BIA response to MHRA consultation on draft rare disease therapies regulatory framework

Overview

The MHRA is consulting on proposals for a new regulatory framework for rare disease therapies. The draft framework is available here.

The BIA strongly welcomes the MHRA's leadership in developing a new regulatory framework for rare disease therapies. We agree that the UK has the foundations to be a global leader in rare disease innovation and the new framework provides an opportunity to cement this.

In order to fully deliver on this ambition, we recommend several improvements to ensure the framework is practical, attractive to developers, and capable of delivering patient access.

- **Broaden the eligibility criteria:** Replace the strict prevalence threshold of 1 in 50,000 with a an alternative approach whereby treatments for conditions with a prevalence below 1 in 50,000 could automatically qualify for the framework, and rare conditions with a higher prevalence threshold are assessed based on unmet need, disease severity, and demonstrable barriers to conventional development and licensing. The framework should apply more widely across rare diseases, not only ultra-rare conditions.
- **Provide greater regulatory clarity:** Work with stakeholders to develop clear criteria for Rare Disease Designation, Investigational Marketing Authorisation (IMA), evidentiary thresholds, review timelines, and decision-making processes. Case studies and examples should be included to improve predictability.
- **Create a viable reimbursement pathway:** Work with NICE, NHS England and other system partners to develop an alternative assessment and reimbursement pathway for rare disease therapies which does not use cost-effectiveness-based assessment, instead adopting a budget impact-based approach which considers the clinical and socioeconomic value of the treatment. Regulatory flexibility alone will not improve patient access or encourage investment.
- **Improve incentives for developers:** Introduce clear incentives for developers in the pathway, which could include market exclusivity provisions, fee reductions, and enhanced advice.

- **Enhance system and international alignment**: Improve system alignment, including with newborn screening programmes and other related policy and initiatives, and work towards international alignment to support global development programmes.
- **Address evidentiary uncertainty explicitly:** Acknowledge that residual uncertainty is inherent in rare disease development and provide clear guidance on how uncertainty will be balanced against unmet need and disease severity.
- **Simplify the pathway:** Streamline the proposed eight-step process, clarify mandatory versus optional stages, and provide expected timelines to reduce complexity and administrative burden.

Consultation questions

Overall aim of the framework and the involvement of patient views

1. In your view, is it desirable for more pharmaceutical treatments for rare diseases to be brought into a regulated pathway rather than used 'off-label' as many are at present? Please explain your answer.

We agree it is desirable for more rare disease treatments to be brought into a regulated pathway rather than used 'off-label', as this would provide more robust oversight of efficacy and safety and a potential route for more equitable patient access across the UK and better commercial predictability for developers.

However, the regulated pathway must be sustainable, pragmatic and provide a clear route to reimbursed access. Without a clear path to commercialisation, the pathway will not provide a route to access for NHS patients.

There will also be treatments outside of the proposed scope of this framework (including greater than 1 in 50,000 prevalence) which would benefit from being brought into a regulated pathway. We address this further in answer to question 5.

2. The consultation sets out challenges associated with the development and regulation of treatments for rare diseases. Please identify any other challenges you are aware of that have not been considered or elaborate on those already identified. (optional)

The consultation paper captures challenges associated with population size, randomised controlled trials (RCT) infeasibility, natural-history gaps, endpoint validation, and modality complexity. However, some of these challenges are not consistently recognised throughout the framework. For example, in section 5.5.5 on IMA application, the paper states that "strong emphasis is placed on clear definition, reliable endpoints, and high quality, traceable data", which appears to contradict other parts of the paper which recognise the challenges associated with developing all of these for rare disease products.

Other challenges associated with the development and regulation of rare disease treatments include:

- **Reimbursement:** Navigating HTA processes to enable reimbursed patient access is already challenging in rare diseases, with only 50% of orphan medicines approved by the EMA reimbursed for use in England.[1] The proposed IMA framework would require reimbursement decisions to be made at an earlier stage with less mature data. This challenge is not sufficiently addressed in the paper.
- **Diagnosis and newborn screening:** Diagnosis remains one of the central bottlenecks in the development and regulation of rare disease treatments. Many conditions take years to identify due to non-specific symptoms, limited clinician awareness, and the sheer number of distinct rare diseases. Newborn screening offers a route to earlier diagnosis for some conditions, but the UK's programme currently only includes ten rare diseases, and there is no clear or timely link between a treatment being developed or approved and the corresponding condition being added to the newborn screening panel, meaning patients can go undiagnosed even once an effective therapy exists. The framework should encourage alignment with newborn screening and other early diagnosis programmes, so that evidence can be generated to support the rollout of screening in parallel to IMA approval.
- **Defining the patient population:** Defining the patient population is often challenging in rare diseases due to issues including disease heterogeneity, diagnostic limitations, and a lack of data. This challenge should be recognised in relevant parts of the framework, including in determining eligibility.

