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PRACTICAL STEPS TO ACHIEVE ORPHAN DRUG DESIGNATION STATUS

Including Eligibility Criteria, Incentives, Marketing Approval, Market Exclusivity, EU & FDA Requirements Approach

WHITEPAPER

As an overall trend, the number of requests for Orphan Drug Designations (ODD) and approvals have increased dramatically between 1983 and 2020.

In terms of when to apply for ODD, the incentives and benefits increase for drug developers the earlier in the development process you apply. So, while you can apply any time prior to the Marketing Authorisation Application (MAA), the New Drug Application (NDA) or the Biologics Licence Application (BLA), it is more beneficial to apply earlier.

Both the US, Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) have **minimum requirements** for ODD.

EMA

The minimum requirement for the EMA is the provision of:

- Preclinical data and/or clinical data.
- Pharmacological concept supported by appropriate evidence.

FDA

The FDA require enough information to establish a medically plausible basis for expecting the drug to be effective in the rare disease, which is best supported by clinical trials of the drug in that disease. In the absence of human data, you may support your application with preclinical data.

EUROPEAN MEDICINES AGENCY (EMA)

The EMA definitions criteria for the application to the Committee for Orphan Medical Products (COMP) is that for orphan drug designation, the compound 'must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating'. In addition to this, the prevalence of the condition must be less than 5 in 10,000 patients within the EU, or the marketing of the product is unlikely to generate sufficient return based on all development costs and expected revenue.

The drug must also meet one of two other criteria.

- There is no current satisfactory treatment method for the condition.
- The new drug proposes significant benefit compared to existing treatments.

Prevalence, revenue calculation and significant benefit to the patient population are the three topics that form the basis of the application and so therefore must be handled carefully.

Prevalence

Prevalence must be demonstrated on peer reviewed journals, databases, and registries. The EMA publishes a document of accepted, relevant prevalence data sources, which includes ones that have been accepted by the EMA in other ODD.

Revenue calculation

When it comes to revenue calculation, a detailed analysis needs to be included on grants, tax incentives, past costs, future development costs, manufacturing and production, and expected revenues based on prevalence. These must be certified by a registered accountant.

Significant benefit

The most important, and possibly most challenging, matter is the significant benefit that must be demonstrated. In firstly ensuring medical plausibility, it is important to ensure that sufficient *in vitro* safety data is available for the actual drug product, and that the end points are relevant to the intended patient population.

There should be limited bridging of the data and assumptions. Significant benefit could also be based on improved efficacy, safety or patient care, such as improved compliance or ease of use. It is also important to note that if you apply for orphan drug designation based on significant benefit, the designation will be reviewed at the time of marketing authorisation application. This means that the data presented in the application will be reanalysed to assess all the data collected and the comparison with existing products. Hence, it is strongly advised to utilise the protocol assistance provided during the development once the ODD is provided.

FOOD AND DRUGS ADMINISTRATION (FDA)

The orphan drug designation requirements for the FDA are either that the drugs and/or biologics are for the safe and effective treatment, diagnosis or prevention of rare diseases or disorders that affect fewer than 200,000 people in the U.S. Or alternatively, that there is no reasonable expectation that costs of research and development can be recovered within 7 years by sales of the drug in the USA, even if intended for a population greater than 200,000. In terms of patient population, for a drug, this means that fewer than 200,000 persons in the US have been diagnosed as having the disease or condition for which the drug is being developed. This is defined at the time of the filing of the request for Orphan Drug Designation.

Fewer than 200,000 persons in the US have been diagnosed as having the disease or condition for which the drug is being developed.

In the case of vaccines, diagnostics, or preventive drugs, the magic number is how many people will be administered the drug per year. The criteria that form the basis of the FDA application are prevalence and scientific rationale, revenue calculation and clinical superiority for the same drug.

Prevalence

For prevalence, it is important to ensure that sources of disease and populations metrics are those that are verifiable and acceptable to the Agency, and the FDA expects the sponsor to look at the most recent incident data from the US Census, peer reviewed journals, databases, and registries.

