CLINICAL DEVELOPMENT PLANS FOR RARE DISEASE AND ONCOLOGY THERAPIES TO IMPROVE YOUR NET PRESENT VALUE

Attendees from selected biotechnology companies across the Nordic region were welcomed by the Simbec-Orion team at our symposium hosted at the British Embassy in Copenhagen on 16 May, supported by the UK's Department of International Trade (DIT).

The 'Clinical Development Plans for Rare Disease and Oncology Therapies to Improve your Net Present Value' symposium included presentations from Dr Simon Hutchings, Dr Fabrice Chartier, Dr Alain Thibault, Sadiq Lutfi, Sivakumar Muthusami and Ronald Openshaw.

The symposium started with an address from Her Majesty´s Ambassador to Denmark, Dominic Schroeder, going on to the following presentations encompassing areas which can significantly impact an organisations financial value.

Dr SIMON HUTCHINGS

DIRECTOR OF SCIENTIFIC AFFAIRS, SIMBEC-ORION

"Effective implementation of the revised EMA guidelines for First-into-Human studies, including integrated protocol design for rare disease"

The presentation from Dr Simon Hutchings demonstrated that integrated & adaptive FiH/early phase studies accelerate early clinical development without compromising the safety and wellbeing of participants. Within the EU, the UK is particularly experienced with early phase studies and data shows that the UK conducts the highest percentage of FiH studies. Between 2005 and 2017, there were a total of 2,206 FiH studies in the EU, of which 24% were performed in the UK.

Regarding FiH studies, there are guidelines available from the EMA which serve to advise on the best clinical practice and promote effective and ethical study design, originally published in 2007. The guidance was revised in 2017 as a response to the BIA-10-2474 incident which occurred in France 2016, which had an Integrated Protocol with 4 separate parts: single ascending dose (SAD), multiple ascending dose (MAD), Food Effect and PD. As more studies choose Integrated Protocols to save time and therefore cost, the 2017 revisions introduced guidelines for combination and integrated protocols (e.g. combined SAD/MAD/Food Effect/ DDI among others) to ensure patient safety.

Within the revised edition, much of the 2007 guideline remains, however there is a clear focus on sound science and the application of pharmacology & toxicology. The revised guide addresses combination/integrated protocols and emphasises that dose selection/escalation should be reviewed based on all emerging human PK and PD data in previous cohorts and should not be considered fixed based on pre-clinical data.

Some key points on the revisions from Dr Hutching's presentation included:

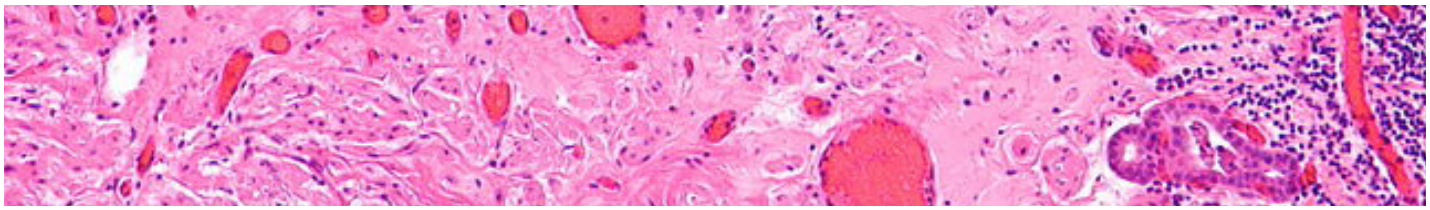
- The progression from SAD to MAD parts should be based on PK-PD modelling where possible
- Sentinel dosing should be used for all cohorts (SAD and MAD)
- Submission of interim report to Competent Authority between SAD and MAD should be considered but is not mandatory

Using an adaptive protocol for FiH studies allows trials to run without the need for individual regulatory submissions (CTA/REC) for each protocol/study which contributes to their popularity for trial design as they save time, and therefore cost. However, Adaptive Protocols are complex.

They require experienced pragmatic Competent Authorities, who understand what we are trying to achieve with these protocols, and who are comfortable in allowing Clinical Trial Authorizations. Adaptive Protocols also require experienced Phase I units, which know how to effectively run and adapt, and have processes in place to effectively run such studies.