[1] EFPIA WAIT Indicator 2025, https://www.efpia.eu/media/mnfdwzax/efpia-patients-wait-indicator-2025.pdf

- **CMC development:** CMC development can present challenges in rare diseases, especially under accelerated timelines. While the framework appropriately recognises the need for risk-based and proportionate GMP requirements for rare disease therapies, further clarity is needed on how this will operate in practice. Developers would benefit from guidance on process validation expectations, comparability requirements, stability programmes, analytical testing expectations and lifecycle management for therapies manufactured at very small scale or using established platforms. Examples would improve regulatory predictability and investment confidence.
- **Class-effect safety signals:** Where several products in a mechanistic class have generated adverse findings, a sponsor must proactively differentiate its candidate. The framework asks for "expectations based on class effects" in the projected safety profile (section 6.4) but gives no methodology for how a sponsor rebuts an adverse class narrative, nor how the MHRA weighs disease-context differences (e.g. distinct target tissue or patient population) against a class signal observed in a different indication.
- **Dose justification with sparse data:** The paper endorses model-informed drug development and in silico modelling (section 6.4.2) but does not address how dose-selection uncertainty is resolved at the IMA stage when conventional dose-ranging is not feasible.
- **International data:** For very small populations, clinical trials are multi-national to generate sufficient data for regulatory and reimbursement approvals. The paper does not specify a mechanism to support international data within the framework, nor does it set out how data generated in the UK via this framework can be used to support regulatory decisions in other countries.
- **Cross-border follow-up:** The paper acknowledges scenarios in which patients travel to the UK for treatment and subsequently return to their home country (section 5.5.5), but leaves the operational approach undefined, noting only that it "may involve the establishment of local trials." Without this detail, this could create significant operational uncertainty for sponsors.
- **Assessment of clinical benefit:** Rare diseases are often heterogeneous and may affect multiple aspects of a patient's health and functioning, making reliance on a single endpoint inappropriate. The framework should recognise that evidence of benefit may be generated through a range of complementary measures and provide clarity on how the MHRA will apply a totality-of-evidence approach when assessing therapies for rare diseases, particularly where

treatment effects are demonstrated across multiple domains of disease burden rather than through a single endpoint alone.

- **Managing evidentiary uncertainty:** Rare disease development frequently requires regulatory decisions to be made on the basis of more limited datasets than would be expected in more common conditions. The framework should acknowledge that residual uncertainty is often an inherent consequence of rare disease development and provide greater clarity on how such uncertainty will be considered within benefit-risk assessments and regulatory decision-making.
- **Paediatric development requirements:** Many therapies eligible for the framework will target rare or ultra-rare paediatric conditions. Given the close regulatory oversight and ongoing alignment on evidence generation that the framework is designed to facilitate, a separate Paediatric Investigation Plan (PIP) may represent an additional administrative burden without providing meaningful regulatory benefit. The framework should therefore clarify whether, for products treating rare or ultra-rare paediatric conditions accepted into the framework, paediatric requirements could be streamlined and PIP waivers considered where scientifically justified.

3. Patient engagement is a key feature of the framework. How can patients and their families and carers contribute most effectively to the regulatory process? Please explain your answer. (optional)

The emphasis on patient engagement within the framework is welcomed. Particularly in rare diseases, the patient community is central to the clinical development and regulatory approval of new treatments. The proposed framework will enable more risk-based decision making, and the involvement of patients is crucial in determining balanced risk-benefit assessment.

