliverables successfully achieved. 4.2 Informed whitepaper obtained and shared.

Objective 5. **Dissemination and transfer of knowledge**, tools, research results, and the proposed solutions to a broad audience (EU agencies, SMEs and industries, general public, etc.) via a common website, scientific papers (codified knowledge), conference contributions, newsletters, social media, and integration of existing guidelines. Achievements of new patents on new compound class with H&A action (codified knowledge). Input to stakeholders in particular SMEs, industries and governmental institutions to strengthen the partnerships on the drug discovery programs of the Action. This will facilitate broad cross-sectorial dissemination and implementation of results, and a network with strong potential to stimulate new interest by EU and other agencies granting systems. **KPI**: 7 metrics adopted to measure dissemination and exploitation activities that will be continuously updated, at least every 6 months 1. Visits to the Action's website; 2. Social Medias followers; 3. Contacted Stakeholders; 4. Papers on peer-reviewed international journals; special issues on international journals; 5. Organized conferences/workshops/webinars, organized special sessions at major international conferences; 6. Fairs and events attended, events directly organized or co-organized; 7. Attendees, web and media coverage.

1.2.2.2 Capacity-building Objectives

The COST Action will pursue the following capacity building objectives:

- To build a sustainable network of European stakeholders from the fields of human and veterinary drug discovery, parasitology, pharmacology, omics, environmental and health science and communication, collaborating within and across disciplines towards the common goal of discovering and developing new drugs against VB parasitic diseases.
- To facilitate, through investigations, training schools, workshops, and STSM, an expansion of the currently separated R&D platform for the development of new drugs against H&A. This objective is particularly important for Young Researchers and Innovators and for less research-intensive countries.
- To cooperate with non-European world-leading experts within each scientific field covered, thereby ensuring mutual benefits and the best possible platform for any research and educational activities within the Action.
- To increase the interest of SMEs, industries, local, national governmental institutions in drug discovery research to implement the research activity in the field and ensure a constant feeding of the drug discovery pipeline with new chemical entities with One Health profile, thus supporting the innovation needed in the field.

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Although there are some similarities with research consortia/programs targeting (or that have targeted) aspects of One Health and/or parasitic diseases, these are either rather specific because focused on specific infections, or they only investigate different aspects of the One Health. **This Action is unique in gathering drug research scientists, health specialists in human and veterinary fields, patients' organizations, industry and policy makers to advance knowledge, sharing protocols, expertise, and information on the on-drug R&D in the field of parasitic VBD diseases. OneHealth*drugs* is in deep focused on new leads and candidates through innovative discovery programs integrating the environmental chemistry protection principles and green approaches**. The Action is shaping the work of the future on One Health drug research by advancing the current effort at European/international level for all the 5 identified challenges. To fulfil these aims the Action will establish strong interactions with existing projects and initiatives at the European levels. Efforts around Medicinal chemistry, One Health on parasitic diseases, targeting one specific disease ("COMBAR" against Drug resistant helminth populations)[53], or only investigate vector control concepts like Infravec2 project an European network[54]. IMI (Innovative Medicine Initiatives) is relevant for the medicinal chemistry activity regarding drug resistance in antimicrobials. OneHealth*drugs* will involve DNDi and other private associations, veterinarian, chemists and environmental chemistry societies (EFMC, European Federation of Medicinal Chemistry and national society), EFPIA including academic-private partnership so that more private institutions, SMEs and big Pharma will be coordinated to the Action objectives. OneHealth*drugs* will ensure concerted action of drug research with innovative technologies and integration of the environmental impact and sustainability in all steps of the R&D process with existing COST Actions and initiatives. At the international level many initiatives such as the One Health initiative funded by the European Joint Platform (EJP) in which the *laboratories for infectious disease in humans and animals aiming to integrate and align work processes of joint priority and joint research.*

Therefore, networking meetings of the Action will involve those relevant experts. The European Centre for Disease Prevention and Control (ECDC) is focused on sharing data on the geographic distribution of vectors transmitting human and animal diseases agents (Vectornet).[54] OECD (Organisation for Economic Co-operation and Development) is also one organization of reference for the environment protection including pharmaceuticals.

Benefits of larger geographical width. The Action will represent different countries and hence it will reach geographically a unique OneHealth*drugs* stakeholders from multidisciplinary field of research and activities within a large number of countries. Public health control vector diffusion, establish vaccination programs, and perform therapy management, the drug R&D programs are not implemented. In particular One Health concept integration remains difficult to translate into practice. The Action will facilitate identification of local stakeholders including contributors of the large pool of data needed for the Action, (WG1, WG2, WG3) in their home countries. Furthermore, knowledge of local infrastructure is crucial for national communication and implementation of results. The OneHealth*drugs* Action offers a) a broader approach to combat VBD through the achievement of qualified new leads and candidates integrated with environmental impact consideration b) provide criteria to empower drugs' efficacy against H&A VB parasitic diseases; c) favours an integrated platform for drugs R&D where different stakeholders may work together.