It also should be noted that in order to make these studies as efficient as possible, rapid turnaround of PK/PD data is advantageous, so therefore having on-site laboratories in Phase I units is highly desirable.

To find out more about the effective implementation of the revised EMA guidelines for First-into-Human studies, you can listen to Dr Hutchings discuss this issue in our webinar, here.



Dr FABRICE CHARTIER
GROUP CHIEF OPERATING OFFICER, SIMBEC-ORION

"Efficient trial design to minimise cost in orphan drug development"

The presentation from Group Chief Operating Officer Fabrice Chartier focused on efficient trial design for orphan drug development, a key consideration while attempting to improve your NPV. The presentation began by stressing an important point to remember: orphan conditions are rare conditions or subgroups of larger indications. For example, data from the EMA in 2013 demonstrated that in the US 38% of orphan drug designations were in oncology, and while there are many rare oncology subgroups, orphan drugs developed for rare indications may later offer a treatment option for larger indications.

By definition, rare disease has a small patient population. However, the list of recognised rare diseases is growing with advances in diagnosis, and now totals over 7,000. There are around 350 million people living with a rare disease, and of this most diseases are serious, often life-threatening, 80% are genetic and around 50% of those affected are children. While there are regulatory incentives in place for developing orphan drugs, there are also many challenges which need to be considered to ensure the most effective trial design. Rare diseases often are accompanied by limited disease knowledge, complex regulatory pathways, few suitable patients and the potential for unknown obstacles throughout the drug development process. However, these challenges have done little to slow the development of orphan drugs. In fact, around a third of new drugs each year are for rare diseases.

One of the major advantages of developing an orphan drug is the dramatically reduced development time. In the US, for example, the average time a non-orphan drug spends in clinical trials is around 69 months, whereas for an orphan drug is around 51 months. Orphan drugs also spend, on average, less time in FDA review – around 9 months in comparison to 17 for non-orphan drugs.

Due to internal pipeline and drugs going off-patent, pharmaceutical companies started acquiring rare disease-focused drug developers and began showing interest in establishing their own drug development units for targeting rare diseases. Moreover, as more orphan drugs become applicable to multiple indications, market exclusivity is extended. These label extensions, along with patents, will keep orphan drugs from facing generics competition early.

After giving some background on orphan drug development, Dr Chartier went on to look at the differences which need to be considered when looking at trial design. With small populations, there is limited opportunity for study and replication in clinical trials. There are few treating physicians, and few treatment centres. Rare diseases are a highly heterogeneous collection of diseases, and they are generally poorly understood. Diagnosis is difficult and there can be years between presentation and diagnosis.

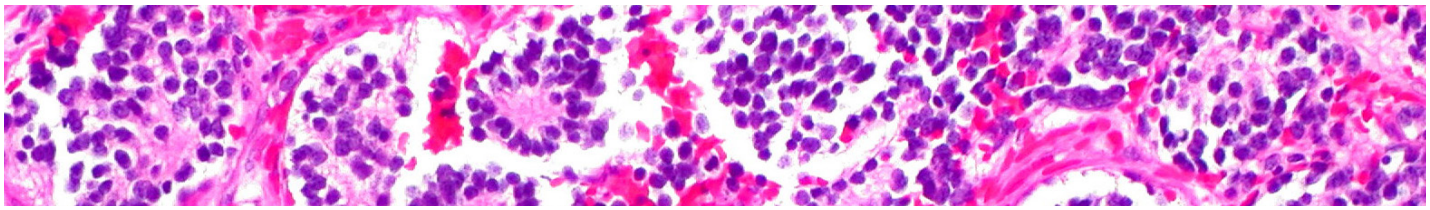
Some ideas put forward by Dr Chartier for protocol design include using a historical cohort as a control group, or natural history. Or using observational or interventional non-therapeutic protocol to enrol patients into a study - with a therapeutic roll-over protocol.

It is important to note that deviating from regulatory guidelines does not mean that you do not know the guidelines, it can be acceptable when there is a strong rationale to do so. However, the more you deviate from guidelines the more you have to demonstrate to the regulator that you are fully aware of the guidelines, and support the need for deviation with sound scientific evidence. Meetings with regulatory bodies such as the FDA, EMA and MHRA are encouraged to assist with the process.