In section 4.2, the paper sets out the importance of open, accessible communication with patients and carers through an ongoing informed consent process, as part of enabling more patient-centred and risk-proportionate regulation. This is welcome, however more detail is needed on how this will enable a two-way dialogue which involves listening to patients about their experiences and concerns. More detail is also needed on how this will work in practice in a way which is compliant with other areas of legislation and guidance. For example, in section 4.2.1, it states that developers provide clear and ongoing communication to patients, carers, patient organisations, prescribers and clinical teams. This is likely to create compliance difficulties due to legal restrictions on companies interacting with patients, and the terms of the ABPI Code of Practice. Further clarity is also required

on how the proposed ongoing consent process would be implemented for different types of therapies (including one-off gene therapies), and this process will require detailed guidance from the Health Research Authority (HRA).

Engagement with patient advocacy groups (PAGs) is central to this process, as recognised in section 4.2.2. The role of PAGs should not be limited to communication and supporting patient understanding, as they also have a broader role to play in representing patient perspectives and informing decision-making, particularly in areas such as unmet need, meaningful outcomes, treatment burden, risk-benefit considerations and acceptable uncertainty. Further guidance should be provided on how to best facilitate the meaningful participation of PAGs, which will require sufficient notice, resourcing and structure. Engagement should be documented and auditable so its influence on regulatory decisions is transparent.

The framework would benefit from explicitly recognising the complementary role of patient experience data collected both within and outside of clinical trials. This includes systematically collected evidence such as patient-reported outcomes, observer-reported outcomes, patient preference studies, and real-world data reflecting lived experiences. Such data, collected through scientifically robust methodologies, can demonstrate a broader and more representative patient perspective, and can be decisive where endpoints are not yet validated. Patient experience data provides valuable context on outcomes that matter to patients (e.g. signs and symptoms that matter most, impact on quality of life, treatment burden, and risk tolerance) and can meaningfully complement traditional clinical trial evidence and patient engagement activities.

We therefore recommend that the framework more explicitly encourages the generation and use of patient experience data by sponsors, and clarifies how such data can inform regulatory decisions, including the development of novel endpoints.

Elements of the framework

4. A fundamental question is how much evidence is enough for a decision to be made on the use of a medicine? Using novel approaches to evidence generation, the pathway aims to strike a balance between the nature and amount of data needed to support the safety and efficacy of a treatment before patients can access it and the time it takes to generate that data. Do you agree that the proposed approach has found the appropriate balance?

- **Strongly agree**

- **Agree**
- **Neither agree or disagree**
- **Disagree**
- **Strongly disagree**

Please explain your view on this fundamental consideration (optional)

We support the framework's intention to enabling a patient-centred benefit-risk approach to managing uncertainty in regulatory decisions, and section 6.4 is helpful in setting out different methods for risk-proportionate evidence generation to enable this.

However, we are not able to conclude whether the proposed approach has found the appropriate balance without greater understanding and examples of how this will be applied in practice. Much of the framework's practical operation depends upon decision criteria, evidentiary thresholds, review timelines and legal tests which have yet to be published. Until these are defined it is difficult to determine whether the framework has achieved the correct balance between flexibility and regulatory robustness. Publication of illustrative examples and decision criteria should therefore be a priority.

For example, the criteria and threshold for granting an IMA are not specified in the paper, so it is not clear whether this will strike the appropriate balance. MHRA should engage closely with relevant stakeholders as it develops the criteria, which should set out the minimum safety and plausibility data package required for an IMA and how surrogate or unvalidated biomarkers can support these decisions.

In addition, the framework should provide greater clarity on how the MHRA will assess clinical benefit in situations where a treatment effect cannot be adequately captured through a single validated endpoint. Many rare diseases are heterogeneous, affect multiple aspects of health and functioning, and lack well-established outcome measures. In these settings, regulatory decision-making may need to draw on a totality-of-evidence approach, considering evidence generated across multiple complementary sources, including biomarkers, functional assessments, patient-reported outcomes, natural history data and other clinically meaningful measures. Clarifying how such evidence will be integrated into benefit-risk assessments would improve predictability for developers and support the evaluation of therapies for complex rare diseases.

The framework should also recognise that some degree of residual uncertainty is an inherent consequence of rare disease development. Small patient populations, limited natural history

knowledge and challenges in conducting conventional clinical trials mean that evidentiary uncertainty cannot always be eliminated prior to approval. As such, the criteria for granting and maintaining an IMA should clearly set out how uncertainty will be weighed against factors such as disease severity, unmet need and the feasibility of generating additional pre-authorisation evidence. Similarly, the framework should acknowledge that robust external controls or natural history datasets may not always be available in rare conditions and provide clarity on how evidence packages will be assessed where such data are limited or unavailable.

