Interview with Dr Pavel Balabanov, European Medicines Agency
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An interview with Dr Balabanov from the Human Medicines Evaluation Division of the European Medicines Agency (EMA) was held as part of the clinical trials and trial design session of the International ataxia research conference 2015. Prof Massimo Pandolfo (Université Libre de Bruxelles), one of the session Chairs, posed the questions. In addition, the opportunity was given for the conference delegates to ask questions. A brief overview of the interview is provided together with web links for further information.

1) What kind of preclinical proof is required and what would you expect before moving to the clinical stage?

It is important to ensure that pre-clinical data are available to provide some evidence of

a. Proof of concept – regarding the theorized mechanism of action
b. Preliminary definition of safety in order to guide the planning of the first-in-human trial

Regarding a), it is possible for a medicinal product to reach the EU market and be available to the patients without a clear proof of what its mechanism may be, but this has to be supported by a robust clinical package resulting in outstanding clinical performance in the pivotal trials, and bears a risk for the developers. The ultimate goal should be that a strong scientific rationale is provided to create a logical chain of evidence, building upon the best available non-clinical and clinical data, to ensure that any claims are backed up by results (and not assumptions).
The ideal approach (with preliminary/non-clinical Proof of concept) would include:

- Demonstrating a strong rationale/mechanism of action at molecular level and modern *in vitro/in silico* techniques together with high throughput analyses that can be performed also on ex-vivo human/animal samples and really enable researchers to characterise the primary mechanism of action in great detail.
- Following this work, *in vivo* animal models should usually come into play, mainly to refine the dose-range and confirm whether the results of the *in vitro* tests are matched *in vivo*. A common approach with animal disease models (transgenic, chemically-induced or other) is often to select various models in order to capture as many aspects of the human disease as possible. Of course the closer to the human situation, the better, although it is of course accepted that all aspects often cannot be recapitulated in one model.

In summary, it is strongly recommended to have pharmacological data in animal models (when such models are available) before starting human trials.

Regarding b), the requirements depend mainly on:

- Type of medicinal product and its mechanism of action – please refer to the GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS.

- The characteristics of the patient population (i.e. what is considered an acceptable risk compared to the seriousness of the indication, alternative treatments, etc.)

The "standard" requirements to go to the first in human trials are outlined in ICH M3(R2) and for biologicals ICH S6(R1). Some specific micro-dosing approaches for FIH trials are also proposed in ICH M3(R2).

2) At what stage should researchers start a dialogue with the EMA?

Contact the EMA for advice at the earliest stage possible. The EMA provides scientific advice in all stages of developing a medicine. Even before completing the pre-clinical studies, if someone has a drug in development, it is advisable to contact the EMA. For more information on scientific advice at EMA, please visit the official webpage.

There is a fee for scientific advice. The fee varies depending on the scope of the advice. There is a **reduced scientific-advice fee** for these types of medicine:

- orphan medicinal products: these medicines are eligible for fee reductions for protocol assistance. Information on fee reduction for a protocol-assistance application is available in fee reductions for designated orphan medicinal products
- medicinal products for paediatric use: scientific advice is free of charge
- medicinal products under development by registered small or medium-sized enterprises (SMEs): information on the level of fee reductions available to SME applicants, how to apply for SME status and how to submit a letter of intent requesting scientific advice is available in the SME office;
- advanced-therapy medicinal products: these medicines are eligible for a 65% fee reduction for scientific advice.

It is important to mention that ataxias will cover the requirements for a rare disease in the sense of the EU legislation, and orphan drug developers in this field will be entitled to the relevant fee reductions(as per the above), which can reach 100% in the case where the developer is a registered SME.

Academic researchers –Many researchers based at universities are deterred from contacting the EMA for advice, as the fees are usually considered too high for this setting. One option to deal with this difficulty is by creating a spin-off company and applying for a SME status at the EMA. Thus the company can become eligible for the financial and administrative support provided by the SME office. For advice on setting up an SME, and any relevant questions, please contact the SME office.

Innovation Task Force - This is a specific platform for emerging therapies and technologies. Free advice can be given by the Innovation Task Force to all researchers to encourage early engagement. Questions can be posed and the EMA can set up meetings. Examples of areas of recent engagement of the Innovation Task Force are: nanomedicines, pharmacogenomics, synthetic biology, biomaterials, modelling and simulation, and 'mobile health' (the use of mobile devices to support healthcare).

For rare diseases such as ataxias there is the option of getting conditional approval for a drug on the basis of providing further data at a later stage.

4) What are the links between EMA and the US FDA? Is there any harmonisation between the agencies particularly in rare diseases?

The two agencies do talk to each other, for example, there are monthly teleconferences on the CNS field and they share ideas on topics. There are no Guidelines in ataxia, as there are in some other conditions. If there were, then the EMA and FDA would strive to work closely from an early stage and this process as well as any other interaction is facilitated by the existing confidentiality agreements between the regulatory bodies.

There is no specific advice as to whether one should contact the EMA and FDA in parallel or one after the other. It is unlikely in an area such as ataxia that there would be major disagreements between the two agencies, but the important issue is not to delay communications and to start a dialogue early.

5) What input can patients and patient groups have in the process?
Patients are well involved at all levels within the EMA and there are no steps which do not involve patients. Patient representatives are present in most scientific Committees. Eurordis is heavily involved in providing patient input and it is the platform used to get patient representatives to attend meetings (Scientific advice, Scientific Advisory Groups for Committees and others) as required. For example, any assessment for market approvals would in most cases involve relevant patients/ patient group representatives at different stages of the procedure (pre-submission i.e. at scientific advice stage, or during submission – as part of scientific advisory groups).

[Questions from the floor]

6) Given the huge pressure from the public and the media to decrease the use of animals in research, do the EMA support patient trials without the prior preclinical testing in mouse models?

The unjustified use of animals is discouraged. However, doing human trials without the prior testing in animal models is often difficult. There would need to be a justification for doing a human trial without the expected preclinical data in models and in animals.

7) If there is early success of a trial, can you address how you can justify the compassionate use of the drugs, as that can then slow the trial?

Compassionate use rules are not central but decided by individual member states, thus the EMA cannot exert much influence on this.

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