One of the biggest challenges faced when running rare disease trials, is patient recruitment. It is important to put patient needs first and improve patient engagement and retention. Dr Chartier recommended considering the following in his presentation:

Collaborate with patient support groups:

- Help patients feel like they are not alone
- Give them a trusted place to find information about trials
- Educate patients about treatment options



Helping support groups by:

- Providing research materials
- Educational support
- Building a trusting relationship
- Review of PICF
- Participation at investigator meeting

Identify barriers to participation

- Small and widely dispersed patient populations
- "losing" patients is not an option
- Making small changes (such as scheduling of appointments or offering on-site childcare) can be enough to make the trial more accessible for hesitant recruits

Build sites around patients

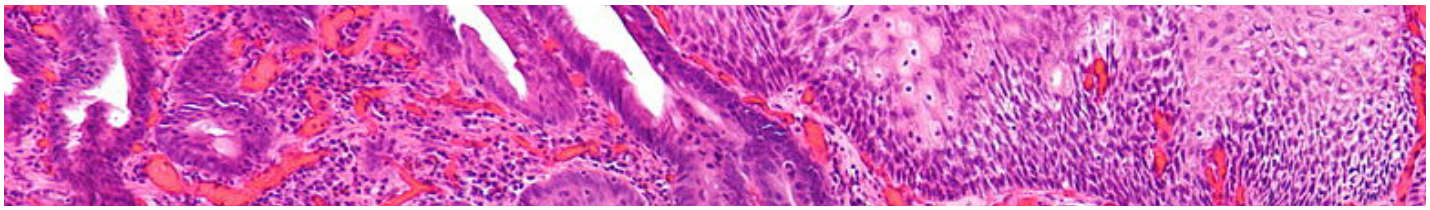
- Dispersed patient population (almost always the case)
- Instead of opening 200 sites and hoping patients will turn-up -> create sites around the patients
- This eliminates 2 major barriers to recruitment: geography and trust
- Home nurses
- Intensive site training
- Expand the network of sites for future trials

And finally consider 'bringing the trial to the patient'.

- Leverage rapid study placement approaches
- Clear Regulatory / ethical pathways - gap analysis, critical thinking
- Early training programme
- Securing primary study endpoint – missing data will not be an option
- Resource at site

Data shows that around 30% of Phase 3 studies fail due to enrolment. The paucity and scattered rare disease patient population, along with the fact that more than 50 percent of the rare diseases affect the paediatric population, are regarded as the major factors that impede faster patient recruitment. For a Phase 3 clinical trial enrolling 20 to 100pts, every single patient's participation is critical in assessing the drug's effects; the more patients, the more evidence-based data for regulatory authorities, as well as for payers to use to determine pricing and reimbursement..

Considering your trial from a patient's perspective and designing the trial around their needs is the best possible choice when attempting to speed up recruitment and ensure patient retention, therefore in return helping to minimise cost and maximise your NPV.



Dr ALAIN THIBAULT
MEDICAL DIRECTOR, SIMBEC-ORION

"Optimising early phase oncology study design; modular multi-arm approach"

Medical Director Dr Alain Thibault focused his presentation on modular multi-arm trials in oncology study design. The presentation began with a simple question: why are phase I trials changing? The answer is that a modular, multi-arm approach can accelerate drug development to bring active compounds to the clinic faster. Our knowledge of molecular biology is expanding, technology is advancing, and new types of drugs are entering development.

Dr Thibault comments on a paradigm change in phase I trials. As we have a better understanding of cancer, we have multiple biomarkers. With multiple biomarkers there are segmented indications, with multiple targets there has been an expansion of combination therapy, and with multiple biology rationales there has been an explosion in clinical trial numbers, as well as stiff competition for patients with the availability of data.

A phase I trial now can now look to prove safety, efficacy and POC for the indication all in one trial design

CHALLENGES

- **Targeted Therapy**
  - Toxicity profile more complex than chemotherapy
  - Time of onset often later
- The **Maximum Tolerated Dose** (MTD) is being replaced by Efficacy
  - Biologically active dose (BAD)
  - Minimum Active dose (MAD)
- **Tumour Response** (RECIST)
  - May not occur with monotherapy (e.g.: bevacizumab)
  - May not predict clinical benefit

Questions Regarding the Design of Large First-in-Human Cancer Trials – keeping regulation in mind

Is there a compelling rationale for including multiple expansion cohorts?

