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Clinical studies in lysosomal storage diseases

Past, present, and future

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Lysosomal storage disorders (LSDs) consist of over 40 diseases, some of which are amenable to treatment. In this review, we consider the regulatory context in which LSDs studies are performed, highlight design specificities and explore operational challenges.

Orphan drug legislations, both in Europe and US, were effective to stimulate LSDs drug development. However, regulators flexibilities toward approval vary leading to global discrepancies in access to treatments.

Study designs are constrained because few patients can be studied. This implies LSDs treatments need to demonstrate large levels of clinical efficacy. If not, an appropriate level of evidence is difficult to achieve. While biomarkers could address this issue, none have been truly accepted as primary outcome.

Enrichment of study population can increase the chance of success, especially with clinical outcomes. Adaptive designs are operationally challenging. Innovative methods of analysis can be used, notably using a patient as his/her own control and responder analysis. The use of extension phases and patient registries as a source of historical comparison can facilitate data interpretation.

Operationally, few patients are available per centers and multiple centers need to be initiated in multiple countries. This impacts time-lines and budget.

In the future, regulators flexibility will be essential to provide patients access to innovative treatments.

Introduction

Lysosomal storage disorders (LSDs) are made of over 40 diseases, each resulting from the deficiency of a lysosomal enzyme that is responsible for the degradation of macromolecular substrates in lysosomes.[1]

A main objective for conducting clinical studies in LSDs is to evaluate new treatment options. Over the last two decades innovative treatments have been developed for LSDs, most of them, Enzyme Replacement Therapies (ERTs). Because LSDs are rare, only few patients can enroll into clinical studies and this limitation impacts every aspects of clinical development. With this limitation in mind, how can clinical researchers plan, finance and implement complex clinical programs and collect enough safety and efficacy data that will convince regulators that a drug should be made accessible to additional patients?

In this review, we will consider the regulatory context in which LSDs studies are performed, discuss specific design issues and highlight some particular operational aspects. We will conclude with some considerations for the future.

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Regulatory Considerations

Orphan drug status and drug development flexibility

The orphan drug status laws, in the US[2] and in the European Union (EU),[3] have been credited as effective policies to stimulate drug development for rare diseases. For instance in the US, tax credits (50% of clinical drug testing costs), the Food and Drug Administration's (FDA) grant availability (Phase 1 studies are eligible for up to $200,000 per year for up to 3 y. Phase 2 and 3 studies are eligible for up to $400,000 per year for up to 4 y), exclusive market rights (seven years market exclusivity) and application fees waiver (currently $719,000) are indeed appropriate incentives.

While sponsors have embraced these incentives, there are conflicting opinions on whether regulators are more flexible in granting approval for orphan drugs compared with non-orphan drugs. For LSDs, no review of drug development has been published and it is thus difficult to assess regulators flexibility. Oncology, where many orphan drugs have been developed, is an informative example. When compared with non-orphan drugs, pivotal cancer studies for recently approved orphan drugs were more likely to be smaller, to have non-randomized, un-blinded designs and use surrogate endpoints of efficacy.[4] At least for rare cancers, it appears that regulators are embracing flexibility in study designs. Opinions concerning drug development for other rare diseases are conflicting. Regulators highlight their own flexibility[5] but other sources argue that their cautiousness limits drug development.[6,7] The term flexibility is evidently imprecise itself. Admitting evidence from one pivotal study instead of the more traditional two well-controlled pivotal studies mandated but the FDA is viewed by some as "flexibility"[8] but is also a consequence of the low number of patients that can be enrolled in these clinical studies.

In our opinion, any general statement regarding regulators flexibility is misleading. LSDs are different from one disease to the next and each drug development program poses unique

Table 1. Orphan drugs approved for LSDs in the European Union from 2001 up to 2010

Commercial name/year of approval	International non-proprietary name	Indication
Fabrazyme 2001	Agalsidase β	Fabry disease
Replagal 2001	Agalsidase alfa	Fabry disease
Zavesca 2002	Miglustat	Gaucher disease
Aldurazyme 2003	Laronidase	Mucopolysaccharidosis-I
Naglazyme 2006	Galsulfase	Muccopolysacchridosis-VI
Myozyme 2006	Alglucosidase alfa	Pompe Disease
Elaprase 2006	Idursulfase	Mucopolysaccharidosis-II
Vpriv 2010	Velaglucirase alfa	Gaucher disease

problems. For instance, the efficacy criteria for type 1 Gaucher Disease (GD), such as spleen size, is objective, easy to measure and to standardize. This is not the case for type 2 or type 3 GD which are difficult fields of investigations. Also, within the same LSD, phenotypic expression is so variable that this makes clinical studies more challenging. Infantile Pompe disease (PD) can lead to a rapid death by cardiac and/or respiratory failures but late-onset PD is characterized by a slowly progressive myopathy. Fabry disease (FD) heterogeneity is exemplified by different level of severity in affected organs, such as the kidney, the heart or the nervous system. For this multi-systemic disease there is no clinical or biochemical marker that is accepted, or validated, as a primary efficacy outcome in a registration study. As a consequence, some LSDs development programs were rapid[8] but others were convoluted.[9]

Regulatory options for faster drug approval

Politicians, governments and patient organizations are sensitive to the needs of patients with rare diseases to access new drugs.[10] Beyond the orphan drug acts, special provisions have been inserted into the law to facilitate regulatory reviews.