Stronger platform for dissemination and communications. The multidisciplinary and cross-sectorial nature of the Action and its dedicated target on drug discovery of anti-parasitic drug for H&A is unique. The large network of Action Participants from different disciplines and sectors working towards a single goal will ensure high quality outputs and a strong voice for communication of results and opinions (3.2.2).
Better education of PhD students and Young Researchers and Innovators. Young Researchers and Innovators will be involved in all tasks of the Action and work closely together with established experts, both during the investigations and as part of mentor-based career planning (see section 3.2.1). This approach is different from many ongoing educational activities such as specialised colleges and institutions (Universities) where PhD students and Young Researchers and Innovators are exposed to a high degree of self-study and exams. Combined with the organized training schools, workshops, and STSMs, this networking and collaboration between experts and Young Researchers and Innovators provides the best possible frame for education of new specialists in drug discovery for H&A infections in the field of VB parasitic diseases and environmental impact within the One Health concepts and mentality (WG5, 3.2.2).

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

The Action will be represented by experts in all disciplines required to fulfil the objectives listed in section 1.2.2.
Specifically:

- Medicinal chemists: important for WG1 and WG2 (Chemical Science).
- Computational chemists: important for WG1 and WG2 (Chemical Science).
- Structural biologists: important for WG1 and WG2 (Chemical Science).
- Bioinformaticians: relevant for WG1, WG2 and WG3 (Biological science).
- Parasitologists: important for most activities in WG1, WG2, WG3, and WG4 (Biological science).
- Pharmacologists: important for WG2, WG3 and WG4 (Biological science and veterinary science).
- Veterinary health scientists: important for WG1, WG3, WG4 (Veterinary).
- Nanobiotechnologists: relevant for WG1 and WG3, WG4 (Chemical Science).

- Environmental scientists: WG1, WG3 and WG4 (Chemical Science and Earth and related environmental science).
- Ecotoxicologist: important for WG2, WG3 and WG4.
- One Health scientists: important for WG1, WG2 and WG4.
- Communication specialists: Important for dissemination to ensure maximum impact and implementation of the Action outcomes through the most appropriate communication channels and perform together with all participants, the activities in section 3.2.2. (WG5).
- Transfer of knowledge specialist: important for ensuring IP management, exploitation plan (WG6).

During all **WG and Management Committee (MC) meetings** discussion will be opened about needs and recruitment strategies for additional experts and Young Researchers and Innovators, e.g., to meet specific scientific challenges such as delivery systems for H&A treatments and others (see 3.2.2). In particular more environmental scientists will be invited, due to their fundamental role in the Action. Specific activities for Young Researchers and Innovators recruitment will be organized as an important seed for innovation and for broadening the interest in the field. They will familiarize with the European RTD organizations and will be involved in **meetings only dedicated to Young Researchers and Innovators**. Workshops, webinars and training schools will be a mean to address the involvement of scientists from those European countries not represented in the Action from its starting. The Action will benefit of the involvement of international organizations such as WHO, DNDi, Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R), OECD and BVGH (BioVenture for Global Health, USA). For this activity the Action can rely on ECDIT (Egyptian Centre for the Innovation and Technology), NCDC (National Centre for Disease Control, Georgia), One Health initiatives (OHI, USA) that already are networked with those organizations (4 institutions). EFPIA representers will be invited to the workshops and training schools. A network of national organizations that cover H&A health can be established within the Action. (See section 2.2.2 and 2.2.3). They will be invited at workshops and WG meetings as experts (see 3.2.2 with details).
Depending on the role required, additional stakeholders will be enrolled for specific tasks (e.g. as speakers at workshops), or more permanently as Action Participants. Among those a specific interest is already expressed by Collaboration Pharmaceuticals Inc., USA based company (ICP) with specific activity in NID drug development. A fundamental task will be the involvement of more SMEs in some specific area (such as nanotechnology) also interested in networking within Private Public Partnership (PPP) for developing aspects of drugs discovery and development. Young talents and next generation leaders (under the age of 40) will benefit from the expertise via a strong training program. The training will be organized in form of **two training schools per year** that will help the **younger researchers** to learn about the scientific issues and teamworking and problem-solving within the specific OneHealth*drugs* NID drug development field. During the schools it is foreseen to promoting working opportunities for Young Researchers and Innovators.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Overall, stakeholders working on drug discovery and development in the field of H&A VB parasitic diseases will be invited to participate when their specific expertise is required. This will bridge the Action with other related efforts in the area, prevent duplication of activities, and create possibilities for synergistic collaboration, e.g., **joint training schools, joint investigations, or joint campaigns promoting** antimicrobial stewardship for drug resistance control. Special efforts will be devoted to involve environmental scientists that will be integrated in all activities to help the integration of the environmental impact in the synthetic and nanotechnology other than animal trials. The Action will organize conferences and participate in external events that are open to a high number of external stakeholders, in order to promote and increase awareness about the Action. Drug R&D actions are starting but are slowly embedded in the health plans of European countries; such plans are often not

largely and actively reviewed in the light of the VB parasitic infections field, despite their growing impact in Europe. In order to facilitate impact and awareness raising of the Action, a **stakeholder engagement strategy** will be defined.

- Among the most relevant stakeholders there are the veterinary and pharma industry; human and animal health professionals will be involved through the **RRI tools** project (https://www.rri-tools.eu/homepage).
- An **initial workshop** will be organized involving patients-linked organizations (migrant associations, medical assistance associations), practitioners, veterinary organisations and Health scientists and pharma representers to share ideas about what kind of drugs are expected by the end-users.
- Furthermore, **specific workshops and webinars**, involving speakers from pharma working in the field and other stakeholders interested in the exploitation of the concepts developed.

