Committee Secretariat
Standing Committee on Health, Aged Care and Sport
PO Box 6021
Parliament House
Canberra ACT 2600
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12 October 2020

Re: Standing Committee on Health, Aged Care and Sport:
Inquiry into approval processes for new drugs and novel medical technologies in Australia

Dear Secretariat,

Thank you for the opportunity to respond to the terms of refence in relation to the inquiry into the approval process of new drugs and novel medical technologies in Australia.

About GUARD

The GUARD Collaborative is a coalition of peak body organisations; Genetic Support Network of Victoria, Genetic Alliance Australia (NSW), Syndromes Without A Name (SWAN) Australia and Genetic and Rare Disease Network (WA). We stand together to represent the voice of people living with genetic, undiagnosed and rare disease and those who support them. We stive for a fair, equitable and collaborative approach to health and wellbeing for all members of our population.

Our submission is in the context of the National Strategic Action Plan for Rare Disease, a focussed plan outlining the priorities and areas of action required to improve the lives of people living with rare disease. We have addressed the four terms of reference on the following pages.

I would be happy to provide further information about our submission if required.

Kind regards

Monica Ferrie
Chief Executive Officer
Genetic Support Network Victoria (GSNV)
On behalf of the GUARD Collaborative

RECOMMENDATIONS

- **Prioritising patients' quality of life over economics**
- **Inclusion of the patient voice and consumers at every step of the developmental process**
- **Attracting investment and partnerships between Australia and overseas for development of novel drugs and clinical trials**
- **Easier process to get lifesaving treatments on the Life Savings Drugs Program**
- **Sustainable government investment into rare disease research**
- **Adopting a new price setting model around how pharmaceutical companies charge for drugs**

About Rare Disease

According to the Australian Government - Department of Health, it is estimated 8% of Australians are living with a rare disease of which 80% have a genetic origin. Over ,10,000 rare diseases, 7000 rare diseases are life threatening or have a chronic illness associated with them.[1] This correlates to approximately the same proportion of people living with diabetes or asthma.[2] Unfortunately 30% of affected children will not see their fifth birthday.[3] Obtaining a diagnosis and/or treatment can be a long and difficult journey. About half of children with learning disabilities and approximately 60% of children with multiple congenital problems do not have a definitive diagnosis to explain the cause of their condition. [4]

We live in the rapid genomics era where we are discovering new rare diseases every week. Some of these gene changes are complex and we are only just learning about the relationship between some genes and the environment. Discovery can bring hope and possibility; understanding and knowledge; fear and despair. Lack of diagnosis can bring frustration and isolation and with limited access to research, drugs and clinical trials.

People living with genetic, undiagnosed and rare disease are amongst the most vulnerable groups in society. Their diseases are highly complex, often chronic, and severely disabling conditions, which generate specific care needs.

For a vulnerable population it is imperative that additional measures and access to research, treatment plans (new drugs and novel medical technologies) and clinical trials be available to support them in an equitable, fair and timely manner to ensure their quality of life. We call on this inquiry to ensure this outcome.

[1] https://www.health.gov.au/health-topics/chronic-conditions/what-were-doing-about-chronic-conditions/what-were-doing-about-rare-diseases

[2] https://www.racgp.org.au/afp/2015/september/rare-diseases-are-a-%E2%80%98common%E2%80%99-problem-for-clinicians/

[3] https://www.mcri.edu.au/content/rare-disease

[4] https://www.undiagnosed.org.uk/support_information/what-does-swan-or-being-undiagnosed-mean/

Terms of Refence

1. **The range of new drugs and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies**

A review of what we have in place

We cannot discuss what Australia needs to do without focussing on the lived experience of patients. We need to also focus on Australians being well positioned to access new drugs and novel medical technologies in a timely manner.

Our process of bringing drugs and technologies to market is thorough and comprehensive but it is slow, it is over medicalised where clinical utility and costs remain the most influential factors in decision making. We welcome the review of MSAC Guidelines and the proposed move to include personal utility as part of the decision making but are concerned that this will further add time and qualitative measures will not be equal in weight to quantitative measures. People die while our process undertake its slow churn.

When we are able to have clinical trials, these are often influenced by a well-connected or influential team of health professionals with particular interests and who in turn may be influenced by the loudest voices in the patient community.