In the US, these include the Fast Track Designation (FTD), the Priority Review (PR) and the Accelerated Approval Program (AAP).

FTD is designed for the development and the review of drugs that treat serious diseases and fill an unmet medical need. With the designation, early and frequent communication between the FDA and a sponsor is encouraged throughout the review process so issues are resolved quickly. FTD must be requested by the sponsor and can be initiated at any time. For LSDs, it is unclear if this provision has had an impact.

Most drugs that are eligible for FTD are likely to be considered for PR. PR is given to drugs that offer major advances or provide a treatment where no adequate therapy exists. The goal for completing a review with PR is six months compared with the standard 10 months. Again, in the absence of systematic study, it is unclear that PR has had an impact on the review of drugs for LSDs.

AAP allow for earlier approval, based on a surrogate outcome, for drugs that treat serious diseases and fill an unmet medical need. A surrogate outcome is a marker that is used in a study as a substitute to a clinically meaningful and well documented outcome. The use of a surrogate can considerably shorten the time to approval. Sponsors will still be required to conduct phase IV studies to confirm the anticipated clinical benefit. If the confirmatory trial shows that the drug provides a clinical benefit, then a traditional approval is granted. If not, the drug can be removed from the market. This process has been successful to develop drug for HIV infection and cancers.[11] In LSDs, we will see that there have been many barriers to establish the surrogacy of a biochemical or clinical marker.[12]

Beyond the US, the European Union has introduced the conditional approvals (CAs) and the approval under exceptional circumstances (ECs).

CA is similar in its principle to the US-AAP but has rarely been used, actually never used for LSDs.[13]

In contrast, six of the eight drugs used to treat LSDs were approved in Europe under ECs. ECs mean that the applicant is not reasonably expected to provide comprehensive evidence on the safety and efficacy of the drugs owing to the rarity of the indication. While ECs offer a possibility to provide access to drugs that would otherwise not be marketed, it is not clear that this pathway accelerates the approval process. In a recent review, EC approvals were associated with longer clinical development time.[14] EC for LSDs drugs were also frequently associated with a request to develop a registry after registration.

LSDs drug development: US vs. Europe

Despite harmonization efforts,[15] countries still favor their own way to do things. As a result, sponsors of LSDs research may have to tailor their programs to local needs.

In the EU, the Committee for Orphan Medicinal Products (COMP) of the European Medicine Agency (EMA) reviews applications for orphan products. These products are intended to treat a serious or life-threatening condition that affects no more than five in 10,000 people. COMP is made up of members from European states and uses external experts to evaluate applications. A recent review indicated that up to 2010, 850 orphan drug designations were granted and 60 orphan drugs received marketing authorization. Of these, eight were for LSDs (**Table 1**).

In the US, an orphan disease affects less than 200,000 patients. Applications are reviewed by the FDA staff. Orphan status is granted by one division and applications are reviewed by a distinct "review" division that indifferently reviews orphan and non-orphan products. For LSDs, more applications are now reviewed by the Gastro-Intestinal division. A recent work evaluated 135 non-cancer orphan drugs application handled between 1983 and 2010.[8] Of these, 9 were for LSDs (**Table 2**).

There are additional differences. For instance, for registration studies the US FDA favors placebo-controlled trials, an ethical challenge for the development of new drug for LSD.[16] In EU, if a drug is already available, active-controlled studies are favored. However, superiority against an active drug is more difficult to

demonstrate due to the limited number of patients and equivalence studies are especially challenging because of the difficulty to define an equivalence margin that do not require an unrealistic number of patients to be studied.

These differences have led to paradoxical situations for patients' availability to new treatment. In PD, Myozyme® and Lumizyme® (both alglucosidase alfa) were considered different products by the FDA and similar products by the EMA. This led to considerable delays in the US in the availability of Lumizyme® compared with EU. In GD, taliglucerase alfa is available in the US and other countries but, not in the EU because of the exclusivity granted to a competitor. In FD, agalsidase alfa and β have been available in Europe and other countries since 2003. Patients can choose from two ERTs, a significant benefit in case of shortage of one of the drugs.[17] However, agalsidase alfa was not approved in the US. The level of evidence provided to obtain a registration in Europe was not sufficient for the FDA. The sponsor of algasidase alfa decided not to further pursue activities to meet US regulatory requests.[9]

Table 2. Orphan drugs approved for LSDs in the US between 1983 and 2010

Commercial name/year of approval	International non-proprietary name	Indication
Ceredase 1991	Aglucerase	Gaucher disease
Cerezyme 1994	Imiglucerase	Gaucher disease
Fabrazyme 2003	Agalsidase β	Fabry disease
Aldurazyme 2003	Laronidase	Mucopolysaccharidosis-I
Zavesca 2003	Miglustat	Gaucher disease
Naglazyme 2005	Galsulfase	Muccopolysacchridosis-VI
Myozyme 2006	Alglucosidase alfa	Pompe Disease
Elaprase 2006	Idursulfase	Mucopolysaccharidosis-II
Vpriv 2010	Velaglucirase alfa	Gaucher disease

Considerations for Clinical Study Designs

It is said that clinical study designs for rare diseases must meet the same rigorous standards as those for more prevalent diseases.[18] In practice, this is frequently not the case. As we will see, flexibility and pragmatism can prevail.