Publications addressed to **national Government's agencies**, to be kept informed of the added value of the Action to support nationally funded research projects. Such agencies will be also invited to conferences arranged within the network, and recommendations released in the form of publications on progress about new drug discovered, including novel tools and strategies developed within the network; publications and information guidelines mainly, will be prepared and circulated to relevant academic and research institution departments at national and European levels throughout the investigations, to enable potential collaboration. Through the interaction with Animal Health Europe (International Forum on Advancements in Healthcare, IFAH), the Action may gain access to contact lists of H&A health departments, health and research institutions throughout Europe. In this field NNC such as ECDIT (Egypt) and IPC as OHI (USA) could be helpful in connecting different R&D research platform among Europe-USA-North African countries. The Action will involve National Agencies from different countries around Europe. Other stakeholders such as STAR-IDAZ IRC (International Research Consortium for Animal Health, coordinating animal health research globally to accelerate delivery of disease control tools and strategies. https://www.star-idaz.net) which develops research roadmaps, also considering VBDs; DISCONTOOLS, (Filling the knowledge gaps in animal disease control) which publishes research gaps for control of animal diseases, could be a useful platform for dissemination of knowledge generated in the actions; GCRF https://www.ukri.org/what-we-offer/international-funding/global-challenges-research-fund/. Their regular advice and ideas sharing will inspire and provide quality control for the Action activities.

EC members belonging to IMI, JPI One Health initiatives and representatives of EFMC scientists, EFPIA companies (**European** Federation of **Pharmaceutical** Industries and **Associations**) representers, WHO, DNDi, OECD with international strategies for R&D programs/ Health management/ environment protection monitoring activities will be invited to participate in an **advisory board** of the Action.

A **final white paper and a guideline** will be provided from the integration of all the Action expertise/experiences with recommendations for future research and for the implementation of more effective, lower cost, reduce/controlled environmental impact, highly impacting R&D for H&A across Europe. This will likely have a higher political impact in particular if used for rising fundings for discovery and development programs specific for the area that are definitely missing in these times.

2.2.3. MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

The mutual benefits from collaborating with partners outside Europe are highlighted in the following:

Near Neighbour Country (NNC) Institutions: 1. **Egyptian Centre for Innovation and Technology Development (**ECDIT) (Egypt). They will have two main roles in the Action**: ì.** drug discovery and development area. ECITD will contribute to innovation intelligence and innovation management (WG5) helping in profiling novel leads/candidates that will be discovered during the 4 years project. ìì. connections between NNC and the European Countries. ECITD has established interactions at the regional level (mainly North Africa region) that will foster connectivity and networking activities and will contribute to enlarge the Action network (WG5). ECDIT has also collaborations with EU international programs (Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR)), GLOPID-R and the H2020 Health NC network in One Health activities. NNC participants will benefit of the educational activities of the Action. 2. **Theodor Bilharz Research Institute Public health and pharmacology division (Egypt)**. Role in the Action: they will contribute to the drug resistance studies, parasitic infections data management. Artemether repurposing in parasitic diseases. 3. **NCDC and Public Health** [One Health Division] (**Georgia**[1]). This is the National Organism for Health surveillance in Georgia and they have a division on leishmaniasis. The Head of the One Health division has expertise on a number of vector-borne and zoonotic diseases, and in Health Sciences in the Epidemiology. Role in the Action: will support the knowledge about NNC parasitic diseases, about drug efficacy in the field, availability of strains from the field and clinical isolates (WG3); experience in One Health approaches.

International Partner Country (ICP). 1. **One Health initiative (OIH, US) will be involved through one of the major representative partners from the Caribbean Island.** One Health promotional activities this website autonomously, probing in collaboration with Crozet BioPharm One Health Initiative team and website https://onehealthinitiative.com Role in the Action: contribution in One Health strategies with pharma industries and dissemination activities. **2. Laval University Quebec** (Canada) is a well renowned institution in Quebec. They coordinate preclinical pharmacology studies on non-human primate on *Leishmania infantum*. Role in the Action*:* non-human primate studies on advanced candidates. **3. University of Minas Gerais, Belo Horizonte**, (Brazil) has a strong involvement in the research of new treatments of leishmaniasis. The institution investigates the mechanism of action of antimonial drugs, and advanced drug delivery approaches with experience in canine pharmacology. Role in the Action: pharmacology and nanotechnology studies in dogs to advance drug candidates and innovative formulated drugs such as nanoparticles for gene delivery (mRNA, siRNA, pDNA). **4. Saudi Arabia** has experience in plants for the extraction of natural products. Role in the Action: they will provide expertise in medicinal plants. 5. **Cameroon** has expertise in extraction and testing of natural products. Role in the Action: they will provide expertise on natural products extraction and testing.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

The scientific impacts of the Action will be:

- a shared experience for researchers, industry stakeholders and national/international organizations opening the way to novel fruitful collaborations for transfer of knowledge/ new knowledge creation

[1] At the time of proposal submission Georgia was a Near Neighbour Country. Since 31 March 2022, Georgia is a COST Full Member.

about targets, drug research strategies, hits and leads elaboration, assays for HTS approaches, nanotechnology for drug delivery and animal studies; ecotoxicology and environmental tools applied to the research process.