Is the sample-size range consistent with the stated objectives?

Is there an appropriate statistical analysis plan for all stated end points?

Are the eligibility criteria appropriately tailored?

Is there a defined end to the trial?

Is there a system in place to communicate with all investigators in a timely fashion?

Does the informed consent reflect the current knowledge of safety and efficacy?

Is there an independent oversight committee?

Has there been communications with regulatory agencies?

Questions to consider with operations in mind

PROTOCOL REVIEW

- Study diagram: Patient flow
- Decision points (dose escalation, DSMB, efficacy/ biomarker review)
- Understand Protocol Flexibility

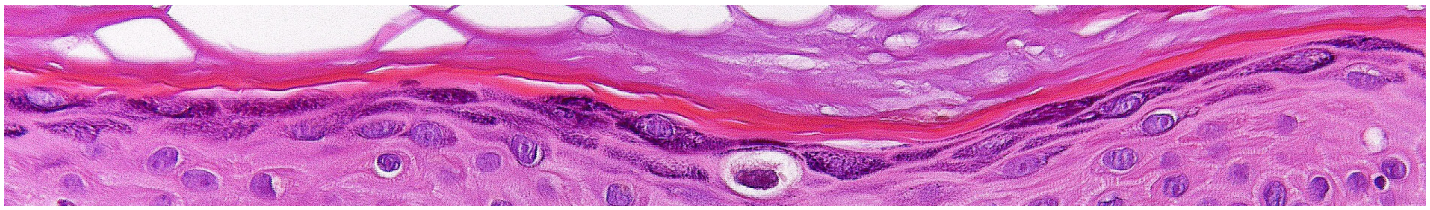
RECRUITMENT PLAN

- Pre-screening for patient –enrichment strategies
- Quality Screening (e.g. Marsden criteria)
- 'Modular' site selection (all comer dose escalation vs biomarker-defined expansion)

STUDY COORDINATION

- Weekly Team TCs
- Rolling Database locks

'Modular' Clinical Study Reports



SADIQ LUTFI
REGULATORY AFFAIRS MANAGER, SIMBEC-ORION

"Practical steps to achieve Orphan Drug Designation status including, eligibility criteria, incentives, marketing approval, market exclusivity, EU & FDA requirements approach"

Regulatory Affairs Manager Sadiq Lutfi concentrated his presentation on a brief overview of the EU and FDA orphan drug designation (ODD) process, including the incentives available for orphan drug developers. The presentation began with an overview of FDA data on orphan drug designation requests, the number of designations, and the number of approved orphan products by year. As an overall trend, the number of requests, designations and approvals have increased dramatically between 1983 and 2017. In comparison to the two orphan products approved in 1983, for example, there were 77 approvals in 2017. This trend is also reflected in the EMA data, with zero approvals in 2000, and 14 in 2017.

In terms of when to apply for orphan drug designation, 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, the New Drug Application or the Biological Licence Application, it is more beneficial to apply earlier.

Both the FDA and the EMA have minimum requirements for ODD. 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. The minimum requirements for the EMA Preclinical data and/or clinical data Pharmacological concept supported by evidence.

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. In addition to this, the drug must also meet one of two other criteria, either there is no current satisfactory method for the condition, or the new drug proposes significant benefit compared to existing methods.

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.

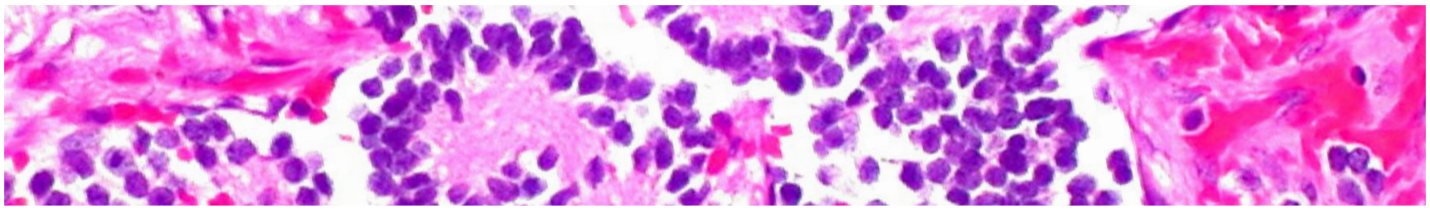
Prevalence for example must be demonstrated on peer reviewed journals, databases and registries. The EMA publishes a document of accepted relevant prevalence data sources which includes ones that have been accepted by the EMA in other ODD.