Scientific Rationale

Safety or toxicology data need not be included unless the information is being used to demonstrate that there is a plausible hypothesis for clinical superiority, in which case *in vivo* and, to a lesser extent, *in vitro* data should be presented

In vitro data along with supporting information such as the mechanism of action of the drug and the pathogenesis of the disease may be provided when there is no relevant animal model of the disease and in the absence of human data.

Revenue Calculation

Revenue calculation should take into consideration all past and future development costs and expected revenues. There should be detailed explanations of costs, which include costs outside of the US, and how they affect the US market. All revenue calculation data should be certified by a US accountant.

Clinical Superiority

For clinical superiority, the OOPD may grant orphan drug designation to a drug that is otherwise the same as a drug already approved in the USA for the same rare disease or condition, only if the sponsor can present a plausible hypothesis that its drug may be "clinically superior" to the previously approved drug.

Clinical superiority may be established by means of greater effectiveness, greater safety in a substantial portion of the target populations or, in unusual cases, a major contribution to patient care. It is important to realise that only a plausible hypothesis of clinical superiority is needed at the orphan drug designation stage if there is a same drug already approved for the same use.

> However, to be eligible for the 7-year marketing exclusivity upon approval, the sponsor needs to demonstrate that their drug is clinically superior to the previously approved same drug, or drugs, and this may require head-to-head clinical studies.

EMA INCENTIVES

There are many incentives provided by the EMA for designated orphan drugs, of which market exclusivity is a key one.

- The EMA provides 10-year market exclusivity with orphan drug designation, which covers similar active substances as contained in a currently authorised orphan medicinal product that are intended for the same therapeutic indication. Market exclusivity extends by an additional 2 years if a Paediatric Investigational Plan (PIP) is followed.
- Another benefit is automatic access to a centralised procedure, with only one application for entire EU.
- The EMA also offers protocol assistance, which is a form of scientific advice at a reduced cost, or in some cases no cost at all.
- There are also fee reductions available, including further discounts for small and medium-sized enterprises.

EMA TIMELINES

The EMA's orphan drug designation process adheres to strict timelines. Once the submission has been made, there is a set process which will result in a decision. However, the EMA do offer and encourage free-of-charge pre-submission, which can prevent the application being withdrawn if omissions are not resolved within the 90-day process.