The patient and support community for genetic, undiagnosed and rare disease is a tired community who have been fighting for a long time. Progression is difficult, it's a crowded marketplace and it's hard to be heard.

A recent survey of the genetic, undiagnosed and rare disease community provided the following insights.

22%	Patients were given the opportunity to participate in research in Australia
25%	Patients provided with the opportunity to participate in research overseas because there were no research opportunities being offered in Australia about their rare disease
19%	Patients had difficulty in accessing drugs/medicines in Australia
22%	Patients had to seek access to drugs overseas to treat their rare disease as they were unavailable Australia
28%	Patients had trouble accessing the right treatment options in Australia
9%	Patients had to seek treatment options from overseas due to lack of availability in Australia
50%	Patients had trouble accessing the right therapy options
9%	Patients were given the opportunity to participate in clinical trials in Australia
6%	Patients offered access to clinical trials overseas

These results are horrifying for individuals let alone a community as large as the diabetes community in this country. This is an unacceptable state to be in. The National Strategic Action Plan for Rare Diseases (bipartisan supported and endorsed) *Priority 2.4 calls for All Australians to have equitable access to the best available health technology.* [5] Clearly, we are not achieving this.

In 2020, patient support groups are more than advocacy groups, they are providing lifeline connections, helping people navigate the health system, they are establishing medical and scientific committees to stay on top of the latest research and opportunities, they are providing case management, access to health experts like dieticians, counsellors and nurses, they are producing information, setting up registries, lobbying for more trials and access, holding events and family days, raising funds to survive, working to decipher and support for NDIS meetings, providing practical assistance, managing diversity and cultural needs, they are being there….and still trying to fight for the quality of life for their communities.

It's critical to recognise this because the traditional 'lobbying' on your own behalf for access to trials, for access to testing, for MBS and PBS approvals is even more challenging yet somehow seems to be even more expected. The burden cannot continually be placed on patients and their families.

For many conditions it is sometimes difficult to even find a researcher in Australia who is interested in your condition. Individuals, families and support organisations find it difficult to stay across what research is happening in Australia and globally, sometimes coming across attitudes of professional ownership and an unwillingness to share when knowledge does become available. How can the patient voice be so undervalued?

Our European colleagues have long ago recognised this problem and recognise that

> *"There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. The way forward is to increase collaboration".*

They committed to

> *"Gathering national expertise on rare diseases and support the pooling of that expertise and the sharing of' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients."* [6]

Patients and support groups often do not have the capacity or resources to bring about the collaboration that is required but are the experts in our individual rare disease, are the experts with lived experience, are the experts in what our expectations are of our medical experience and the lives they wish to lead.

The GUARD Collaborative, in the spirit of building on the UN Right to Health, and the UN Sustainable Development Goals of *"ensuring healthy lives and promoting the well-being for all at all ages"* and of *"leaving no one behind",* believes that all people are entitled to the same quality of care and opportunity.

Internationally the number of therapies for rare diseases has increased dramatically in the past decade and will continue to increase in the foreseeable future. People living with a rare disease must be able to hope for access to new drugs and treatments in Australia and to benefit from them rapidly and fully, all across world, as soon as they are approved.

[5] https://rva.blob.core.windows.net/assets/uploads/files/NationalStrategicAPRD.pdf

[6] https://www.eurordis.org/content/breaking-access-deadlock-leave-no-one-behind

There is much influencing our current process and engagement in the development of new drugs and novel technologies and our ability to provide access. We need a complete re-think as the current model does not serve us well.

The issue of access to the growing range of drugs and technologies has been well recognised as an increasing problem over recent years for a number of reasons:

- The persistence of an unpredictable global economic environment and more recently a global pandemic, and its consequences on the economy and on the availability of funding and therefore access;
- Competing health priorities such as ageing of populations, which in turn amplifies the demand for care and treatments;
- The very organisation of healthcare system itself, which needs to be revisited and adapted. We now know that this possible and can be done quickly;
- The increasing cost of the development of an innovative drug, treatment or technology, all the way from bench to marketing approval;
- The cumbersome process we have in place for approvals; and
- The arrival of very innovative drugs for widespread conditions put on the market by their manufacturers at unprecedented high prices.