- relevant scientific training for Young Researchers and Innovators in a multidisciplinary context favouring their career development.
- the engagement of novel and specific targets based on H&A biology comparative studies in particular in the field of degradome and soluble protein transporters (membrane proteins) for drug design, including specific targets against vectors;
- the discovery and optimization of high number of antiparasitic hits and lead compounds for H&A use with expected environmental low impact and higher quality profile than before;
- the development of multitarget compounds with different profile (finalized at PROTAC and other multitarget strategy) with chimeric structures; host-parasite chimeric compounds design
- the identification of novel hits and leads from organic material from the human activity (hemp, hives, frass and others) recycling the waste from industrial production;
- improvement of procedures and use of reagents within the green chemistry field to reduce the environmental impact;
- the prevention or overcoming of drug resistance such as host-parasites targets engagement using chimeric compounds as an innovative approach, more effective in drug resistance;
- omics and imaging studies, with synthetic conjugation technologies and structural biology in combination with advanced molecular biology for the mechanism of action studies, new targets identification;
- new biological assays for HTS and HCS screening and for lab scale studies of the mechanism of action together with the reduction of parasite growth;
- ecotoxicology-based model organism selection for biomarkers and indicators assay;
- the development of biodegradable drug formulations with engineered targeting and engineered conjugates ensuring better *in vivo* animal efficacy.

The long-term benefits could be:

- substantial improvements of the biological profile in treating parasitic diseases caused by VB parasitic diseases affecting H&A;
- substantial increase of the One Health awareness in Young Researchers and Innovators and all participants working together on drug discovery and environmental health;
- a long-lasting impact on antiparasitic drug development in Europe due to targeted training of Young Researchers and Innovators;
- a permanent on-line network of stakeholders in antiparasitic drug discovery and development to maintain a transfer of knowledge, new One Health knowledge creation and strengthen collaboration;
- engagement of RTD platforms active in the field;
- increased funding into antiparasitic drug development integrated with environmental scientists due to the improved multidisciplinary and multi-centre applications resulting from collaborations between participants in the Action and successful activity of contact and networking within this Action.
- reduction, recycle and reuse of waste material with consequent long term positive environmental impact in the long term.

Innovation.

Cross-sectorial and interdisciplinary networking approach to advance the drug discovery and development field in VB parasitic diseases in H&A (because an effective cure of the human infections can be achieved if animals' infections are cured or eliminated). Integration of the innovative approaches with the environmental impact concepts, will involve also pharmaceuticals manufacturing and use. Some of these tools may be breakthrough approach for the field (waste material use, host-parasite interactions strategies), while other are not, but the potential for them to collectively advance the field through an effective transfer of knowledge among the OneHealth*drugs* participants definitely represents an innovation. Hits and lead compounds database tailored on H&A VB parasitic diseases and obtained during the Action lifetime will foster new research activities. The Action will facilitate such innovation

through active promotion of the database (IP regulated) and search for collaborators in academia and industry. IP on new advanced candidates with promising or relevant pharmacological activity will be promoted. The integration of existing guidelines summarising results, highlighting knowledge gaps, and providing ideas for future drug discovery research in Europe (through the Action white paper) will support the EC and national policy makers in prioritising future initiatives within this field. Therefore, a strategic platform will be enabled to inspire about new funding opportunities and thereby increase the possibility to impact further through research.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation. The development of European-based research and technological networks in the scientific or interdisciplinary domain of 7 disciplines focused on the development of novel drugs with links among (medicinal, analytical, nanotech and structural) chemists and biologists in the field of parasitic infections, veterinary and environment health scientists and would not be possible for individual scientists or Countries. The exploitation of the research outcomes will result by intensifying the links between the scientific communities, companies, governmental institution and society at the European level, ITC, neighbouring and international countries. *This will generate a new knowledge about the One Health concept in VBD in which the drug research will fully integrate low environmental risk procedures and scientific activities in all steps of research*. Most of the knowledge created will be readily applicable by medicinal chemists, parasitologists and pharmacologists besides SMEs and Industries for H&A drug discoveries. There will be long-term impacts (3.1.1) and the potential for more basic research during and after the Action, e.g., increasing the number of compounds databases, improve the quality of the leads and candidates through the application of advanced omics technologies freely available in RTD platforms, include low environmental impact approaches new knowledge in new generated projects.

Knowledge transfer. Important aim of the Action is to expand the critical mass of medicinal chemists and veterinary experts in VBD integrated with environmental scientists in Europe. Both existing knowledge of the participants and new knowledge generated during the progression of the Action should therefore be disseminated as broadly as possible. This is possible through the planned investigations, training schools, workshops, and STSMs, described below and in section 4.1.1. Importantly, the Action is open to new participants, and a strategy for recruiting participants (especially Young Researchers and Innovators), who may both contribute to and benefit from the Action, will be made by the MC and individual WGs. Knowledge created during the Action will be transferred broadly through the dissemination channels described in section 3.2.2.

Intellectual Property Rights (IPR) strategies along with research and commercialisation rights will be established and agreed at the beginning of the Action by the Action MC in a framework which will include guidelines on how to conduct research in accordance with ethical principles and with respect to the principles set out in the “Rules and Principles for COST Activities”. The Action will adhere to national and EU strategies and guidelines that recommend the investment into this hot topic and stimulate networking and collaboration at the international level. The ECDIT participant from NNC will help in the management of the IP and BVGH through WIPO will be invited to support the Action, because they have experience at the worldwide IP level (section 2.2.3).

