IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 3rd WG on Orphan Drug-development and Regulatory Processes teleconference

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Organization

Organized by: Scientific Secretariat

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Agenda

- Expedited programs and early dialogues
- Small population trials

REPORT

Participants briefly introduced themselves as there were several new members in the WG.
The purpose of this teleconference was to discuss potential practical actions for the WG.

Expedited programs and early dialogues

Expedited programs

The representatives of the several regulatory agencies briefly presented the programs and processes for proposing regulatory flexibility for orphan products.

The FDA has several Expedited Programs:

- **Fast Track** offers more frequent meetings and more frequent written correspondence. It is a process through which queries can be made and answered quickly.
- **Accelerated Approval** is a conditional approval based on a surrogate or intermediate endpoint thought to predict clinical benefit. Post marketing confirmatory studies are required to verify clinical benefit. This program enables drugs to reach the market much sooner.
- **Breakthrough Therapy** program is the newest. Eligibility is based on existing preliminary clinical evidence and demonstration of substantial improvement. Interactions with Senior Managers ensure a faster decision-making process. Breakthrough Therapy designation is eligible for Priority Review and Fast Track designations.
- **Priority Review** is a program that decreases the review time clock to 6 months instead of 10 months.
- **Expanded Access** grants an emergency use if sufficient clinical information is available. This program is based on a request from a well-qualified treating physician and a need to try the particular therapy in a particular patient. This process allows early availability of a drug and gives the FDA the opportunity to acquire additional information about the efficacy of the product in small populations. Thousands of these expanded access requests are granted every year.

All of these programs expedite the review of promising therapies and are especially useful in the area of rare diseases (RD). About 80% of new molecular entity drugs in the US benefit from one of these Expedited Programs.
The EU has 2 keys tools to ensure an early access to treatment in EU, when a company does not yet have the exhaustive package of clinical data.

- **Authorization under Exceptional Circumstances** is accessible to companies that will never obtain all the data, as the condition is so rare for example. It will generally never be switched to a normal marketing authorization (MA). The authorization under exceptional circumstance is valid 5 years with a yearly review of the conditions.
- In the case of the **Conditional Marketing Authorization**, the company continues to generate the data and will be able to get an entire set of data to switch to normal MA. The conditional marketing authorization is valid for one year and may be renewed annually.

In both cases, it is possible to accelerate the scientific assessment (150 days instead of 210 days).
The EU is considering how to extend the use of these tools to ensure an early patient access to treatment in the next few years.

In addition to these programs:

- EU also proposes incentives from the orphan legislation: orphan designation gives access to reduced fees for scientific advices and for MA. However, in Europe, reduction fees are only available for SMEs (less than 205 people), but not for Not-For-Profit organizations or academic sponsors. In these cases, it is difficult to define and understand the funding behind these kinds of organization. Applicants that at first sight are independent can in fact be heavily funded by industry. As the regulation only refers to SMEs, more flexibility would require a change in the legislation.
- Member states can also authorize an unauthorized medicine at national level for **Compassionate Use**.
- In the US, Orphan Drug Designation qualifies the sponsor of the drug for various development incentives, including tax credits for qualified clinical testing. In addition, a marketing application for an orphan designated prescription drug product is not subject to an application drug user fee and may be eligible for orphan drug marketing exclusivity for seven years. The FDA also offers an orphan product grants program for clinical trials of promising orphan drugs.
- In the US, there is also a new Rare Pediatric Disease Priority Review Voucher Program that is intended to provide a new review incentive to sponsors to develop drugs for pediatric rare diseases.

The question of MA withdrawal was raised:

- FDA can strongly recommend the withdrawal of a product from the market, but it remains a voluntary decision/action taken by the sponsor.
- The EU has the authority to suspend or withdraw the Conditional MA or the authorization under exceptional circumstance, if the company does not have the complementary data stated in the condition of the authorization. In practice, EMA would be re-discussing the conditions and the reasons why the conditions were not fulfilled. Withdrawing a product would be problematic, particularly in the field of RD.

Early Dialogues

Both EMA and FDA have informal early discussion with stakeholders and sponsors.

The RD program, Review Offices and the Office of Orphan Product Development have the flexibility to engage in informal discussions with stakeholders, patients and families and individuals who are interested in trying to develop therapeutics for disorders that may affect them or a member of their family. These discussions can be a very effective method to improve stakeholder understanding of the process.

There are discussions within the EMA about improving early dialogues with the sponsors. There is no formal forum in place but many informal discussions, particularly in the field of RD where there are

independent sponsors - academic, small companies - approaching the agency with questions on the development. These informal meetings have existed for 6-7 years, where companies present their pipeline and discuss questions about the potential development of the product, the nature of the product, and qualification of products in term of development.

Action point

It was proposed to present in a common document, under the umbrella of IRDiRC, a discussion on the different programs the EMA and FDA have and the opportunities for early dialogues, in the context of RD development, to increase awareness of developers.

Two types of document were discussed:

- A scientific publication presenting the programs and an analysis of their outcomes.
- A document to be published on the EMA and FDA respective websites

⇨ Although the members recognized the interest of analyzing the usefulness of the programs, they agreed to develop a document to be published on the regulatory agencies' websites as there is not enough data for some of the programs to get a meaningful evaluation of the program's impact. In addition, the scientific publication might be quickly outdated as the programs are evolving. With a publication on a website, it will be clearer when the document was last updated. Representatives of EMA and FDA should decide how regularly the document should be updated (quarterly, biannually, or at least yearly) as well as how to publish the document on their respective websites and how to link them.

A member of the WG raised the problem of the difficulty of the 'Risk management plan.' For some drugs, there is a request for clinical data that can be very difficult to obtain – such as adding 10-20 more patients in a year. As representatives of the regulatory agencies are interested in the view of the sponsors on this topic, members of the WG that raised the point will collect information regarding conditions on risk management plan(s) focusing on the potential to include more patients in the dossier and potential associated problems with obtaining the information.
The collected information should remain confidential.

Small population trials

In addition to the different definitions of RD in EU and US, there are no clear definitions for less common rare diseases. This situation may have an impact on the regulatory framework and type of accommodations that can be proposed for drug development.

Members of the WG agreed that a better definition of the rarer RDs might be useful and could impact the clinical development plan and design of clinical trials. Discussions on this topic will continue at future meetings.

There are 3 research projects funded by the European Commission working on new methodologies for small populations trials (ASTERIX, IDEAL and INSPIRE). EMA is considering a workshop next year to discuss new methodologies and how to methodologically approach trials in small populations.
Members of the WG were informed that the IRDiRC Executive Committee recently defined the target areas for a workshop. Small population trials is one of these priorities.

- ⇨ Members agreed that the workshop should be organized under the umbrella of IRDiRC with the help of the regulatory agencies, and include the leaders of the 3 European projects and patient perspective. Organization by IRDiRC would bring a global approach.

Deliverables

- Send a summary of agreements
- Write a small text about program available
- Collect information regarding conditions on risk management plan
- Provide recording of the workshop on small population
- Organize next teleconference for 2015