Furthermore, in order for the proposed framework to be operational, data and evidence requirements must be feasible for developers and system partners to meet. This includes post-market monitoring requirements, which should reflect what is realistically achievable and clinically meaningful in small, heterogeneous populations.

5. Defining rarity is a challenge due to the limitations of using a fixed prevalence (frequency) limit, changing disease classifications and the evolving nature of genetic and molecular disease definitions. Whilst retaining some flexibility, the framework is targeting diseases with a prevalence of around 1 in 50,000 of the UK population, which is deliberately distinct from the orphan designation threshold of 25 in 50,000. Do you consider that this threshold considered appropriate to encourage development of treatments for rare diseases?

- **Strongly agree**
- **Agree**
- **Neither agree or disagree**
- **Disagree**
- **Strongly disagree**

Please provide your rationale if another threshold should be considered (optional)

We recommend that the MHRA adopts an alternative approach whereby treatments for conditions with a prevalence below 1 in 50,000 could automatically qualify for the framework, and those with a higher prevalence threshold are assessed based on unmet need, disease severity, and demonstrable barriers to conventional development and licensing. MHRA could provide examples to indicate the types of treatments which may qualify outside of the 1 in 50,000 threshold.

The proposed prevalence criteria of 1 in 50,000 for eligibility to the framework is too restrictive, even with potential flexibilities, as this will limit the applicability of the framework to ultra-rare diseases. The name of the framework and the designation suggests that the aim is to encourage development

of novel treatments for all rare diseases, which is misleading if only ultra-rare therapies are eligible. This could also harm the UK's reputation if international investors feel misled. A more flexible approach, as outlined above, would better reflect the realities of rare disease development and ensure that patients with serious rare conditions, and companies developing treatments for them, are not excluded from the potential benefits of the framework.

If MHRA considers an overarching prevalence threshold necessary, we would encourage alignment with the UK and European definition for rare diseases of 1 in 2,000 prevalence.

Furthermore, any prevalence threshold should be used as a guide rather than a strict eligibility requirement. This is especially important in rare diseases where it can be difficult to accurately define patient populations due to data limitations and diagnostic challenges. Moreover, many rare diseases are made up of genetically-defined subpopulations, which could benefit from targeted therapies. The framework has significant potential to support the development of novel therapies for these targeted therapies, and it is important that the criteria does not exclude them.

Section 1 recognises that elements of the framework may also be applied to higher prevalence conditions that fall within the orphan designation. MHRA should set out more detail on how this would work in practice to enable greater regulatory flexibility to be applied to these products.

6. Do the Scientific Opinion and Designation steps add a tangible incentive for research and development of rare therapies? Are they best delivered at predefined points or on a flexible basis depending on the individual development? Please explain your rationale. (optional)

The Scientific Opinion and Designation steps have the potential to add tangible value, especially for SME biotech companies where they may be used to support investor confidence. However, they do not provide economic incentives for development.

MHRA should clarify how early engagement meetings and Scientific Opinions will differ to normal scientific advice, and when each route should be used.

These steps should be delivered on a flexible basis depending on the individual development. The framework should enable interactions between the MHRA and developers to occur iteratively throughout development, and the framework needs to be resourced within MHRA to enable this. The MHRA should specify the timeframe from requesting a Scientific Opinion to the developer receiving this, so that developers can plan effectively. Transparent fee structures should be established to avoid financial uncertainty and support planning, particularly for smaller companies.

The timing of publication of Scientific Opinions should also be flexible and agreed with individual developers, as in some instances the developer may not want a Scientific Opinion made publicly available during the early development stages. In these cases, the Scientific Opinion could be published as part of the IMA public assessment report, to allow for transparency and accountability at a time point that is more suitable for information to be shared amongst a wider audience. Developers should also have the opportunity to redact commercially confidential information prior to publication.

We agree that negative opinions and decisions should not be published. MHRA could instead publish aggregated and anonymised data on applications and decisions, similar to the data it provides on ILAP. MHRA should also provide developers with clear, substantive feedback when their application is unsuccessful.