Career development. The Action will promote career development of Young Researchers and Innovators in different ways: ì. Young Researchers and Innovators will be encouraged to participate in all activities together with established experts thereby creating opportunities for future collaboration and

jobs; ìì. each Young Researcher and Innovator could be affiliated to a mentor from the Action outside their home institution. The role of these "Action mentors" will be to assist Young Researchers and Innovators with career planning. Whenever possible for each WG, a Young Researchers and Innovators Vice- WG Leader will be appointed. These Young Researchers and Innovators would benefit from increased leadership experience. Young Researchers and Innovators will also be invited to propose webinars on specific topic of interest for the Action. The career development will be supported by the two annual training schools for young researchers. To maximize the impact of this personalized training programme and identify all the training actions and scientific objectives that best suits the needs of the younger researchers, a personal career development plan will be defined. Their career will benefit of the engagement in RTD expert validation technologies application and lab experiments for leads and candidate validations. This career plan in the OneHealth*drugs* field will include the following issues: (i) How to recognize your own individual potential, develop vision and design your professional future, (ii) How to identify and focus on activities that give the greatest returns, and (iii) How works the job hunting (identifying the employment and business opportunities that best fit with your profile).

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

The Action will produce a Plan for Exploitation and Dissemination of the Results (PEDR), divided into 2 sections: **Dissemination Plan** focused on a strategy to disseminate the Action outcomes both at scientific level and at policy makers & stakeholders level, and **Exploitation Plan** targeted on a number of concrete measures to exploit at a maximum level, all the network's achievements during and after the Action duration, covering IP rights, sustainability, future market penetration and replication strategies. **Internal Dissemination**: knowledge, know-how, expertise and technical skills, will be disseminated through i) WG and Management Committee (MC) meetings and specialized Young Researchers and Innovators webinars (two per year) and ii) technical meetings, called to solve specific problems; iii) website. **External Dissemination**: To the ***scientific community*** through iv) Scientific Publications in peer reviewed journals in the specific disciplinary and in multidisciplinary fields other than when possible in high ranked journals such as Science, Nature journals, PNAS, etc, both in regular and Open Access form and v) participation to key parasitic-diseases in H&A drug discovery/One Health conferences, workshops, symposia; vi) distribution of publishable results about topics such as Veterinary/One Health-sustainability/ environmental impact of pharmaceuticals among Veterinary, Pharmacy and Health and Earth science faculties and exchange of the educational materials among Universities Faculties and Research Centres vii) organizations of yearly scientific workshops and webinars on specific themes related to drug R&D in parasitic diseases advances and integration with environmental impact of pharmaceuticals; and viii) **training schools (twice a year) to train young scientists in the following topics and some speakers suggested:**

1. Human and animals drug discovery process: main assets and sharable technologies. (WG1-WG4).
2. Medicinal chemistry innovative synthetic approaches and leads to candidate progressive concepts. (WG1-WG2).
3. Natural products derived leads: from the identification through chemistry and leads exploitation. (WG1) (EFPIA speakers and RTD platforms speakers invited).
4. Novel source of drugs from bioorganic material of the industrial waste. (Industry speakers invited).
5. High throughput screening technologies in drug discovery: assays, probes chemistry, ADME-TOX assays, on-target/on parasites screening. (WG1-WG2-WG4). (RTD platforms speakers).
6. Nanotechnology and targeting: nano system and target engineering methods and applications.
7. IMAGING in drug discovery and leads/candidates' validations. (WG3). (IMI, ICP countries speakers).

8. Structure-based drug discovery of parasitic diseases to be co-organized with the crystallography expert centers and the RTD organization (Diamond Lights Centre, ESFR, EMBL, OPENSCREEN).

Workshops organized within each WG (2 per year). General **titles**:
1. One Health principles and sustainability of the drug R&D process (WG1)
2. Environmental impact of pharmaceuticals and International Organizations monitoring" (WG4) (OECD-DNDi-WHO-European JPI invited) (WG1-WG4)
3. Regulatory issues in drug R&D in antiparasitic drug discovery (participating pharma and WIPO) (WG5-WG6).
4. Animal models in parasitic diseases and pharmacokinetic/toxicology studies. Dose regimen, formulations and targeting *in vivo*. (WG3-WG4)

Training schools will be open to all Action participants with the aim to attract Young Researchers and Innovators.
Patients-linked associations, practitioners, Health managers and environmentalist organisations will be actively involved in the training schools, in the scientific workshops/webinars, in joint investigations, and in joint campaigns promoting antimicrobial stewardship for drug resistance control and use of pharmaceuticals to prevent environment pollution and its consequences. An initial workshop will be organized to identify properly which kind of drugs are expected by the end-users (TPP definition).
Exploitation of Action's results will be considered alongside the aims of complementary national projects. IP implications and commercial exploitation of Action achievements will be dealt through confidentiality agreements signed by all participants when they enter the Action. The Action will respect fundamental ethical principles as described in the COST Code of Conduct.
A continuous **dialogue with the general public or policy** will be activated. The ***general public*** will be regularly informed about the Action activities through press releases, social media, targeted mailing, forum, flyers, posters and brochures. The 24-month and final Action meeting will be opened to key scientific and industry experts, stakeholders and end-users in animal health. During these meetings, participants will present the major **Action** results through WGs deliverables. **OneHealth*drugs*** will develop a logo and an Action-specific output newsletter. The Action will have a profile presented in LinkedIn, ResearchGate and in other professional and social media (Twitter, YouTube) in order to trigger public discussion in current and emerging subjects. It is planned to dialogue with ***national Government's agencies*** through i) publications on policies; ii) invitations to Action's events; iii) recommendations released in the form of progress publications about new drug discovered, including novel tools and strategies; iv) information guidelines prepared and circulated to academic institutions to enable potential collaboration; and v) a final white paper including guidelines integration. All events are reported in the GANTT. Dissemination activities will be stored in the FAIRDOM database with free-access from the website. The impact of these activities will be monitored throughout the Action lifetime.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORKPLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