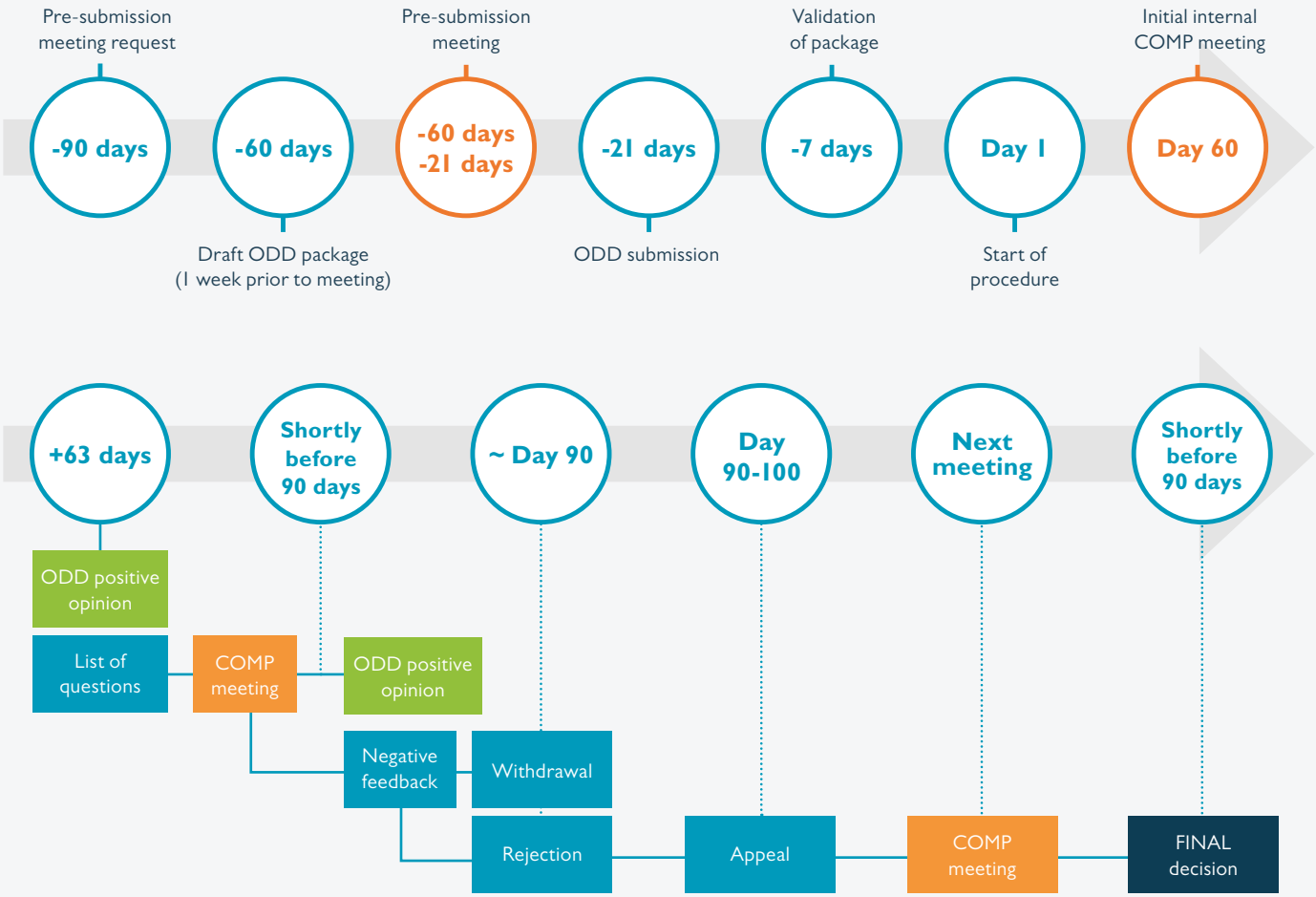
Three days after the meeting and based on outcome, you might either receive a **positive opinion,** or a list of questions. You will be invited to either provide your responses in writing and in some cases further invited to present at the next COMP meeting. The opinion will be reached before day 90 and the summary report will be revised to reflect any updates.

If a **negative opinion** is likely, the sponsor will be informed immediately about the negative trend and advised on possibility of withdrawal.

The outcome of the meetings will be published on the EMA website, but withdrawn applications will not identify the name of the product or the name of the sponsor.

In all cases, the final decision will be adopted by the EU commission 30 days after the COMP opinion is provided.

The figure below illustrates the EMA submission and approval timeline.



FDA INCENTIVES

The benefits of obtaining orphan drug designation include tax credits for qualified clinical testing, however, in general, no credits are allowed in relation to any clinical testing conducted outside the United States, unless there is an insufficient testing population within the USA.

In addition to the tax credits, there is:

- A waiver of the User Fees required under the Prescription Drug User Fee Act, which exceed 2 Million US dollars, payable at NDA filing.
- Eligibility for a 7-year marketing exclusivity.

This goes beyond Waxman-Hatch patent life extensions usually granted upon traditional drug approval.

Additional incentives and support are also provided to offset the costs and administrative burdens associated with conducting research on Orphan Indications.