We disagree with the MHRA's proposal that there would be no right of appeal for negative Scientific Opinions or negative Designations. This removes a procedural safeguard available under conventional routes and may become a disincentive for developers to use the framework. This is particularly important given that Designation and IMA decisions will involve significant scientific judgement and may materially affect a developer's ability to progress a programme.

7. Do you agree that open registration of all clinical trials which are linked to the pathway and transparent sharing of safety and efficacy data—especially from early-phase studies—will help in any of the following ways? (optional)

- **To foster public trust**
- **To enhance scientific learning**
- **To support sustainability of the framework**
- **To support development of treatments for rare (and more common) conditions**

Please add any further comments here (optional)

Open registration and transparent data sharing have the potential to support all four of these aims, if implemented in the right way. Data sharing should be accompanied by well-managed information sharing, ensuring that data is communicated effectively to appropriate stakeholders. Safeguards should also be in place to protect patient privacy.

Public registration of studies and sharing results is already required in the existing clinical trial regulations, and existing mechanisms should be leveraged rather than creating new administrative requirements to reduce burden on businesses.

Crucially, these requirements must be implemented in a way which avoids eroding the commercial protection a sponsor needs to justify investment. Early-phase efficacy data are highly commercially sensitive and mandatory early disclosure could deter developers from the pathway.

8. Proposals for managing market exclusivity have not been addressed in the framework document. How should market exclusivity be managed to balance the potential benefits of incentivising investment with the risk of creating unintended barriers to future innovation? (optional)

The framework should include robust market exclusivity provisions, recognising the importance of protected periods in incentivising investment and ensuring continued innovation in the rare disease space. Exclusivity periods should be clearly defined to give developers certainty.

Because UK orphan exclusivity runs from the date of marketing authorisation, the framework should clarify that the exclusivity period commences on conversion to a full or conditional marketing authorisation, not on grant of the IMA. This would provide an incentive to seek an IMA while ensuring it is not eroded by early authorisation on immature evidence, which is especially important as reimbursement processes for products with an IMA have not yet been established.

The framework should also clearly set out how market exclusivity will be applied in the context of platform technologies, which this framework seeks to enable. Orphan exclusivity blocks “similar” products in the same indication, and it is not clear how “similar” would be defined to platforms in a way which strikes the right balance between incentivising development and avoiding creating unintended barriers to future innovation, including follow-on innovation and therapies targeting subgroups within broader diseases.

Lastly, for products treating rare/ultra-rare paediatric conditions eligible for the framework, given the close regulatory oversight and proactive alignment on sufficient data requirements the framework facilitates, the requirement for a Paediatric Investigation Plan (PIP) should be waived. In these cases, an automatic additional two years market exclusivity should be granted upon grant of the conditional or full MAA, where therapies would otherwise have earned PIP-related rewards.

9. Should decisions regarding market exclusivity and reimbursement be made on the basis of a combination of pre-determined transparent criteria rather than fixed prematurely within the framework? (optional)

Market exclusivity and reimbursement should be treated separately. Market exclusivity should be clearly defined within the framework, as set out in our response to the previous question.

Reimbursement decisions should be based on transparent, pre-defined principles but not fixed prematurely. Existing HTA requirements are not fit for purpose for rare diseases, with only 50% of orphan medicines authorised by the EMA between 2021 and 2024 having been reimbursed for use in England.[2] This framework rightly recognises the need for an alternative approach to managing uncertainties in rare disease, and an alternative approach is also needed in reimbursement decisions and the MHRA should work closely with NICE, SMC and DHSC/NHS England to ensure alignment. A lack of clarity on the end-to-end pathway is likely to deter investors.

The framework references managed access as a potential route to reimbursement, and while this may be appropriate in some cases, we are concerned that it will not provide a viable route to access for all medicines in this pathway. Managed access still requires treatments to demonstrate cost-effectiveness at the end of the managed access, which is challenging for many innovative rare disease medicines due to unavoidable evidential uncertainty. Moreover, previous managed access agreements for rare disease medicines have demonstrated challenges with real-world data generation and its acceptance by NICE committees.

The BIA has set out proposals for an alternative assessment pathway for rare disease medicines which does not use cost-effectiveness-based assessment, instead adopting a budget impact-based approach which considers the clinical and socioeconomic value of the treatment.[3] We believe this approach is necessary in addressing existing barriers to patient access to rare disease treatments, as well as providing a sustainable and risk-proportionate route to access for treatments which go through this IMA framework. This proposal should be considered by system partners as part of the solution in enabling an end-to-end pathway for rare disease therapies which can actually deliver faster and broader patient access.