Attracting investment for the development of therapies for life-threatening or debilitating diseases for thousands of Australians who today have either no treatment at all or no satisfactory treatment is difficult particularly when organisations are faced with a costly and lengthy development process before any reward begins to be delivered for the bottom line or for patients.

Solving the issue of accessing the range of drugs and novel medical technologies in development in Australia and overseas will depend upon changing:

- An unsustainable economic model that can lead to mistrust between stakeholders and wasted investment.
- A vast disconnection between the value of a product and the price claimed: we see real life cases of new products for diseases with high unmet medical needs being approved for commercialisation but never making it to the patients who need them most because they are deemed too expensive or not seen as presenting sufficient value
- The cost of developing new therapies remains too high, despite advancements in modelling and assessment techniques that could decrease investments dramatically

It is our view maintaining such an approach is fundamentally unsustainable. All stakeholders including government, regulatory agencies, industry, leading corporate players, investors and the community, must take a firm stance towards a fairer pricing strategy and business model.

We must remember that the majority of people living with a rare disease at this very moment have delayed or no access at all to the medicine they need, or that there is no existing medicine/drug/treatment option available to them. If a therapy is approved but does not reach those who need it, it has failed in its primary purpose. We need to close the gap between innovation and access through improved process.

2. Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions

The most important incentive can only be viewed as the opportunity to ensure that all people have the same opportunity to live their best life. There is still a significant lack of investment into research for drugs for rare disease compared to more common diseases such as breast cancer. A cheaper option may well be to repurpose existing drugs as new treatment options if they will meet the needs of the patient. How does one decide which rare disease takes priority? An equitable approach needs to be taken and the utilisation of what exists must be most equitably and wisely utilised and distributed. Incentives for developing new drugs and novel technologies must come through efficiencies of workflow and strategic decision making.

The National Strategic Action Plan for Rare Diseases[7] in Action 2.1.5. calls for The Voice of People Living with Rare Disease and their families and carers to be embedded throughout structures and systems that impact rare disease. This must be enabled and supported.

We need to change the way we are working. New partnerships, new practices are necessary to achieve different results and that is needed for the genetic, undiagnosed and rare disease communities. Industry (diagnostics, bioinformatics, cloud, data, pharma and technology), in collaboration with the rare disease community has the opportunity to champion Australia as a leader in research, development and commercialisation or new drugs and medical technologies, repurposing drugs and treatments, to contribute and collaborate, to redefine disease prevention and care and provide optimal and equitable outcomes for patients, while contributing to sustainable genomics Industry.

A collaborative that is independent, trusted, and brings a credible industry perspective to inform and develop genomics policy and to work collaboratively with patients and patient support groups, research, agencies, government and service providers across the genomics and health sectors is critical. It must focus on access and reimbursement, development of drugs and treatments, digital infrastructure and principles to underpin genomics, workforce planning and skills development, consent and consumer-centricity. It needs to enable improved outcomes for Australians as well as the economic strength and capability of Australia to be a global leader in genomics, rare disease treatments and deliver precision health at a population level. And it needs to inform and develop policy, which will enable Australia to:

- Be a world leader in the adoption of genomics in healthcare, and
- Accelerate the potential benefits of genomics including:
    - Improving and saving lives
    - Forging a strategic and coordinated relationship between clinical care, drugs, treatments and technologies
    - Improving health outcomes for population health
    - Contributing to the future affordability of healthcare
    - Strengthening the economy
    - Creating jobs and workforce capacity
    - Providing greater visibility of work underway across the eco-system, and reducing duplication
    - Simplifying consultation processes
    - Providing advice and formulating positions informed by extensive industry expertise

[7] https://rva.blob.core.windows.net/assets/uploads/files/NationalStrategicAPRD.pdf

Federal and State Governments have recognised the promise of genomic medicine and are progressing substantial programs of work to promote the integration of genomic technologies into healthcare. This is not enough. Innovation in approach to discovery, research, development and manufacture of new drugs, treatments and technologies must support this integration. We need to stop seeing things in silos and believe industry is a key group who can come together with consumers to provide a combined, compelling and knowledgeable voice and to improve development practices.