WG1. Compound libraries coordination and integration of compound design. (Challenge 1**)**
Objective: Increase the number of compounds available for the drug research projects that should be screened adopting a coordinated approach (virtually or in phenotypic approaches) to ensure innovation in anti-parasitic drug discovery. Collection and coordination of data and information about compound design. **T1.1** *Collection of the compounds libraries* usable for screening purposes by the participants

and FAIRDOM database recordings. (D1.1) **T1.2** *Coordination of compounds libraries available within the Action participants* (criteria: no intellectual protection, proper characterization, availability from in house libraries, from ongoing medchem research programs during the Action). The compounds will be open access to all participants to increase the number of compounds for screening purpose. (D1.2); **T1.3** *Targets selection, structure-based drug design by advanced modelling/compound* docking on available and novel 3D protein structure (X-ray crystallography and cryo EM-electron microscopy); chemoinformatic methods and artificial intelligence (AI) data analysis from HTS technologies (Bayesan models, and others). (D1.3) **T1.4** *Compounds biodegradability pattern prediction*. This can be performed using in silico tool that can provide insight into the chemical degradation of organic compounds under various environmental conditions. (D1.4)

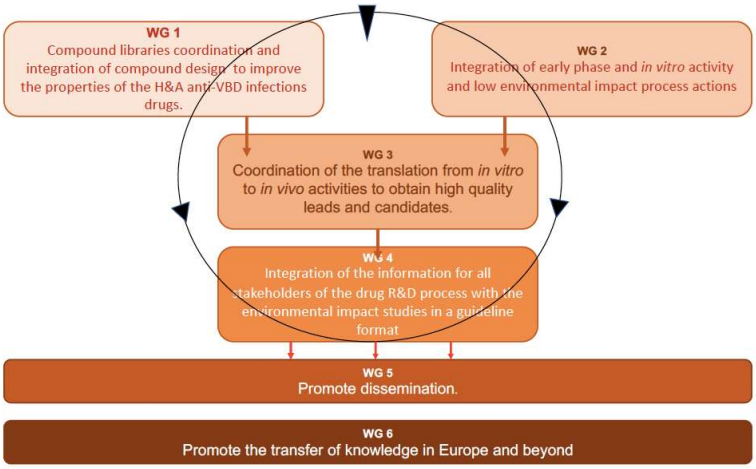
WG2. Integration of early phase studies and low environmental impact actions. (Challenge 2**) Objectives:** Obtain new compounds from different sources and study those compound *in vitro* for profiling and selection for advances in the process.
T2.1 *Synthesis of compounds designed using advanced medicinal chemistry strategies will be applied* (diversity-oriented-synthesis library, microwave and flow chemistry other than application of the principles of green chemistry for the compounds synthesis. (D2.1) **T2.2** Natural compounds from different sources, their fractionation, characterization. Compounds from waste organic materials (hemp, hives, frass from different insects). **T2.3** *HTS screening of library from WG1 and T2.2 to evaluate ADME-Tox properties, biological data from assays panels*. Compounds metabolic degradation analysis. All data are included in FAIRDOM database. Connection with the international database CDD Vault[50] will be established (D2.3). **T2.4** *Coordination of different medicinal chemistry technologies*: degradome PROTAC-like studies, repurposing, multitargeting/chimeric compounds that will generate an iterative loop for rapid improvement of inhibitor potency. Innovative host-parasite interaction strategies will be implemented to overcome drug resistance an adopt a trojan horse strategy (D2.4).

WG3. Coordination of *in vitro*-to-*in vivo* translation *of One Health* leads and candidates. (Challenge 3**) Objectives.** Promoting and strengthening of innovative technologies required in the translation of leads and candidates from animal to humans and vice versa to ensure the progression of qualified leads and candidates to the end of the pre-clinical phase and de-risk studies in clinical phase 1. This is restricted to advanced leads and candidate. **T3.1** *One Health nanotechnology system for animal models studies:* evaluation of the effect of the delivery approaches with biodegradable systems on the *in vivo* pharmacokinetics using different animal models (mice, hamsters and dogs). (D3.1) **T3.2** *Coordination of imaging and target engagement studies.* The EU RTD platforms and centres (EMBL, ESFR, OPENSCREEN, ELF) will be available to collaborate with the Action and accept PhD students for projects and experiments. (D3.2) **T3.3** *Coordination and integration of omics studies (PROTEOMICS, Genomics, TRANSCRITTOMICS) and validation technologies*, to better qualify the mechanism of action and drug resistance. All data will be deposited in the FARIDOM database. Protein targets and biological pathways from the omics studies will be validated through the evaluation of differential expression of proteins and their functional studies in cells models. (D3.3) **T3.4** *SOP coordination on standardization of animal experiments* through the collaboration with the European RTD platforms and Action platforms. *In vivo* studies design, use of prediction tools for reducing the number of animals. (D3.4) **T3.5** *Ecotoxicology assays to detect the expected effect of the advanced candidate on animals and environment*. (D3.5)