[2] EFPIA WAIT indicator 2025, https://www.efpia.eu/media/mnfdwzax/efpia-patients-wait-indicator-2025.pdf
[3] BIA report https://www.bioindustry.org/static/1dd67412-3ae4-4817-989afa4e1b18a0fc/BIA-RDIG-Unlocking-patient-access-to-innovative-rare-disease-medicines.pdf

10. The scope of the framework includes authorised medicines that are being repurposed (being used to treat a different condition). Do you agree that the framework is suitable for these cases?

- **Strongly agree**
- **Tend to agree**
- **Undecided**
- **Tend to disagree**
- **Strongly disagree**

Please tell us why you have given that response (optional)

We support the inclusion of repurposed medicines within the framework.

The framework should provide more detail on how it would be applied to repurposed medicines, including appropriate data requirements where efficacy evidence is limited. It should also set out how market exclusivity and data protections will apply to repurposed medicines, and how already licensed indications would be impacted.

11. Below we have listed six elements of the proposed framework. To what extent do you agree with each of these as an important element?; We are interested to hear of your further thoughts on them.

an adaptive regulatory pathway for very small populations (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

This is the core rationale of the framework and is essential for addressing the unique challenges of developing therapies for small populations.

defined entry criteria (such as rarity, severity, unmet need and biological plausibility (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

Entry criteria are important for predictability and consistency. However, as set out in our answer to Q5, we do not support a 1 in 50,000 prevalence being used as a strict cut-off. The criteria should guide rather than constrain eligibility, with case studies and a decision tree to provide guidance to developers about the most appropriate regulatory pathway for their product.

The framework uses the term 'rare diseases' throughout, and while not all rare disease products will be suitable for the pathway, many of them could benefit from the additional support and flexibility it provides. In order to deliver for the 3.5 million people living with a rare disease in the UK, it must have much broader application than ultra-rare disease, not only "by exception" as currently proposed.

early regulatory engagement and designation (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

This is critical to reduce uncertainty and align development plans. The framework should enable ongoing iterative engagement between relevant stakeholders. The MHRA should ensure the new framework is resourced with the right expertise to provide this service with predictable turnaround times and reliable, consistent advice.

the use of prior knowledge, platform data and adaptive evidence generation approaches (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

These are very important elements of the framework in enabling timely and scientifically robust development in small and heterogeneous patient populations.

To realise the full potential of these approaches, the framework should explicitly support the use of real-world evidence – including natural history data, patient registries, and external control arms – in supporting regulatory decisions, while recognising that these datasets may not meet traditional evidentiary standards.

MHRA should also provide further clarity regarding the extent to which manufacturing, analytical, non-clinical and clinical platform data may substitute for product-specific evidence at Designation, IMA and Marketing Authorisation stages. Case studies demonstrating acceptable evidence packages for different platform types would improve predictability for developers.

MHRA should also confirm who may hold platform prior knowledge. Section 9.2 assumes that the sponsor holds the platform, but in practice the platform is frequently owned and operated by a technology or material provider – for example an LNP formulation process, an AAV producer cell line, a GMP plasmid or mRNA manufacturing process, or a guide RNA design-and-synthesis workflow. MHRA should clarify whether platform prior knowledge can be held and attested to by a technology provider rather than the sponsor, and whether that knowledge is portable across sponsors.

The framework should also clarify whether UK platform recognition will be aligned with the FDA's platform technology designation programme,[4] and whether a platform accepted by the MHRA would be reusable in EMA and FDA submissions.

[4] FDA platform designation program; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/platform-technology-designation-program-drug-development

ongoing safety monitoring with periodic review (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

Ongoing safety monitoring is important in enabling IMAs to be granted, ensuring therapies remain safe and effective throughout their lifecycle. It will also be important to enable transition to fill MA. Periodic reviews allow for timely identification and mitigation of risks, maintaining public trust and regulatory compliance.

Post-market reporting requirements must be proportionate and feasible for developers of all sizes, and reflect what is realistically achievable and clinically meaningful in small, heterogeneous populations. There are a number of existing mechanisms for ongoing safety monitoring (e.g. DSUR), which can be utilised in this framework to minimise the creation of additional reporting requirements.