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, expected revenues based on prevalence and must be certified by a registered accountant.

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

FDA

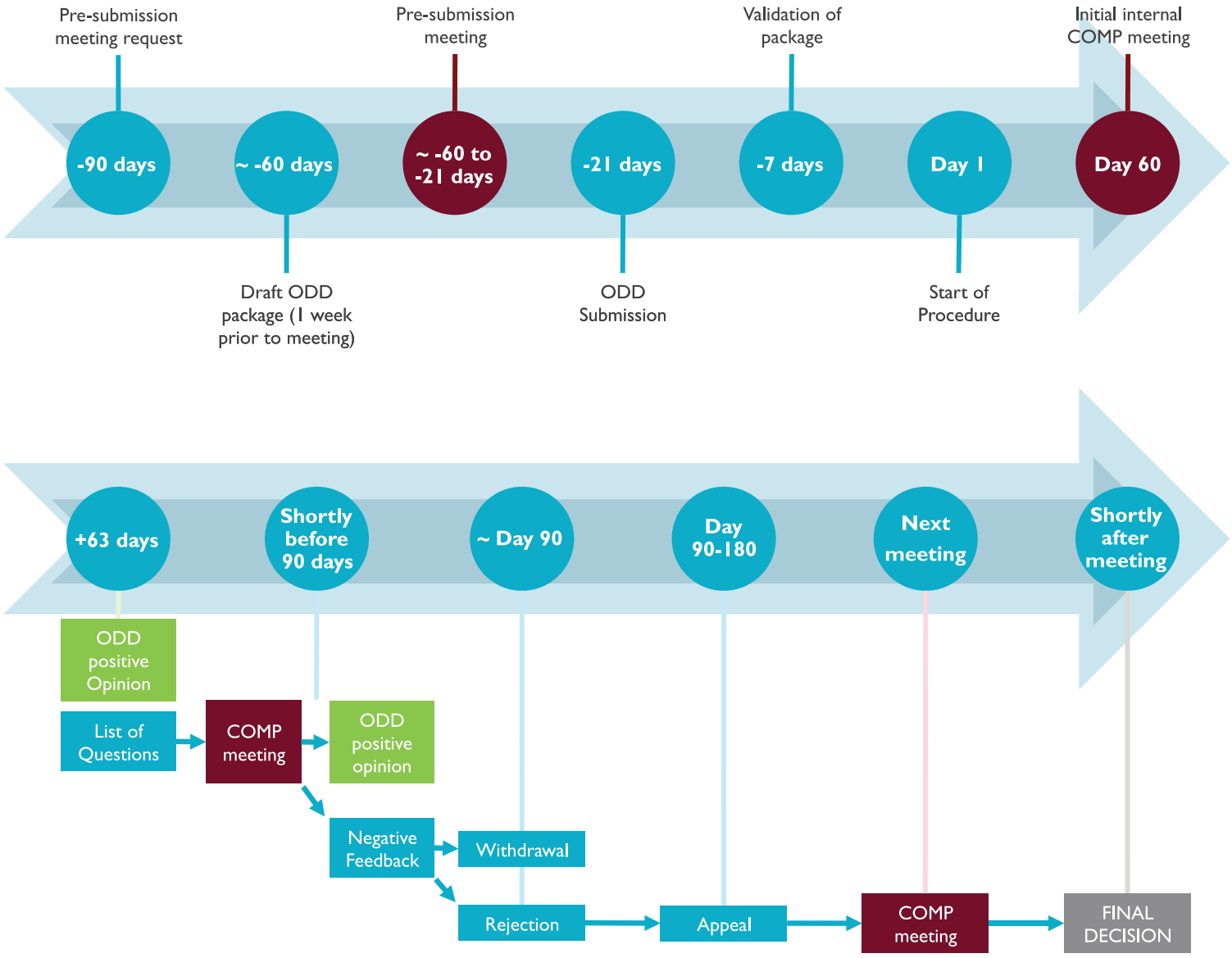
The orphan drug designation requirements for the FDA are either that the drugs and biologics are for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect **fewer than 200,000 people** in the U.S. Or alternatively, that there is no **reasonable expectation that costs of research and development can be recovered within 7 years** by sales of the drug in the USA, even if intended for a