Sample size

In LSDs, as for any rare diseases, the limitation in the number of available patients is the main consideration. Compared with more frequent diseases, the sample size of clinical studies in LSDs is dramatically reduced, notably for key registration studies.

In 1991, when alglucerase (Ceredase®) was approved in the US for the treatment of type 1 GD, the main study demonstrating safety and efficacy enrolled 12 patients.[19] In 1994, when imiglucerase (Cerezyme®) was approved for the same indication, the main study enrolled 30 patients (15 on imiglucerase and 15 on alglucerase).[20] In 2003, when laronidase (aldurazyme®) was approved for the treatment of mucopolysaccharidosis-I (MPS-1), the approval was based on a single placebo-controlled study of 45 patients.[21] In infantile Pompe disease, the pivotal study that led to the 2006 approval of alglucosidase enrolled 18 patients.[22]

Registration studies in adult patients with LSDs tend to be larger but the sample size remain relatively small. The largest pivotal studies in FD enrolled 58[23] and 82 patients.[24] In adult-onset PD, the largest study enrolled 90 patients.[25]

Because of the limitation of study sample size in LSDs, the effect-size of treatments should be large. Otherwise, the study will have no statistical power to demonstrate efficacy. Efficacy might exist, but it might not be large enough to reach statistical significance.[26]

The need for large effect size puts the efficacy bar for LSDs at a high level. Taking into account the clinical specificities of individual LSDs, this could be challenging. For instance, to be approved in the US, the ERT used for FD had to demonstrate a clearance (i.e., a complete response) of globo-triaosylceramide (GL-3), the accumulated substrate. A complete response is a challenging objective for any clinical study in a chronic disease: many drugs developed for cancer or rheumatoid arthritis, to name a few, would fail such a request. In FD this is also challenging, as substrate accumulation varies between multiple tissues and, within the same tissue, between different cell types. For practical reasons, peri-tubular capillary cells of the interstitial kidney tissue were chosen as the cells of interest to evaluate GL-3 clearance. Repeated invasive kidney biopsies had to be performed.[23] While one ERT was able to meet the criteria for complete response, another ERT, despite being considered an equivalent product, studied a lower number of patients and efficacy could not be demonstrated in the same way.[8]

When the measured effect is not large, and this could be because of an appropriate parameter of efficacy is not available, efficacy is more challenging to demonstrate. For instance, for laronidase, an ERT for MPS-1, the distance walked during a Six-Minute Walk test (6MWT) and the percent predicted Forced Vital Capacity (FVC) were co-primary endpoints. Patients treated with ERT had a favorable 38 meters walking difference compared with patients treated with placebo. However, with only 22 patients in the active arm, the p-value was 0.07, above the accepted standard threshold of 0.05. A favorable difference of 5.6% in the predicted FVC was associated with a p-value of 0.01. While the co-primary endpoint criteria for the Six-Minute Walk test and FVC was not met, both criteria had to reach statistical significance; the drug was nevertheless registered, thanks to regulators flexibility.[8]

In the most extreme case, when sample sizes are very limited and a control group is not available, no statistics can be used. The evaluation of efficacy remains a judgment call. For instance, in infantile PD, the study that led to the approval of alglucosidase alfa was not comparative. The demonstration of a survival benefit had to be made in comparison to an historical cohort.[22] The reviewing agency conclusion, again demonstrating flexibility,

"was not based on statistics, per se, but more on the visual inspection of the results."[8]

Enrichment

Enrichment means that study enrolment criteria should favor patients in whom a drug effect, if present, is more likely to be demonstrable.[27] One of the benefits of enrichment is to increase the effect size, hence decreasing the sample size required to demonstrate efficacy. While enrichment makes recruitment more selective, and more difficult, it selects for responders and decreases the risk of an under-powered study. It is thus an option worth considering when designing clinical studies in LSDs. Different types of enrichment exist.

Practical enrichment[28] reduces "noise" by excluding patients who cannot possibly show an effect. For instance, in MPS-I, one would exclude patients with 6MWT that are to high (the chance to see an improvement is low as the patient is close to or normal) or too low (the chance to see a response in a severely affected patient is limited).[21]

Prognostic enrichment[28] refers to the inclusion of patients at higher risk of an event so the risk reduction is demonstrated with fewer patients. The PD study previously mentioned was performed in severely affected infants who had a very limited life-expectancy, rather than in adults with PD as they have a considerably longer course of the disease.[22]

Predictive enrichment[28] selects individuals who are more likely to respond to treatment for a pharmaco-dynamic reason. Although predictive enrichment has been mainly used in oncology, the genetic "revolution" opens this possibility for LSDs. An example from a genetic disease is illustrated by ivacaftor (Kalydeco™), a cystic fibrosis (CF) transmembrane conductance regulator potentiator that was recently approved. The approval was restricted to patients that carried a p-G551D mutation in the *CFTR* gene as they are the only patients that, for pharmacodynamic reasons, can respond to this drug. The pivotal clinical study was "enriched" for patients with this mutation despite the fact that it is only found in 4% of the CF patients in the US.[29] Clinical studies with migalastat HCl, a pharmacological chaperone for the treatment of FD, targeted an enriched population of Fabry patients that were more likely to respond because of a specific mutation.[30] Patients were requested to harbor a mutation that responded to the drug in an in vitro cell-based transfection assay.[31]

Control groups

Because of the rarity and potential severity of LSDs, the use of a control group is not always possible. The use of placebo might also be limited by ethical considerations.[32] This creates a dilemma for regulators as, without a control group, efficacy is more difficult to evaluate.