The Clinical Monitoring Plan should be defined further so that developers have a clear understanding of what is required. The proposed "centralised collaborative solution for the collection of long-term safety data" should also be set out in more detail, including resourcing and governance.

the potential to progress to full marketing authorisation over time (optional)

A. Very important
B. Important
C. Moderately important
D. Slightly important
E. Not important

Further comments (optional)

A clear pathway to progress to full marketing authorisation is very important for the long-term sustainability of the framework and to incentivise developers to use it.

The framework should explicitly recognise that the need for IMA arises from inherent challenges in evidence generation associated with rare diseases, and therefore ensure that full MA requirements are proportionate, targeted, and feasible.

Moreover, the framework should also clearly define the benefits associated with an IMA approval, including a suitable process for reimbursement, and other specific incentives which justify the investment and potential risks for the developer. Otherwise, developers may prefer to use the standard route to MA.

12. Do you have questions or observations about any aspects of the framework including those we have not specifically asked about? (optional)

- **Complexity of the process:** The 8-step process set out in section 5.5 risks appearing long and complicated. Although we recognise the role of each step, there is a risk that the framework appears too complicated as it is presented here. MHRA should consider if any steps can be streamlined, such as combining ethics considerations with the IMA application as part of a joint MHRA/HRA assessment, and whether Rare Disease Designation could be a direct outcome of an Early Engagement Meeting. MHRA should also clearly set out in the diagram which steps are mandatory, and which are optional/dependent on the product. It should also provide expected timelines for each step, and case studies to demonstrate how products would progress through these steps.
- **Scope of the IMA:** The scope of the IMA is not clear from the framework, including limits to its use and what the sponsor can do with it, such as in relation to advertising and health system engagement. For products granted an IMA, it will be critical for the IMA holder to work with relevant specialist centres to support clinician education, appropriate patient identification, monitoring, risk minimisation, real-world data collection and balanced scientific exchange about the evolving evidence base. MHRA should therefore provide clarity through guidance on promotional activity, legitimate scientific exchange and medical information provision for products with an IMA, as well as expectations for educational materials, specialist-centre engagement and communication of residual uncertainty to healthcare professionals and patients.
- **Overlap of clinical trial and marketing authorisation rules:** The proposals state that “all development within the Rare Disease Therapies Regulatory Framework should comply with the principles of the clinical trial framework” (section 5.5.5) but with an IMA also enabling access

outside the clinical trial setting, it is not clear how the clinical trial rules will overlap with marketing authorisation rules, including how ethics approvals will work, and the role of the HRA. This should be clearly set out.

- **Alignment with other MHRA programmes:** The final guidance should clearly set out how the pathway interacts with other MHRA programmes, including ILAP, EAMS and the aligned MHRA/NICE pathway. MHRA should provide a decision tree to help developers identify the right pathway and programmes for their products. MHRA should also avoid using terminology which could cause confusion with other initiatives, such as 'early access' which is typically understood to refer to access before licensing.
- **System alignment:** The paper recognises the importance of system alignment is critical to the success of the framework in recognising that "regulatory flexibility alone will not deliver patient benefit without credible routes to funded access". We understand that many of these areas, including reimbursement, sit outside the MHRA's remit, however we encourage all system partners to provide a joined-up proposal.
- **Global alignment:** Products will not be developed just for the UK market, so MHRA should set out plans to strengthen international alignment on rare disease therapies to ensure UK-developed evidence is accepted internationally.
- **Newborn screening and early diagnosis:** For some rare genetic diseases, the clinical benefit of treatment is greatest when patients are identified and treated before symptoms emerge. The framework should encourage alignment with newborn screening and other early diagnosis programmes, so that evidence can be generated to support the rollout of screening in parallel to IMA approval. This includes clarifying whether an IMA would be considered sufficient evidence of availability and clinical utility to support assessment for inclusion in such programmes.
- **Manufacturing and GMP expectations:** The framework should provide greater clarity on the manufacturing and GMP expectations applicable at different stages of development and progression through the pathway. Given the challenges associated with developing products for very small patient populations and the accelerated, iterative nature of the proposed framework, the MHRA should consider whether risk-based and proportionate approaches to CMC and GMP requirements could be applied where appropriate, while maintaining product quality, safety and regulatory confidence.