'No-Go' decisions sometimes after years of financial, scientific, regulatory and emotional investment in a product, is regrettable for all parties. A collaborative and supported process could provide a more flexible, non-traditional approach to bringing innovative drugs to market. This is also supported by Action 3.2.3 of the National Strategic Action Plan for Rare Diseases[8] calling for collaborative research in Australia.

3. Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies

Historically, it is the United States that has taken the first major political steps to accelerate the development of rare diseases therapies, as early as 1982, with the U.S. Orphan Drug Act that led to a sharp increase in the number of approved medicines. The U.S. Orphan Drug Act – unlike more recent EU Orphan Drug Regulation, did not include any provision related to the "significant benefit" of new orphan medicines.

This makes the USA today more attractive to investors and companies than other markets, and as companies and funders are seeking to secure higher returns on their investments, with the concrete outcome of seeing many more generations of orphan medicines come to commercialisation first in the United States and then, only much later, elsewhere.

Regardless of geography, the costs and difficulties associated with bringing new drugs and technologies from the bench to the patient are very substantial, not least in relation to the innovative mechanisms of action or vectors employed (e.g. gene and cell therapies).

For a company, and for the investors lending their financial support to it, financing the development of an orphan drug for a rare to ultra-rare disease is still far from being an easy or obvious business choice.

Research funding and incentives are offered and we are grateful as without this support, funding could be refocussed to other segments of the economy offering high returns, rather than health and pharmaceutical research. However, we recognise that incentivising research as a key driver ultimately inevitably leads to inequity. The loudest voices get heard when there is not a strategic and agreed approach.

[8] https://rva.blob.core.windows.net/assets/uploads/files/NationalStrategicAPRD.pdf

For Australia to be a world leader in the development of drugs and novel technologies, relies on:

- Strong, strategic collaborations that include the patient voice
- Active support for new discovery and further development of innovative solutions
- Driving value and affordability across the health and care system
- Sharing of genomic and clinical data, in a safe and ethical way
- A productive, thriving and sustainable workforce
- Trust between all players in the ecosystem
- Economically sustainable investment into rare disease research

A key characteristic of rare diseases is that the knowledge base available is very often limited or even sometimes non-existent. As a result, this translates into barriers to development due to cost. Collaborations could relieve this barrier and be extended to include international participants.

4. Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment.

The current access decision framework, focuses disproportionately on the financial dimension rather than on improving patient outcomes based on the generation of additional clinical data, needs to be majorly overhauled as we feel it is outdated and unproductive. The quest for ways to improve and widen access for patients to orphan medicines must begin farther upstream, at the very moment when medicines are being researched and developed.

All stakeholders have an urgent collective responsibility to shape a new approach that will accelerate the transfer of major scientific advancements into new therapies in a predictable and sustainable way. This approach should encompass the following four-pillar approach:

1) A new roadmap to cut costs and accelerate research and development

Several existing tools, techniques or methodologies allow drugs to come to market in greater numbers and for lower investments by accelerating development timeframes but also reducing the costs incurred by companies from early designs to approval. There is good reason to believe that they would dramatically reduce the cost of research and development for rare disease therapies, reduce the number of patients who need to be involved in clinical research and also reduce the overall time necessary for full development. These innovative approaches, which increasingly find their way into common practice with robust levels of reliability, offer new avenues to design and execute clinical trials. These approaches include:

Clinical trials designed for small populations (e.g. cross-over clinical trials, sequential trials, multi-arm studies) and innovative statistical methods (e.g. Bayesian methods) are accepted in Europe and recommended by the International Rare Diseases Research Consortium (IRDiRC). Prioritising and exploring the feasibility of clinical studies which require less patients to be recruited, which allow faster trials, and ultimately which lower the threshold of investment required while still maintaining high standards on the robustness of data. Australia must be more open to engagement and actively seek partnership with other small population countries to facilitate this.

Utilising patient-relevant outcome measures (PROMs) as essential measurements in rare disease therapy development and consensus has emerged in recent years on the need to develop them more consistently. PROMS should be used in agency decision making. The development of PROMs at an early stage of the product development is critical in instigating patients as much as possible into clinical trials. A more extensive use of PROMs may be possible to present more convincing data at time of the marketing authorisation.