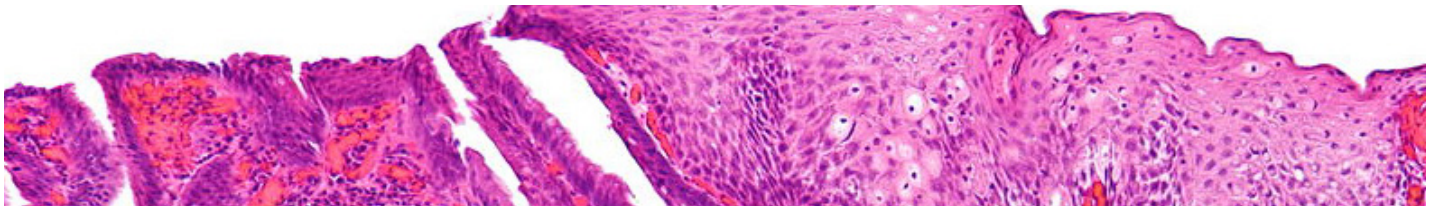


population greater than 200,000. In terms of patient population, for a drug, this means that fewer than 200,000 persons in the US have been diagnosed as having the disease or condition for which the drug is being developed. This is defined at the time of the filing of the request for Orphan Drug Designation. 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 calculatio-nand clinical superiority for the same drug. For prevalence, it's 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 for drug is to determine efficacy based on clinical data, and for this In Vivo and to a lesser extent In Vitro data needs to 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.

FIGURE BELOW ILLUSTRATES THE EMA SUBMISSION AND APPROVAL TIMELINE





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.

For clinical superiority, the OOPD may grant orphan drug designation to a drug that is otherwise the same drug 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 realize 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, in order 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 for no cost at all. There are also fee reductions available, including further discounts for small and medium-sized enterprises.

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 free-of-charge pre-submission, which is strongly advised by the EMA as it 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, which is why you are invited to withdraw.

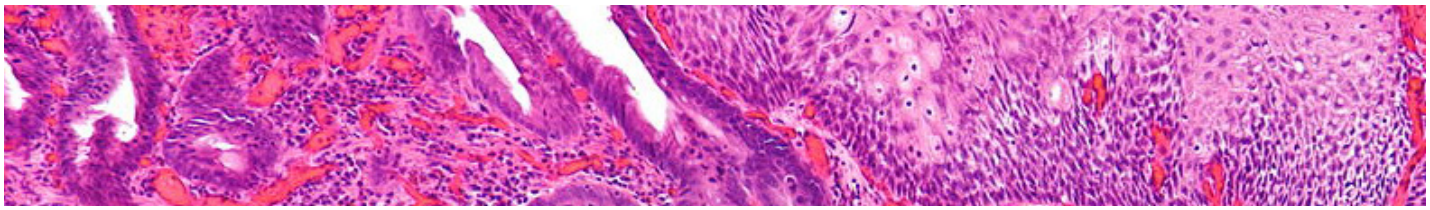
In all cases, the final decision will be adopted by the EU commission 30 days after the COMP opinion is provided.

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 in the States. 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; and 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