Rather than using the central tendency of a group of patients compared with another group of patients, it might be interesting to compare a patient to himself or herself before and after treatment. As long as changes are large and objective, this is an attractive possibility in LSDs. This principle has been helpful in rare diseases drug development[33] and can potentially complement a comparison to a historical control group.

When a treatment is already available, comparing a new therapy to an established therapy is difficult. Equivalence or non-inferiority studies require large sample sizes that are not achievable in LSDs. For superiority trials, the effect size is even more challenging to achieve.

Outcome measures of efficacy

Biochemical markers

Limited by the ability to enroll a large number of patients, biomarkers constitutes an attractive option to study the efficacy of a new treatment. For LSDs none of the biomarkers that have been used can be fully correlated with a clinical outcome. The establishment of the surrogacy of a biochemical marker is a complex process that is established by collecting long-term data in large number of individuals.[34] It took decades and thousands of subjects from Framingham, MA to establish a correlation between an increased level of cholesterol and an increased risk of myocardial infarction.[35] The request, mostly by regulators, to establish the surrogacy of a biochemical marker in a LSD before it can be used as a primary outcome of efficacy is unrealistic. As of now, none of the LSD biomarker, urinary-glucosaminoglycan for MPS,[21,36] urinary-Hex-4 for PD,[37] or serum chitotriosidase for GD[38] has been accepted by regulators. These markers are only considered secondary outcome measure of efficacy and cannot serve as a basis for a treatment approval. The example of FD is worth mentioning to highlight the complexity of using biochemical markers in LSDs. The complete clearance of GL-3 deposition in kidney interstitial capillaries was considered a primary outcome criterion[23] but the confirmatory study was not able to establish its clinical significance.[24] After 10 years on the US market, algasidase β remains "conditionally" approved.

Clinical markers

Because of the reluctance of regulators to accept biochemical markers, clinical outcome remain the cornerstone to approve a treatment for LSDs. This is particularly challenging because of the small sample size available and the heterogeneity between patients affected with the same LSD.

For instance, the 6MWT is the primary criteria to evaluate efficacy of MPS but also adult-onset PD treatments. This is a crude marker and the results can be mixed. The use of pain as a clinical outcome in FD was also challenging: the same data could be seen as being demonstrative of efficacy in Europe but insufficient proof of evidence in the US.

In GD, a decrease in the size of the spleen is considered an appropriate clinical marker.[20] While it is intuitive to think that a decrease in spleen volume is a good thing, there is no data available to demonstrate that a decrease in the size of the spleen is associated with a decrease in severe bleeding or improved survival. This last example just goes to show that, in itself, a clinical marker is not always in itself a surrogate of an important and demonstrated clinical benefit.

Composite endpoints

To address the limitation of single clinical outcome, composite clinical outcomes could be helpful. One advantage is by capturing more events a composite can address some of the heterogeneity of LSDs.

Co-primary efficacy outcome such as a 6MWT and FVC have been used and we have seen that reaching a statistical significant on one of them but not the other could salvage a drug approval.[21]

In FD,[24] a confirmatory study used a composite endpoint. The criterion was the time to first clinical event (i.e., a renal, cardiac or cerebro-vascular event or death). However, while the time to a first event was decreased by 53% with ERT – a large effect for a clinical study -, the statistical threshold was missed (p = 0.06). The FDA did not consider this evidence as sufficient proof of benefit and in this case, there was no flexibility.

While patients reported outcome or disease specific scoring index are interesting, their implementation and their validation according to regulatory criteria are challenging. For instance, none of the clinical index created for FD[39-41] are considered definitive enough to be used as primary efficacy outcome measures in a registration study.

Adaptive clinical study designs

When conducting clinical studies, it is not uncommon to modify a trial and/or statistical procedures through protocol amendments. This is either based on new external information or on a review of interim data.[42] The purpose is not only to identify clinical benefits of the tested candidate treatment, but also to increase the probability of success. An adaptive design should allow modifications of a trial and/or its statistical procedure after its initiation without undermining its integrity.[43,44] This is an important option for a study in LSDs, as most of the time the data that accumulates during the study are informative for the rest of the study.

The FDA however, through its 2010 guidance,[45] defines an adaptive design as a study that includes a prospectively planned modification of one or more specified aspects of the study design and hypotheses based on a pre-planned interim analysis. This is a strict position as illustrated by a study of alglucosidase alfa for the treatment of PD in adults.[25] The statistical analysis of the trial and its duration were modified with information that could only be made available through an interim analysis that could not be prospectively defined, as this was the first registration study performed in this field. This approach was criticized and complicated the approval of the drug.[46] The EMA, which defines an adaptive design as a flexible design,[47,48] did not raise similar concerns on this alglucosidase alfa study.