Alternatives to animal models are not currently widespread, although there is increasing use of in-vivo cellular models or in-silico models. This science and technology is rapidly progressing and needs to be further supported through funding from private and public sectors alike. Alternatives to animal models, whenever they exist and attain a high level of reliability, can help save years of research and massive investments in often complex animal studies.

Utilising patient rare disease registries, inclusive of biological and clinical data, should be a major driver in designing advanced clinical trials in rare diseases and in accelerating patients' recruitment for clinical trials. These need to be a coordinated and funded activities. Registries should be created as early as possible to support the development of new therapies and monitor their impact. Registries have added significance when several products are under development for the same disease, forming a cluster of development. Registries should be developed according to common standards, as recommended by IRDiRC at the international level. Such registries would reduce duplication of effort by industry resulting in more effective resource management. The National Strategic Action Plan for Rare Diseases calls for the establishment of rare disease registries. This could be completed as a national priority rather then again putting the burden for establishment on patient support groups.

My Health Records or alternative electronic records must provide the opportunity to register all patients consulting a medical expert, with a minimum common dataset baseline, standard operating procedures, and full interoperability between all health care providers.

Common datasets at the cornerstone of project should include common disease coding, the genotype, the phenotype based on the Human Phenotype Ontology and the functional abilities or disabilities based on the International Classification of Functioning, Disability and Health (ICF). This would bring Australia in line with global projects increasing the utility of those projects for Australians and vice versa. Previous projects in Europe such as RD-Connect have demonstrated benefits of such an approach. The persons affected or potentially affected by a rare disease are the category of the population which will most benefit from genome and exome sequencing and other future advanced technologies: they are at the forefront of new models of research. Combined with the rapidly growing possibilities of bioinformatics, together they will drive major changes on how future clinical trials will be conducted faster, better and cheaper.

Natural history studies are crucial and need to be imbedded into the development process. They are often missing or started at too late a stage when a product development is already very advanced. Natural history studies provide a better knowledge on the course of the disease as well as its multiple and complex features. They enable a more rapid identification of relevant clinical endpoints, as well as a validation of adequate methods to measure them or a better anticipation of how such methods can be developed. The knowledge derived from natural history studies should be utilised when developing a rare disease therapy or when trying to stimulate therapy development in a disease area.

Clinical Research Rare Disease Networks can offer a structured approach to clinical research, can help "de-risk" investment and, ultimately, can generate a greater development of therapies for rare diseases with fully unmet needs. A shared platform, set of methods and tools, as well as

a standard or minimum common dataset (inclusive of genotype and phenotype data) fed by life-long data collection would be a major enabler in speeding up patient identification and recruitment, but also upstream research on new clinical endpoints and biomarkers, as well as their validation at the international level.

They would also greatly accelerate the scaling up of the training of hospital clinicians (who can often be very highly specialised in rare diseases, but far less so in clinical trials, quality data collection and validation, regulatory affairs and health technology assessments). Currently in Australia, these are too often accidental collaborations and come about through consistent lobbying. As we are aware, not everyone has the capacity to do that.

The involvement and partnership of patient advocates in the lifecycle of development, from the very early stages of development onwards, and based on proven good practices should be non-negotiable. It is required to help shape research questions and base them on patients' needs and preferred treatment options. Structured and transparent conversations upstream (e.g. through patient groups' established Community Advisory Boards) offer a reliable vehicle to better anticipate natural history studies, to form a much more accurate understanding of what it means to live with the disease, or still to lay the groundwork for an initial disease registry, for the identification of expert centres or for the elaboration of PROMs.

According to the experience of companies and patient advocates collected to date, a greater participation of patients contributes in no small measure to "de-risk" the development of the product and to reduce the number of possible mistakes the company can make. The value of patient and patient advocate groups cannot be overestimated and needs to be more formally supported at every part of the process.

These strategies are all the more important in the area of rare disease which is characterised by small to ultra-small patient populations, in which the genetic expression of the disease can be very heterogeneous, even between individuals supposedly affected by the same sub-type of diseases. This, in turn, raises questions as to the possibility, or even simply the relevance, of randomised placebo-controlled trials, and underlines the dire need for new methodologies more attuned to the reality experienced by the patients we represent and defend.