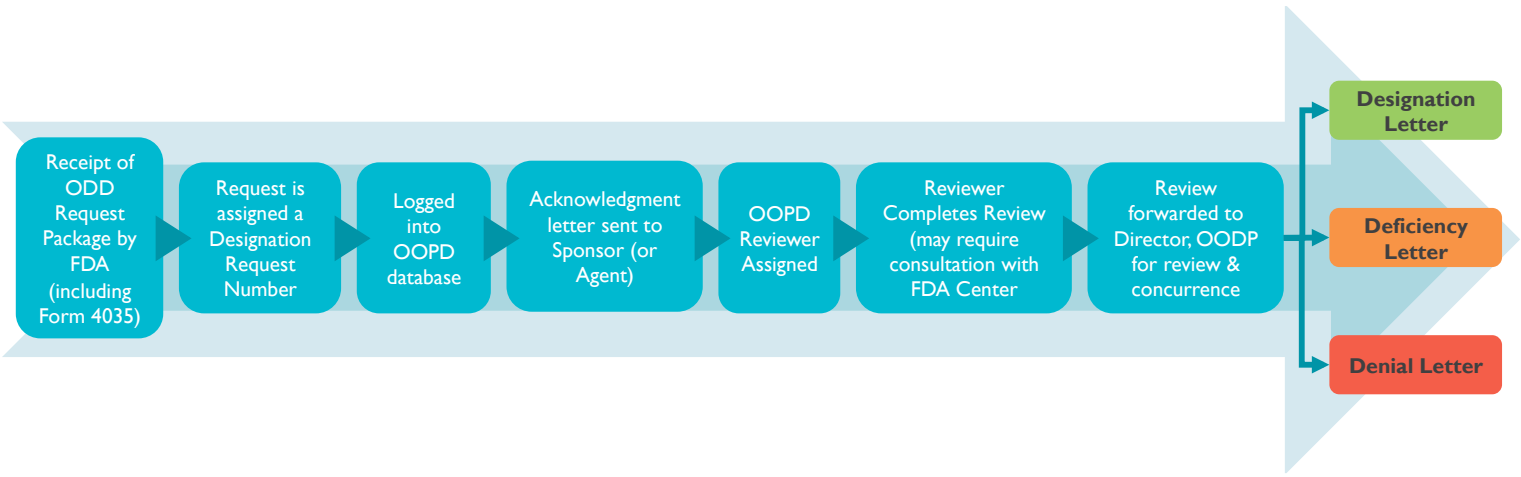
Act) and is subject to certain profit and use restrictions. These exemptions apply to Class III devices, which are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

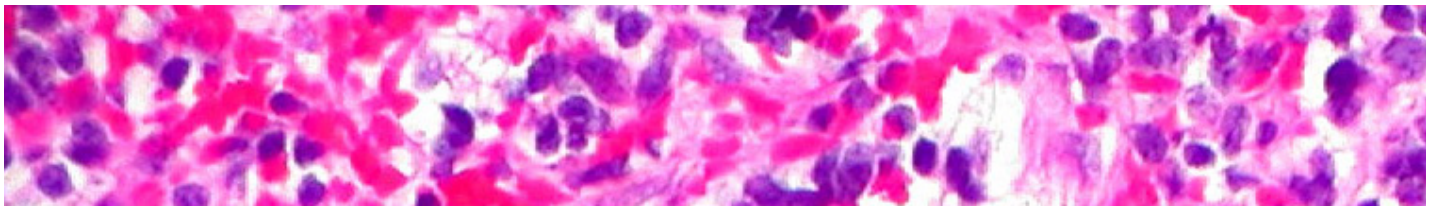
- Extramural Grant Programs that provide funding for Orphan Disease research.

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.

FIGURE BELOW ILLUSTRATES THE FDA SUBMISSION AND APPROVAL TIMELINE





SIVAKUMAR MUTHUSAMI

DIRECTOR OF PHARMACOVIGILANCE, QPPV MDS, SIMBEC-ORION

"Pharmacovigilance, considerations in early phase oncology and rare and orphan studies"

Sivakumar Muthusami opened the presentation on Pharmacovigilance considerations in early phase oncology and rare and orphan studies with a breakdown of reasons clinical trials have been terminated. Although insufficient enrolment had the highest percentage of terminations of the 35 reasons listed, Sivakumar highlights safety, side effects and ethical reasons for pharmacovigilance considerations in early phase studies. While statistically drug safety is often not the reason for ending a trial, it is one of the most talked about issues by the media, outranking media discussions on 14 other pharmaceutical topics, including drug safety and drug prices.

With the heightened media focus on safety, it is especially important to give this as much consideration as possible, especially in early phase studies where it is important to achieve positive outcomes to secure future funding and investment.

Of course, there are legal requirements regarding pharmacovigilance of medicinal products.