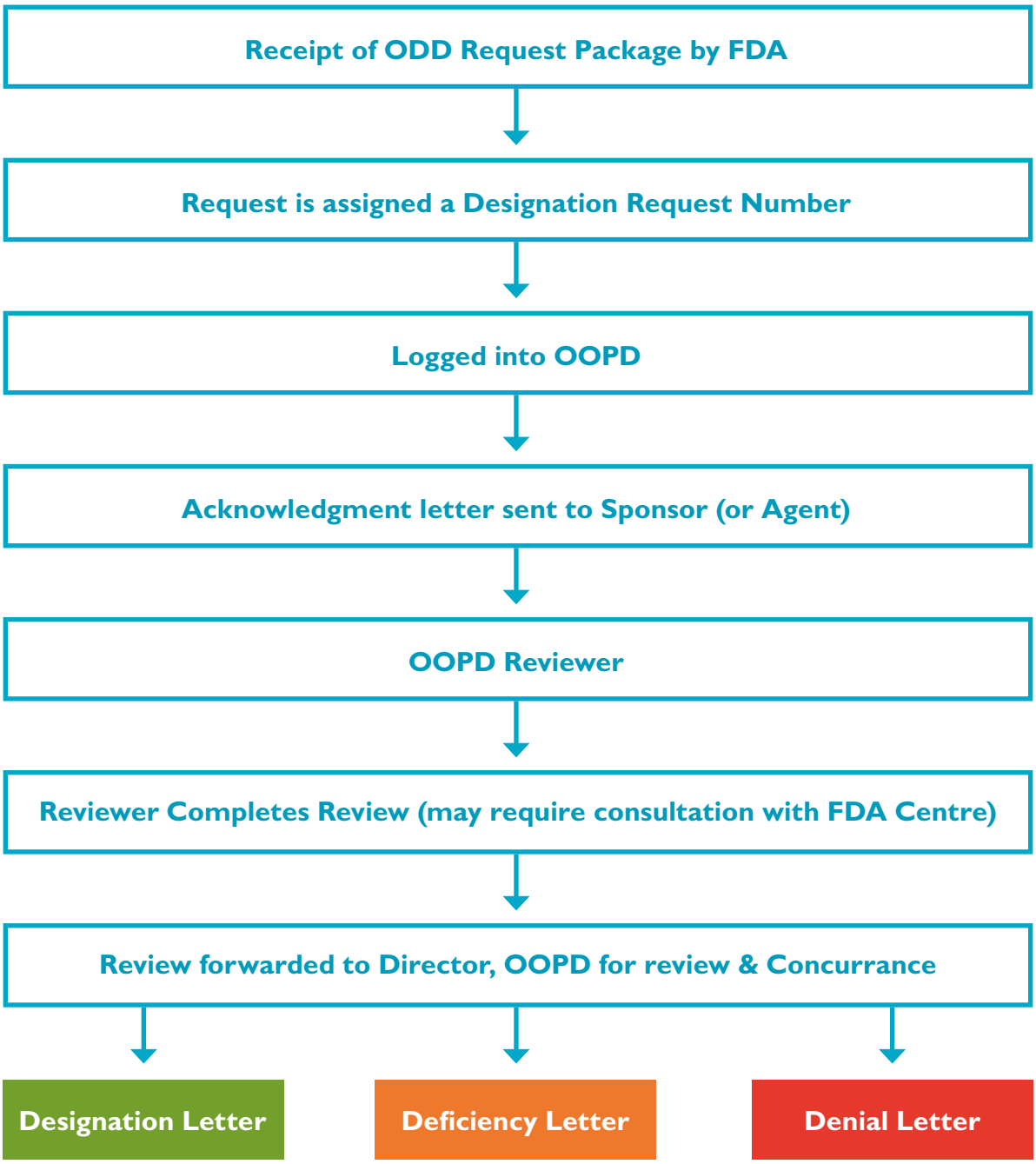
These include:

- Rare Pediatric Disease Priority Review Vouchers which a Sponsor may "redeem" for future FDA priority reviews.
- The Humanitarian Use Device Program, which designates medical devices for use in rare conditions as being exempt from certain effectiveness requirements (Sections 514 and 515 of the FD&C Act) and is subject to certain profit and use restrictions. These exemptions apply to Class III devices, which are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
- Extramural Grant Programs that provide funding for Orphan Disease research.

FDA TIMELINES

In comparison to the fixed timelines of the EMA, the FDA's timeline is more fluid. Following receipt of the orphan drug designation request at OOPD, the request is assigned a designation request number, logged into OOPD database, and an acknowledgement letter is sent to the sponsor.

The review is forwarded to the Director of the Orphan Drug Designation Program for a second level review and concurrence, and following this a designation letter, a deficiency letter requesting additional information, or a denial letter is then issued.



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You can connect with a scientist to discuss any questions you might have relating to your clinical development needs.

Contact us at information@simbecorion.com

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