Extension phases

In LSD studies, extension phases are generally implemented. They offer patients a possibility for an early access to a promising treatment and provide an opportunity for regulators and sponsors to collect long-term safety information. In our experience, the FDA now routinely asks to provide at least 12 mo of drug exposure to evaluate safety.

Registry

In LSDs, registries have been requested by regulators to collect additional information on newly approved therapies. Registries were established, for instance, for GD,[49] PD,[50] FD[51] and MPS.[52]

Registries also provide additional safety information on new treatments and potentially provide information on the disease itself.[53,54]

Registries data are neither controlled nor blinded and their benefit for collecting efficacy data are more limited.[55] Their maintenance creates significant work. Without financial or resources support data collection is incomplete and quality suffers. Mandated registries focus on only one drug and potentially multiple registries for the same disease will be established. The multiplication of registries and the lack of cooperation between their sponsors is a recognized issue that needs to be addressed.[56]

Operational Considerations

Number of centers

In LSDs it is difficult to plan with certitude the number of clinical center that will need to be initiated. If no treatment is available, no previous experience can be relied upon. If a treatment already exists, past experiences might not be reliable. Over the last two decades, the number of patients recruited per site has decreased. More sites need to be initiated with consequences on cost and time-lines.

FD illustrates this point. Starting in March 1999, the first pivotal study that led to the availability of algasidase β enrolled 58 patients with 8 sites (mean 7.3 patients/site). Recruitment was greatly facilitated by one center that enrolled 20 patients.[23] The confirmatory study that began in February 2001 enrolled 82 patients over 26 sites (mean 3.2 patients/site).[24] In September 2009, another pivotal study in naïve FD patients was initiated.[30] At that time both algasidase alfa and β were available and 67 patients had to be enrolled over 38 sites (mean 1.8 patients/site).[57]

Number of countries

With increasing number of centers, sponsors have to increase the number of countries, as within any country, centers specializing in LSDs are few. With more countries, study complexity increases. Multiple regulations, varying medical practices, different treatment availability and language barriers have to be addressed.

Using the example of FD, the first algasidase β pivotal study in 1999 was performed in the US and 3 European countries.[23] The confirmatory trial in 2001 was performed in 9 countries in North America and Europe.[24] The most recent study, in 2009, was initiated in 18 countries over five continents.[30]

Institutional review boards/ethics committees (IRB/EC)

There is no specific ethical rule for conducting clinical studies in LSDs. However, as more studies are conducted at multiples sites, multiple IRB/ECs are consulted. Multiple reviews increase the chance to be faced with different requests to change a study protocol. In our experience, these requests are frequent, especially concerning mundane details of study protocols. Rarely, conflicting ethical opinions concerning a major aspect of a study is formulated.

The practice of multiple IRB reviews consumes resources and creates delays in the conduct of research.[58] In LSDs, this problem is particularly relevant as sometimes, only one patient is enrolled at a center. Also, academic centers that have their own IRBs and do not favorably views external IRB reviews such as central IRBs.[59]

In many countries the practice to have more than one level of IRB reviews is more common. For instance in the FD study previously mentioned,[30] 8/14 US sites contacted required multiple IRB reviews, while 6/27 ex-US sites required multiple IRB/EC reviews. There is little evidence that having multiple IRB/

EC reviews leads to ethical improvement of protocol or consent forms. On the contrary, the practice appeared to diminish study ethical integrity.[59]

Future Considerations

In the US, the Food and Drug Administration Safety and Innovation Act (FDASIA) of July 2012 includes a new breakthrough designation to expedite the development and review of drugs for serious or life-threatening conditions. To receive the designation a drug should have demonstrated preliminary clinical evidence of a substantial improvement over available therapy on at least one clinically significant endpoint. With this designation the FDA is committed to additionally provide more intensive guidance on the drug development program and to involve its senior management in such guidance.[60]

At the time of this writing, 10 drugs had received the designation. They included drugs to treat rare diseases such as cystic fibrosis or epidermolysis bullosa. Other legislative efforts to speed-up drug development for rare diseases, such as the TREAT act in the US (Transforming the Regulatory Environment to Accelerate Access to Treatments) demonstrate the willingness of legislators to speed up drug development. It is however too early to know if these efforts will positively impact clinical drug development for rare diseases.[61]

In Europe, efforts are ongoing to reform the European Clinical Trials Directive and the bureaucratic impact it had on slowing down clinical research.[62]

For a productive clinical research, regulators flexibility will be essential. In this context, the use of biomarkers is an avenue of interest for LSDs but it should be addressed on a disease-specific basis rather than within the constraints of an overarching guidance. Also, the place of companion diagnostics, now common in oncology, will have to be defined for LSDs. Companion diagnostics represent an opportunity for a more patient centric approach but they complicate the development process as both a drug and a diagnostic have to be developed.[63]

Concerning data analysis, the patient, rather than a group of patients, should constitute the unit of analysis. A responder analysis, instead of the evaluation of the central value (e.g., mean) of a group of patients, helps to take into account the variability of phenotypic expression of LSDs. The patient can also be used as his/her own control to evaluate the activity of a drug rather that comparing him/her to another patient on a placebo that might have a very different phenotypic expression of the disease.[33]