The legal framework for pharmacovigilance of medicinal products for human use in the EU & US is given in:

- Clinical trials - Directive 2001/20/EC
- Regulation (EU) No 1235/2010
- Directives 2010/84/EU and 2012/26/EU
- Commission Implementing Regulation (EU) No 520/2012
- 21 CFR 312.32, 312.64(b)
- 21 CFR 314.80

Pharmacovigilance Quality System is a legal requirement in the EU

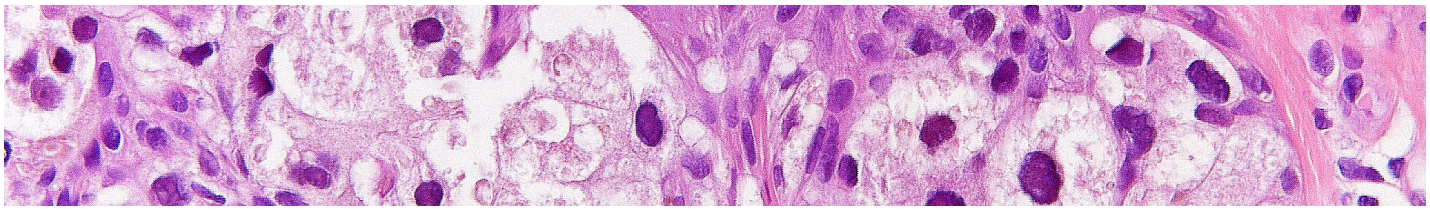
The legal requirement for quality systems was introduced by Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 to strengthen pharmacovigilance in the EU.

Pharmacovigilance is an ongoing process throughout the drug development process, from research and development, through marketing authorisation all the way to post-approval.

Regarding rare diseases, the safety assessment from an FDA perspective covers the following:

- Assessment of the safety of the drug should use "all tests reasonably applicable" to establish safety for its intended use.
- Clinical trials should include a **monitoring plan** adequate to ensure the safety of clinical trial patients. The elements and procedures of the monitoring plan should be based upon what is known about the drug, including nonclinical toxicology and chemistry, manufacturing, and controls (CMC) information, and, if available, previous human experience.
- There is "**no specific minimum number of patients that should be studied**" to establish effectiveness and safety of a treatment for any rare disease. The number of patients to establish effectiveness and safety is determined on a **case-by-case basis**…
- When conducting a **benefit-risk assessment** for a drug or a **serious or life-threatening illness**, FDA also recognizes that "**greater risks may be accepted for a treatment that is an advantage over available therapy".**
- The safety profile may "not be well known" and "greater risks may be accepted."

One of the challenges linked to pharmacovigilance in early phase trials is the ongoing safety assessment. Early phase trials are largely dependent on pre-clinical information, however in the case of rare diseases this is made more problematic with small patient populations and limited duration of exposure. In general, for early phase studies, the study population is unlikely to represent the 'real world', and SAEs may be limited and unrepresentative due to the small number of patients. This leads to an increased challenge with ongoing safety assessment and signal detection.



Multiple confounding factors also provide a challenge for research and development. Factors such as ongoing conditions, concomitant medications and drug-drug interaction complicate the process. It is therefore important to consider the training of the site, monitoring and safety personnel, and consider a Safety Physician in addition to a Medical Monitor.

The third challenge is limited or no RSI - Unknown or limited safety profile- No RSI- potential for increased SUSARs

Be critical with SUSARs. Minutes spent now saves hours in post approval stage

Outsource (to minimize operational, database, and administrative costs)- PV is dynamic; share the burden

Sivakumar finished the presentation with quotes from the publication Unlocking the power of pharmacovigilance; An adaptive approach to an evolving drug safety environment by PriceWaterhouseCoopers' Health Research Institute. "There is no science that dictates that a certain percentage of revenue should be allocated to pharmacovigilance, but—in the face of the potentially huge cost of safety-related withdrawals within the context of heightened stakeholder expectations around drug safety—companies should endeavour to strike a better balance between R&D spending and pharmacovigilance spending."

"The cost of withdrawals—when viewed against a backdrop of annual drug spending growth, that declined from 18% in 1999 to 8% in 2004- demonstrates that companies face a rapidly diminishing margin for safety-related error."

RONALD OPENSHAW

CHIEF EXECUTIVE OFFICER, SIMBEC-ORION

"Meeting your commercial, licensing, M&A and financial objectives by collaborating with your CRO as an ally"

Finally, the presentation by Simbec-Orion CEO Ronald Openshaw focused on giving an overview of how partnering with the right CRO can assist sponsors in meeting commercial, licencing, M&A and financial objectives. While the vast majority of bio-pharma companies will not bring their successful drugs to market themselves, CROs have extensive experience in running clinical trials and getting drugs to market. Working with the right CRO gives sponsors more time to focus on fundraising and development, while the CRO handles the logistics of running the trial.