WG4. Integration of R&D process-environmental studies for the translation in informed white paper. (Challenge 4) **Objectives**: Coordination of the R&D programs innovative strategies and compliance with the overall environmental impact to provide a sharable guideline-like document. This may inform the compounds probability of exposure, an information derived from a more detailed

understanding on the substances environmental fate. The validation against the ecological interpretation of selected indicators (see below) is important to properly inform drug designer and managers of environmental risks compared to societal benefits. **T4.1** *Identify the most relevant ecotox aspects emerged from WG1-WG3 activities*, identify the life cycle principles included in the whole discovery & development design for the responsible pharmaceutical use and disposal, improved environmental monitoring and risk assessment of the drugs (D4.1). **T4.2** *Critical assessment of the steps necessary to achieve the dual sustainable goals of improving health and protecting the environment*. T.4.2 addresses the challenges offered by ecotoxicology and identifies the various possibilities to assess the environmental effects of pharmaceuticals and their degradation products or metabolites following a tiered approach and foster their prevention (D4.2). **T4.3** *Concerted activity of receptor-based and biomarker assays to screen pharmaceuticals* (preclinical and clinical) effects using small volumes of the drug or its degradation product. (D4.3) **T4.4** *Strengthening of omics technologies as impressive possibility to identify potential molecular initiating events in organisms central to ecosystems* and their functioning. Selection of test species for these ecotoxicology experiments (D4.4). The achievements from the above studies are important for the development, validation and use of adverse outcome pathways at early stages of the design of antiparasitic drugs. The validation against the ecological interpretation of such indicators is important to properly inform drug designer and risk managers which balance amongst those environmental risks with societal benefits.

WG5. Promote dissemination. (Challenge 5**) Objectives**: to coordinate and promote dissemination activities of the Action. (See section 3.2.2). The **white paper** will be prepared during the final 18 months and discussed at the final Action meeting. **T5.1** Preparation and *distribution of the white paper along with minutes of discussions at the Action conference to stakeholders*, including governmental Health Institutions in European nations and to EC (D5.1). **T5.2** *Website and social media platform launched and available.* (D5.2) **T5.3** In addition to the WGs, *the Action will include several networking activities as outlined below:* ***Training Schools (2/year) and workshops (4).*** Young researchers will learn new techniques and approaches from different experienced researchers across disciplines and European stakeholders, also from outside the Action. This will facilitate better collaboration and a common understanding across WGs (see section 3.2.2). **4 Thematic** workshops will be organized for in-depth discussions of central issues pertaining to the Action: 1. Degradome technology and PROTAC in drug design (WG1); 2. Medicinal chemistry: methods materials and environmental impact (WG1/WG4). 3. Mass spectrometry advances in pharmaceuticals detection in the environment (WG3). 4. Biomarker and indicators for ecotoxicology's studies in the drug R&D process) (WG1-WG4).



Every year two workshops will take place per thematic areas from the four WGs (see section 3.2.2). (D5.2) **T5.4** ***Short-Term Scientific Missions***. *STSMs will be organized on the topic reported* (see section 3.2.2). **Action meetings** will take place once a year**.** European and international stakeholders with an interest in VBD drug discovery against H&A infections, will be invited to Action meeting. Results of the Action network will be presented, and the Action white paper will be discussed. Management Committee meetings, Core Group meetings will take place every 3 months via conference tool (web meeting) to help mapping the Action progress. **Webinars** will be organized during Action lifetime free from other activities (see GANTT) by Young Researchers and Innovators. Thematic issues are reported in section 3.2.2. And new ones can be activated. All this is developed to reinforce the One Health concepts. **Co-tutoring**

anchored to ERASMUS programs and other transitional networks of PhD students and postdocs by complementary participants adding value to the background of the next generation scientists and improving their employability. This collaborative effort would facilitate the knowledge of the aims and goals of the COST Action. (D5.2)

WG 6 Promote the transfer of knowledge in Europe and beyond. (Challenge 5) **Objective**: The COST Action will promote the transfer of knowledge among the different stakeholders respecting the intellectual property rights management of new knowledge delivered by the Action: **T6.1** 1) IPR applications for new products and services. 2) Information that will be disseminated within the Action and to external bodies, such as publications, presentations, only after the necessary steps for ensuring the protection of IPRs have been made. 3) The Management Committee will provide the whole network with a set of exploitation support services (e.g., access to routes for exploitation, market data, advice on IP protection). **T 6.2** The exploitation plan will be assisted by the industrial engagement strategy on behalf of the network and lead to activities to be performed by a single knowledge holder on behalf of the other IP players involved with that result. Overall, the plan will contain a pre-assessment of the result's market potential and exploitation options, which will be performed by the Action members.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