Last, due to the high cost of drugs developed for LSDs, payers will play a more active role.[64] This could mean that more economic data or comparative data will be requested early on in the development process. Here again, the limitations of the number of patients could indicate that a new paradigm for pricing and re-imbursement has to be invented.[65]

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

References

1. Pastores GM. Therapeutic approaches for lysosomal storage diseases. Ther Adv Endocrinol Metab 2010; 1:177-88; PMID:23148162; http://dx.doi.org/10.1177/2042018810384429
2. Haffner ME. Adopting orphan drugs--two dozen years of testing rare diseases. N Engl J Med 2006; 345:4457
3. Westermark K, Holm BB, Söderholm M, Llinares-Garcia J, Rivière F, Aarum S, Butlen-Ducuing F, Tsigkos S, Wilk-Kachlicka A, N'Diamoi C, et al.; Committee for Orphan Medicinal Products and the European Medicines. European regulation on orphan medicinal products: 10 years of experience and future perspectives. Nat Rev Drug Discov 2011; 10:341-9; PMID:21532564; http://dx.doi.org/10.1038/nrd3445
4. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA 2011; 305:2320-6; PMID:21642684; http://dx.doi.org/10.1001/jama.2011.769
5. Coté TR, Xu K, Pariser AR. Accelerating orphan drug development. Nat Rev Drug Discov 2010; 9:901-2; PMID:21119719; http://dx.doi.org/10.1038/nrd3340
6. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012; 11:191-200; PMID:22378269; http://dx.doi.org/10.1038/nrd3681
7. Gottlieb S. Changing the FDA's culture. National Affairs 2012; 12:108-21
8. Sasinovski FJ. Quantum of effectiveness evidence in FDA's approval of Orphan Drugs [Internet]. Washington (DC): National Organization for Rare Disorders: c2011 [cited 2013 Aug 24]. Available from: http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf
9. Shire Provides Update on US Biologics License Application Filing for REPLAGAL® (agalsidase alfa) [Internet]. Dublin, Ireland; Shire; c2012 March 12 [cited 2013 August 24]. Available from: http://www.shire.com/shireplc/en/investors/irshirenews?id=577
10. Crowley J. Statement of John Crowley, Chief Executive Officer and Chairman of Amicus Therapeutics on behalf of the biotechnology industry organization [Internet]. Washington (DC); US Senate Committee on Health, Education, Labor and Pensions; c2010 July 21 [cited 2013 August 24]. Available from: www.help.senate.gov/imo/media/doc/Crowley.pdf
11. Johnson JR, Ning Y-M, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst 2011; 103:636-44; PMID:21422403; http://dx.doi.org/10.1093/jnci/djr062
12. Anonymous. Reforming accelerated approval. Nat Biotechnol 2012; 30:293; PMID:22491259; http://dx.doi.org/10.1038/nbt.2194
13. European public assessment reports. Conditional approval. Authorized medecines [Internet]. European Medicines Agency; c2013 [cited 2013 August 24]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d125&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=ca&genericsKeywordSearch=Submit
14. Boon WPC, Moors EHM, Meijer A, Schellekens H. Conditional approval and approval under exceptional circumstances as regulatory instruments for stimulating responsible drug innovation in Europe. Clin Pharmacol Ther 2010; 88:848-53; PMID:20962774; http://dx.doi.org/10.1038/clpt.2010.207
15. Molzon JA, Giaquinto A, Lindstrom L, Tominaga T, Ward M, Doerr P, Hunt L, Rago L. The value and benefits of the International Conference on Harmonisation to drug regulatory authorities: advancing harmonization for better public health. Clin Pharmacol Ther 2011; 89:503-12; PMID:21326288; http://dx.doi.org/10.1038/clpt.2011.10
16. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. N Engl J Med 2001; 345:915-9; PMID:11565527; http://dx.doi.org/10.1056/NEJM200109203451211
17. Linthorst GE, Germain DP, Hollak CEM, Hughes D, Rolfs A, Wanner C, Mehta A; European Medicines Agency. Expert opinion on temporary treatment recommendations for Fabry disease during the shortage of enzyme replacement therapy (ERT). Mol Genet Metab 2011; 102:99-102; PMID:21123099; http://dx.doi.org/10.1016/j.ymgme.2010.11.155
18. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA; Rare Diseases Clinical Research Network. Clinical research for rare disease: opportunities, challenges, and solutions. Mol Genet Metab 2009; 96:20-6; PMID:19013090; http://dx.doi.org/10.1016/j.ymgme.2008.10.003
19. Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, Mankin HJ, Murray GJ, Parker RI, Argoff CE, et al. Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991; 324:1464-70; PMID:2023606; http://dx.doi.org/10.1056/NEJM199105233242104

20. Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA, Parker C, Schiffmann R, Hill SC, Brady RO. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Intern Med 1995; 122:33-9; PMID:7985893; http://dx.doi.org/10.7326/0003-4819-122-1-199501010-00005
21. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Swiedler SJ, Kakkis ED, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 2004; 144:581-8; PMID:15126990; http://dx.doi.org/10.1016/j.jpeds.2004.01.046
22. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, Leslie N, Levine J, Spencer C, McDonald M, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. [published correction appears in Neurology 2008; 71:1748]. Neurology 2007; 68:99-109; PMID:17151339; http://dx.doi.org/10.1212/01.wnl.0000251268.41188.04
23. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ; International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human α-galactosidase A--replacement therapy in Fabry's disease. N Engl J Med 2001; 345:9-16; PMID:11439963; http://dx.doi.org/10.1056/NEJM200107053450102
24. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, et al.; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med 2007; 146:77-86; PMID:17179052; http://dx.doi.org/10.7326/0003-4819-146-2-200701160-00148
25. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, Herson S, Kishnani PS, Laforet P, Lake SL, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 2010; 362:1396-406; PMID:20393176; http://dx.doi.org/10.1056/NEJMoa0909859
26. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995; 311:485; PMID:7647644; http://dx.doi.org/10.1136/bmj.311.7003.485
27. Temple RJ. Special study designs: early escape, enrichment, studies in non-responders. Comm Statist Theory Methods 1994; 23:499-531; http://dx.doi.org/10.1080/03610929408831269
28. Temple R. Enrichment of clinical study populations. Clin Pharmacol Ther 2010; 88:774-8; PMID:20944560; http://dx.doi.org/10.1038/clpt.2010.233
29. Kalydeco™ package insert [Internet]. Washington (DC); Vertex Pharmaceuticals Inc.; c2012 [cited 2013 August 24]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203188lbl.pdf
30. Study of the effects of oral AT1001 (Migalastat hydrochloride) in Patients with Fabry Disease [Internet]. Washington (DC); Clinicaltrials.gov.; c2013 [cited 2013 August 24]. Available from: http://clinicaltrials.gov/ct2/results?term=migalastat
31. Wu X, Katz E, Della Valle MC, Mascioli K, Flanagan JJ, Castelli JP, Schiffmann R, Boudes P, Lockhart DJ, Valenzano KJ, et al. A pharmacogenetic approach to identify mutant forms of α-galactosidase A that respond to a pharmacological chaperone for Fabry disease. Hum Mutat 2011; 32:965-77; PMID:21598360; http://dx.doi.org/10.1002/humu.21530
32. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. N Engl J Med 2001; 345:915-9; PMID:11565527; http://dx.doi.org/10.1056/NEJM200109203451211
33. Lagakos SW. Clinical trials and rare diseases. N Engl J Med 2003; 348:2455-6; PMID:12802033; http://dx.doi.org/10.1056/NEJMe030024
34. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996; 125:605-13; PMID:8815760; http://dx.doi.org/10.7326/0003-4819-125-7-199610010-00011
35. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med 1979; 90:85-91; PMID:217290; http://dx.doi.org/10.7326/0003-4819-90-1-85
36. Clarke LA, Winchester B, Giugliani R, Tylki-Szymanska A, Amartino H. Biomarkers for the mucopolysaccharidoses: discovery and clinical utility. Mol Genet Metab 2012; 106:395-402; PMID:22658917; http://dx.doi.org/10.1016/j.ymgme.2012.05.003
37. Young SP, Zhang H, Corzo D, Thurberg BL, Bali D, Kishnani PS, Millington DS. Long-term monitoring of patients with infantile-onset Pompe disease on enzyme replacement therapy using a urinary glucose tetrasaccharide biomarker. Genet Med 2009; 11:536-41; PMID:19521244; http://dx.doi.org/10.1097/GIM.0b013e3181a87867
38. Hollak CEM, van Weely S, van Oers MHJ, Aerts JMFG. Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease. J Clin Invest 1994; 93:1288-92; PMID:8132768; http://dx.doi.org/10.1172/JCI117084
39. Whybra C, Kampmann C, Krummenauer F, Ries M, Mengel E, Miebach E, Baehner F, Kim K, Bajbouj M, Schwarting A, et al. The Mainz Severity Score Index: a new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet 2004; 65:299-307; PMID:15025723; http://dx.doi.org/10.1111/j.1399-0004.2004.00219.x
40. Giannini EH, Mehta AB, Hilz MJ, Beck M, Bichet DG, Brady RO, West M, Germain DP, Wanner C, Waldek S, et al. A validated disease severity scoring system for Fabry disease. Mol Genet Metab 2010; 99:283-90; PMID:19951842; http://dx.doi.org/10.1016/j.ymgme.2009.10.178
41. Hughes DA, Malmenäs M, Deegan PB, Elliott PM, Ginsberg L, Hajioff D, Ioannidis AS, Orteu CH, Ramaswami U, West M, et al.; FOS Investigators. Fabry International Prognostic Index: a predictive severity score for Anderson-Fabry disease. J Med Genet 2012; 49:212-20; PMID:22315436; http://dx.doi.org/10.1136/jmedgenet-2011-100407
42. Chow S-C, Corey R. Benefits, challenges and obstacles of adaptive clinical trial designs. Orphanet J Rare Dis 2011; 6:79-89; PMID:22129361; http://dx.doi.org/10.1186/1750-1172-6-79