If adopted these methods can transform the current model of product development and mutually reinforce one another. If put into practice, they could reduce the cost of research and development for rare disease therapies, reduce the number of patients who need to be involved in clinical studies (this is important from an ethical perspective, but also an important one to maintain a sufficiently large number of naive patients for future clinical trials), and it also reduces the overall time necessary for full product development from proof of concept to approval.

As such, they can best meet the expectations of patients (more and better-quality drugs and technologies), of companies (faster and more predictable approvals), and of national agencies for pricing and reimbursement (less uncertainty and lower development costs). Embracing these activities will empower clinical researchers to develop and run many more trials in Australia for rare and ultra-rare diseases.

2) Early dialogue and cooperation between healthcare systems on the determination of value and on patient access

A new, more sustainable approach for tomorrow must rest on a more systematic and effective practice of collaboration for a seamless and ongoing dialogue on value with product developers, from the very earliest stages of assessment and decision-making onwards, and across all levels of responsibility, with involvement of clinical experts and patient representatives. We urge all stakeholders to embrace collaboration, not doing so is simply laying the ground for difficulties, misunderstandings, tensions and ultimately delayed access. We ask governments, agencies and investors to be considered equally fair. Misalignment is dangerously unsustainable for all stakeholders – not only for patients, but also:

- For regulators for pricing and reimbursement (who may come under criticism for denying access to an approved and much needed medicine on economic grounds only, but also make the conscious decision of leaving patients' unmet medical needs unaddressed, thus running the risk of degraded health outcomes and possibly extra public health costs); and
- For pharmaceutical manufacturers (whose products end up not being commercialised, and whose needs for a predictable market environment and return on investment for their innovation are completely ignored in such a context).

A more sustainable approach is needed to fulfil the needs of all parties. This will involve a more systematic and effective practice of collaboration for a seamless and ongoing dialogue on value with product developers, from the very earliest stages of assessment and decision-making onwards, and across all levels of responsibility, from regulators to HTA authorities and up to funders, with the due involvement of clinical experts and patient representatives.

Early dialogue is multifaceted and covers many different aspects, all of which can be, and have been, explored and applied at different levels and to different extents:

a) **Horizon-scanning** – i.e. a systematic, forward-looking review of which new therapies are likely to enter our national healthcare system and when can better substantiate the implications of new medicines in terms of the possible evolutions to be applied to clinical practice or service design (e.g. when a new therapy offers a marked progress vs. the standard of care accepted until then) but also in terms of budget impact, funding modalities and potential disinvestments or re-prioritisations of resources that may need to affect other therapy areas. This could inform a national research strategy as called for in the National Strategic Action Plan for Rare Diseases.

b) **Early dialogue** at a very early stage, on a specific disease, in a multi-stakeholder format including patients representatives, rare disease clinicians, regulators, HTA experts and industry can help to refine existing assumptions on unmet needs, to review the feasibility of specific clinical or natural history studies, to discuss the relevant endpoints to be considered, the inclusion of patient-relevant outcomes measures, the need for registries … but also to consider the economic assumptions, the potential positive spin-offs utilisation, State strengths and capacities (e.g. new production sites, centres of expertise) or the possibility to bundle other products of the same manufacturer in a wider negotiation.

   Early dialogue at a very early stage on a specific product, either triggered by a company, by an investor or by a patient advocacy group, can help to inform and support major investment decisions on whether the clinical development of a drug or treatment should be continued ("go/no-go") and the expected relevant outcomes, but also an opportunity to clarify the genuine drivers behind a development company's views on the price of a new product (e.g. past and future investment plans, portfolio decisions, anticipations of a future indication, etc).

c) **Tapping into international learnings** - building on the achievements of many pilots in recent years in Europe (e.g. in the 2nd European Network for Health Technology Assessment (HTA) Eunethta.eu (UnetHTA) Joint Action and in the SEED project in particular), the translation of new early dialogue concepts into standard practice has vastly accelerated. The recent HTA Network Reflection Paper on Synergies between Regulators and HTA Issues in Pharmaceuticals from November 2016 sets out a clear and ambitious path, stating that "it is planned that the cross-European processes for parallel advice will become a single common model at the latest by the end of EUnetHTA JA3". EUnetHTA is today advanced, developing the concepts of Early Dialogue, Late Dialogue, and Evidence Generation Plan.