Deliverable	WG	Description	Months	Type of D
D1.1	1	Report about compounds collections	24, 48	Technical report
D1.2	1	Coordination of compound libraries resources	24, 48	Web resource
D1.3	1, 2	Report on target selected and structural biology	18, 36	Technical report
D1.4	1	Report on compounds degradability in silico	24, 42	Technical report
D2.1	2	Report on compounds synthesized	18, 36	Technical report
D2.2	2	Report on compounds identified from natural sources and organic waste	24, 48	Technical report
D2.3	1, 2, 3	Report on HTS assays and ADME-TOX	42	Technical report
D2.4	2	Coordination of medicinal chemistry technologies	36	Report
D3.1	1, 2, 3	Report on One Health nanotechnology system for animal models studies	36	Technical report
D3.2	3	Report on imaging and target engagement studies	18, 42	Technical report
D3.3	3	Report on omics and validation technologies	24, 48	Technical report
D 3.4	3	SOP coordination on standardization of animal experiments	42	Report
D3.5	3	Coordination of ecotoxicology assays on leads and candidates	12 ,36	Technical report
D4.1	4	Report on integration of ecotox studies from WG1-WG4.	24, 42	Report
D4.2	4	Roadmaps to assess the environmental effects of pharmaceuticals and their degradation products/metabolites	36	Technical report
D4.3	3,4	Report on biomarker and receptor-based assays in ecotoxicology	18, 42	Report
D4.4	1, 2, 4	Report on omics technologies applied to model systems for ecotoxicology experiments	24, 48	Report
D5.1	4,5	White paper composed and distributed	48	Report
D5.2	5	Website and social media platform launched and available	4	Media outlet
D6.1	6	Coordination of transfer of knowledge and exploitation plan	45	Report

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

The main anticipated risks associated with the Action and contingencies are listed below:
Scientific risks. High risk: this is associated to largely to WG1 where no sufficient number of leads are identified for progressing from early discovery to pharmacology studies due to lack of PK/PD suitable properties. This is intrinsic risk to the drug R&D programs. The contingency plan (CP) is to go

back to the leads and further chemical modification; adoption of a delivery system to allow a better PK performance. Medium risk: the leads have not enough selectivity or do not improve properly the efficacy in animal testing in both H&A parasites. The CP plan is to go back to chemical modification and plan a delivery system or design a conjugate with better selectivity. Same approach for cross drug resistance issues or toxicity issues. Medium risk: failure in the translation of degradome targets from animal to human infected by parasites of different species (One Health compliance, see pag. 1). The CP is to change the target, not all targets are suitable for translation from one specie to another one. **Coordination risks**: Low risk: lack of time to complete the tasks. The commitment of the Action members in participating to the Action activities is expected to be high, therefore the coordination actions in WG1,2 3 4 and 5 are well planned and organized. The number of participants is expected to be balanced to ensure that all activities can start as planned in the GANTT (4.1.4). CP is to expand the network in particular in the environmental health number and Young Researchers and Innovators. Lack of funding to complete tasks (low medium risk). The lack of funding for OneHealth*drugs* research could imply a risk. CP is to identify other sources of funding to support the research work, e.g., more applications to different entities are performed by the participants to continue the research and coordination activities. The Action members will discuss the possibility to share expenses for the shared objectives such as the database building. Most of the tasks require primarily manpower with little or no funding needed for consumables. This includes the WG6 knowledge transfer, and the WG5 dissemination activities including preparation of the white paper. Therefore, the mentioned activities show no risks.

4.1.4. GANTT DIAGRAM

WG	Activity/Task Titles	Year 1				Year 2				Year 3				Year 4			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	Management committee meetings																
	Core group meetings																
	Young Researchers and Innovators meetings (webinars)																
	Action meetings																
	Workshops general (thematic)																
	Workshops on WG themes (2each WG per year)																
	Training Schools																
	Advisory Board activities																
WG1. Compound libraries coordination and integration of compound design	T1.1 Compound collections								D1.1								D1.1
	T1.2 Coordination of compound libraries resources								D1.2								D1.2
	T1.3 Target selected and structural biology.						D1.3						D1.3				
	T1.4 Compounds degradability in silico								D1.4					D1.4			
WG2. Integration of early phase studies and low environmental impact actions	T2.1 Coordinate compounds synthesis activity						D2.1						D2.1				
	T2.2 Coordination of the natural compounds identification and from organic waste material								D2.2								D2.2
	T2.3 Coordination HTS assays and ADME-TOX													D2.3			
	T2.4 Coordination of medchem technologies												D2.4				
WG3. Coordination of in vitro-to-in vivo translation of OneHealth leads and candidates	T3.1 OneHealth Nanotechnology system for animal models studies												D3.1				
	T3.2 Coordination of imaging and target engagement studies														D3.2		
	T3.3 Coordination of omics and validation technologies								D3.3						D3.3		
	T 3.4 SOP coordination on standardization of animal experiments															D3.4	
	T 3.5 Coordination of ecotoxicology assays on leads and candidates			D3.5									D3.5				
WG4. Integration of R&D process-environmental studies and translation in informed whitepaper	T4.1 Integration of the most relevant ecotox aspects emerged from WG1-WG3 activities								D4.1							D4.1	
	T4.2 Roadmap to assess the environmental effects of pharmaceuticals and their degradation products or metabolites												D4.2				
	T4.3 Coordinate biomarker and receptor-based assay in ecotoxicology						D4.3								D4.3		
	T4.4 Omics technologies applied to model systems for ecotoxicology								D4.4								D4.4
	T4.5 Internal Release of the whitepaper													D4.5			
WG5. Promote dissemination	T5.1 Report on the activities performed and whitepaper composed and distributed																D5.1
	T5.2 Website and social media platform launched and available	D5.2															
WG6.Promote the transfer of knowledge	T6.1 Coordination of transfer of knowledge exploitation plan															D6.1	

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