43. Chow SC, Chang M, Pong A. Statistical consideration of adaptive methods in clinical development. J Biopharm Stat 2005; 15:575-91; PMID:16022164; http://dx.doi.org/10.1081/BIP-200062277
44. Gallo P, Anderson K, Chuang-Stein C, Dragalin V, Gaydos B, Krams M, Pinheiro J. Viewpoints on the FDA draft adaptive designs guidance from the PhRMA working group. J Biopharm Stat 2010; 20:1115-24; PMID:21058107; http://dx.doi.org/10.1080/10543406.2010.514452
45. FDA Draft Guidance for Industry - Adaptive Design Clinical Trials for Drugs and Biologics. The United State Food and Drug Administration, Rockville, Maryland. 2010.
46. Yao L. Clinical background materials. Alglucosidase alfa 2000 L product for the treatment of Late-Onset Pompe Disease [Internet]. Washington (DC); FDA CDER. The Endocrinologic and Metabolic Drugs Advisory Committee Meeting; c2008 Oct 21 [cited 2013 August 24]. Available from: www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4389b1-01-FDA.pdf
47. European Medicinal Agency (EMA). Point to Consider on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan. The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use. CPMP/EWP/2459/02, London, UK 2002.
48. European Medicinal Agency (EMA). Reflection paper on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan. The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use. CPMP/EWP/2459/02, London, UK 2006.
49. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, Rosenbloom BE, Scott CR, Wappner RS, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002; 113:112-9; PMID:12133749; http://dx.doi.org/10.1016/S0002-9343(02)01150-6
50. Byrne BJ, Kishnani PS, Case LE, Merlini L, Müller-Felber W, Prasad S, van der Ploeg A. Pompe disease: design, methodology, and early findings from the Pompe Registry. Mol Genet Metab 2011; 103:1-11; PMID:21439876; http://dx.doi.org/10.1016/j.ymgme.2011.02.004
51. Mehta A, Beck M, Elliott P, Giugliani R, Linhart A, Sunder-Plassmann G, Schiffmann R, Barbey F, Ries M, Clarke JT; Fabry Outcome Survey investigators. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet 2009; 374:1986-96; PMID:19959221; http://dx.doi.org/10.1016/S0140-6736(09)61493-8
52. Hendriksz CJ, Giugliani R, Harmatz P, Lampe C, Martins AM, Pastores GM, Steiner RD, Leão Teles E, Valayannopoulos V; CSP Study Group. Design, baseline characteristics, and early findings of the MPS VI (mucopolysaccharidosis VI) Clinical Surveillance Program (CSP). J Inherit Metab Dis 2013; 36:373-84; PMID:22127392; http://dx.doi.org/10.1007/s10545-011-9410-9
53. Deegan PB, Baehner AF, Barba Romero MA, Hughes DA, Kampmann C, Beck M; European FOS Investigators. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 2006; 43:347-52; PMID:16227523; http://dx.doi.org/10.1136/jmg.2005.036327
54. Mehta A, Clarke JT, Giugliani R, Elliott P, Linhart A, Beck M, Sunder-Plassmann G; FOS Investigators. Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. J Med Genet 2009; 46:548-52; PMID:19473999; http://dx.doi.org/10.1136/jmg.2008.065904
55. Jones S, James E, Prasad S. Disease registries and outcomes research in children: focus on lysosomal storage disorders. Paediatr Drugs 2011; 13:33-47; PMID:21162599; http://dx.doi.org/10.2165/11586860-000000000-00000
56. Hollak CEM, Aerts JMFG, Aymé S, Manuel J. Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders. Orphanet J Rare Dis 2011; 6:16; PMID:21496291; http://dx.doi.org/10.1186/1750-1172-6-16
57. Nicholls K, Germain DP, Feliciani C, et al. Phase 3 Study of Migalastat HCl for Fabry Disease: Stage 1 Results. February 15, 2013, 9th Annual Lysosomal Disease Network WORLD Symposium (LDN WORLD)
58. National conference on alternative IRB models: optimizing subject protection, November 19-21, 2006 [Internet]. Washington (DC): Associations of American Medical Colleges; c2006 [cited 2013 August 24]. Available from: http://www.aamc.org/research/irbreview/irbconf06rpt.pdf

59. Menikoff J. The paradoxical problem with multiple-IRB review. N Engl J Med 2010; 363:1591-3; PMID:20942660; http://dx.doi.org/10.1056/NEJMp1005101
60. Frequently asked questions: breakthrough therapies [Internet]. Washington (DC): US Food and Drug Administration; c2013 [cited 2013 Aug 24]. Available from: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.htm. Accessed 4/16/2013.
61. Anonymous. Reforming accelerated approval. Nat Biotechnol 2012; 30:293; PMID:22491259; http://dx.doi.org/10.1038/nbt.2194
62. Cressey D. Europe sets out to reform its clinical trial rules. Nat Rev Drug Discov 2012; 11:660-1; PMID:22935791; http://dx.doi.org/10.1038/nrd3843
63. Numerof RE, Abrams MN. The growing orphan-drug paradigm. Pharmaceutical Tech 2012;May:105-6.
64. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J Rare Dis 2011; 6:42-50; PMID:21682893; http://dx.doi.org/10.1186/1750-1172-6-42
65. McCabe C, Edlin R, Round J. Economic considerations in the provision of treatments for rare diseases. Adv Exp Med Biol 2010; 686:211-22; PMID:20824448; http://dx.doi.org/10.1007/978-90-481-9485-8_13