d) Product developers should consider the **specific methods of clinical trials** in small populations as the first and preferred approach, they should anticipate the development of PROMs, natural history studies, initial steps in disease registry development, biomarkers and alternatives to animal models, with the primary objectives of reducing the number of patients involved in clinical studies, reducing the overall time of studies from proof-of-concept to regulatory approval, and reducing dramatically the financial investment in research and development.

e) **Patient organisations be supported to create Community Advisory Boards** composed of trained patient advocates, per disease or per group of diseases, in order to enable a structured, high quality, and transparent dialogue with all stakeholders.

f) All stakeholders should support a much greater integration of care and research so as to accelerate the identification and recruitment of patients in clinical trials, to produce more natural history studies and longitudinal studies, and provide solid economies of scale in a structured, high performance research environment for product development in a more competitive Australia.

3) A transparent cooperation framework between our healthcare system for the determination of fair prices and of sustainable healthcare budget impacts

A transparent framework for the determination of prices based on costs, value and policy-defined priorities, supported by a set of well-defined and well-accepted criteria, will help ensure a better and more evident linkage of drug prices to the fundamental components of their value.

The standard adherence to "value-based pricing", supposedly thought to offer a better and fairer deal by setting a price according to, and in proportion with, the perceived or estimated value of a medicine does not work, in particular for rare diseases:

- In most cases, there is no available information about the current burden of the disease on the healthcare system, nor on the human losses for society.
- An assessment of the value of a given medicine does not automatically deliver an accurate and indisputable figure at which to set the price of that medicine.

Experience shows on the contrary that a product assessed by Health Technology Assessments as having a high therapeutic added value can eventually be priced high or low – and the same largely applies to products assessed as having a moderate therapeutic added value.

Considerations regarding pricing are complex and include a focus on the research and development in investment, the cost of failure associated with other products which did not make it to commercialisation, the cost of investment in innovation towards new products, the development strategy of the company, the return-on-investment expected by investors or the target assigned to the company in terms of shareholder value creation, etc.

We encourage and support efforts to better define the principles and determinants based on which the value of a rare disease therapy should be debated and assessed. However, while stakeholders have spent, and continue to spend, considerable time and resources to refine such principles and methods on value, a vast disconnection continues to exist in real life between the value of a product and the price claimed. Furthermore, when applied to rare diseases, value-based pricing runs into several methodological difficulties that ultimately invalidate it:

- the high level of uncertainty at the time of the initial assessment of the value of an orphan medicine, and the limited knowledge about the disease;
- the uncertainty about the capacity to collect the additional data needed after-market authorization.

If our national healthcare system is serious about achieving the objectives of (a) trying to provide as fast as possible new treatments to patients and as early as possible, in order to assess clinical use evidence to reduce uncertainties, and (b) to pay lower prices than today and to reduce the budget impact for each new product.

If pharmaceutical and biotech companies are serious about the objectives of (a) trying to get their treatments as fast as possible to the wider possible relevant patient populations in the scope of the indication of their new medicine and to collect quality evidence from post-marketing research activities, and (b) to generate revenues as fast as possible during their period of market exclusivity then, we should all recognise these objectives and develop a system that delivers them. A new approach to ultimately offering access to all patients in need will need to be based on a collaborative, transparent set of standards.

These standards must ensure that there is no de-incentivising effect on the private sector or increased unpredictability for investment in pharmaceutical research. Ultimately, an evolution towards fair and often significantly lower prices, in exchange of wider and faster patient access to treatments, must be based on well-negotiated, reliable and mutual commitments. To bring this about we need to put in place:

- A trusted space for a well-informed dialogue, helping stakeholders to engage early.
- A commitment to approaching pricing and reimbursement decisions on a balance of three factors: value, volume, and evidence generation – i.e. its estimated value in its broadest sense, the volume of patients who should receive access to it over time, and plans for the continuous generation of real-world evidence post approval to reduce uncertainties.

While the previous steps focused on the determination of a fair price, the proposed approach would not be complete without also considering the sustainability of the overall impact on healthcare budgets –funding mechanisms and ways in which necessary budgets can be freed up and allocated to enable access to the new drugs, novel technologies and other treatment that rare disease patients need.

Payment based on outcomes as a system may be more suited for innovative medicines in general, rather than for new drugs for rare diseases for which the process for real-world evidence generation may at the moment still present added complexities. However, such a system may already be applicable for certain well-defined rare diseases for which the collection of real-life clinical use data or of real-world evidence is already an established practice.

Australia should seek mutually beneficial collaborations to join forces for the common sourcing, price negotiation and eventual procurement of all or certain medicines, access to trials and innovations. The Asia Pacific Economic Forum could be a catalyst here.

4) A continuum approach to evidence generation linked to healthcare budget spending

The proper assessment of an innovative technology must include reviewing at the very moment when the innovation is being rolled out or implemented in real clinical practice and even later when we can see a 360° view of the full impacts of the innovation. The reduction of uncertainties is an essential need, not only for our national healthcare system but also to a no less important extent for patients and clinicians.

New drugs for rare disease pose many different challenges for pricing and reimbursement, with higher levels of uncertainty on efficacy and effectiveness. This is particularly true, but not exclusively, when a product is approved with a conditional marketing authorisation, or an approval under exceptional circumstances, or a marketing authorisation at the end of phase 2 studies. These earliest possible approvals are generally based on risk-benefit assessments: the patients' unmet medical needs are high, the product has a good safety profile and sufficient evidence on efficacy to go ahead for approval and often enough evidence to support significant benefit over existing treatments if any. Living evidence models could be utilised as is being done in a rapidly changing health environment for COVID-19 clinical guidelines.

This approach of early access, seeking the right trade-off between risks and benefits, and in line with patients' treatment preferences is to the benefit of patients to speed up access to new therapies and address their medical needs. However the level of evidence available is often not sufficient for health technology assessors to perform a stringent effectiveness assessment and for well informed decisions on pricing and reimbursement.

This level of uncertainty is linked to many different elements: the nature of the therapy itself (e.g. in the case of a new class of products with a new mechanism of action or a gene therapy), the heterogeneity of the patient populations in what is generally assumed to be a same family of rare diseases (the natural history of rare diseases always offers a large range of patient courses of the disease, with phenotype-genotype links not always so well defined in each sub-population), or still the difficulty or even impossibility to conduct a clinical trial on broader patient populations and therefore the impossibility to fully predict how the new drug shall perform in real life.

Our current practice paves the way to what can be very acute tensions further downstream between the drug manufacturers and other stakeholders, tensions which are usually resolved through fierce negotiations and commercial deals (e.g. clawbacks, extra rebates, caps, etc) focusing solely on the price and budget impact. In Australia, we need to create more opportunity to develop a critical mass of highly specialised clinicians and researchers to share expertise, knowledge and resources across borders.

We need to adopt common standards with regard to data collection and interoperability and continue to develop practice in virtual clinical consultations for rare disease patients across the country, ensuring sharing of best practices and technologies in diagnosis and care, the collection of shared common datasets, the development of disease patient registries, etc that reach every person include remote and regional, indigenous, CALD communities and people with intellectual disability to be truly accessible.

Australia must build public trust in our data management, health industry and agencies. There are models such as the Patient Participant Panel in the UK which are great examples of deliberate action to build public trust in data management.

It is essential that all stakeholders take full stock of what exists around the world, and act accordingly when planning or implementing decisions related to evidence generation and the optimal use of current and future therapies.

In Conclusion

It is a profound misunderstanding and a misleading approach to believe that the debate on access to medicines can be summarised and reduced to a merely technical discussion about approval processes.

Instead, it is our view that this debate remains fundamentally and stubbornly a political one, the cornerstone of which is our direct responsibility in deciding today what we collectively want our communities to stand for, and in contributing to a political framework that better serves the genetic, undiagnosed and rare disease communities.

We need to ask:

- Are we ready to agree that, from a social justice perspective, it is right and just to give all persons living with a rare disease the treatments they so urgently need, as soon as these treatments exist and are available?
- Are we ready to agree that it is no less important, ethical and desirable to improve the health of a small fraction of the population with dire unmet medical needs, than to address the needs of the multitude?

Indifference and/or Inaction is not an option. Patients and patient support groups generally, do not have the capacity or energy to participate in endless submission writing while their loved ones suffer. It's time to stop placing the burden on the community and to work collaboratively for more rapid, more effective and, more innovative solutions. We are privileged to serve and represent them.