- **Master files:** We welcome the MHRA's consideration of expanded master file approaches for biological products and advanced therapies. However, the current proposal may not be workable where the MA holder is using a third party supplier to produce the material. Section 9.3.1 rejects the closed-part concept for biological active substances on the grounds that an MA holder cannot take responsibility for the product without full and transparent access to quality-related data, and Section 9.3.2 therefore proposes an open dossier in which confidentiality is managed through commercial agreements rather than regulatory compartmentalisation. This conflates two distinct categories of information: the data an MA holder requires in order to control critical quality attributes and own the benefit-risk assessment, and the manufacturing know-how a third-party supplier uses to produce the material. The former must be open to the MA holder; the latter need not be, and requiring its disclosure will either cause suppliers to withhold data – degrading dossier quality – or transfer proprietary process knowledge to every sponsor purchasing a material.
- **Collaborative development models:** The framework is welcome in recognising applications from both commercial and non-commercial organisations. Further guidance would be helpful regarding regulatory responsibilities where therapies are developed through partnerships between academic institutions, NHS organisations and commercial partners.
- **N-of-1 and highly individualised therapies:** The framework is welcome in explicitly recognising therapies developed for a single patient or very small numbers of patients. Given the increasing importance of personalised genetic medicines, MHRA should provide dedicated guidance or case studies setting out evidentiary expectations, GMP requirements, monitoring obligations and routes to authorisation for these products.
- **Fees:** More detail is needed on fees for each stage of the pathway, and the guidance should include examples to illustrate potential total fees for a developer using the pathway. We also encourage MHRA to provide fee waivers or discounts for SME developers to ensure that fees are not prohibitive.
- **Appeals:** We do not support MHRA's proposal that there is no right of appeal for negative Scientific Opinions, Designations or IMA decisions. We particularly oppose this in the case of IMAs, as this is a decision which will have an impact on companies' rights and obligations, and they should be able to challenge a decision if it is not taken in line with the law. Without this right of appeal, developers will be deterred from using the framework.

- **Broader application:** In section 5.2, the paper states that "elements of this guidance can be considered for conditions with higher prevalence when randomised controlled trials are not feasible or are impractical", but it is not clear how this would happen, and whether developers would still need to apply for a Rare Disease Designation in order to benefit from specific elements of the framework. We encourage MHRA to exercise regulatory flexibility as required for all rare disease treatments.
- **Implementation:** The framework notes that the full implementation of an IMA would require legislative change, while other elements of the framework could be implemented immediately. Further detail is needed on the expected timelines and processes for these changes, including opportunities for further stakeholder engagement and consultation.

Impact of the framework

13. In your view, will the flexibility and adaptability of the proposed pathway provide sufficient encouragement to developers of treatments for rare diseases to bring them within a regulated pathway? Please explain your answer.

- **Strongly agree**
- **Agree**
- **Neither agree or disagree**
- **Disagree**
- **Strongly disagree**

Please add any further comments here and if you don't think this aim will be achieved please explain why.

The flexibility of the proposed framework is welcome. However, treatments will not be developed just for the UK market, so international alignment is important in encouraging developers to use the pathway.

Moreover, regulatory feasibility is only one area of consideration for developers. Commercial feasibility is also crucial, and the framework does not include enough detail on reimbursement or incentives for developers to have confidence that their product could be commercially viable in the UK market. For reimbursement to be possible for products with an IMA, it is clear that alternative approaches are needed which can provide access to these treatments despite limited data sets and inevitable uncertainties.

The MHRA should incorporate clear incentives into the pathway to encourage developers to use it. We recommend that the MHRA considers the following incentives as part of the framework:

- Data exclusivity and market protection – exclusivity periods should start at conversion to MA instead of granting of an IMA, or products in this pathway should benefit from longer exclusivity periods.
- Linking the framework to enable pre-approval Orphan Drug Designation in the UK, for example it could be awarded alongside Rare Disease Designation.
- Free or discounted iterative advice from rare disease experts for developers in the pathway, including joint scientific advice with NICE where suitable.
- Concierge-style support for developers to navigate processes, with a dedicated account manager assigned at the point of Rare Disease Designation to support the developer in navigating processes, including the steps in the MHRA framework, as well as reimbursement and access.
- Support for RWD collection, utilising UK health data assets.

MHRA could also explore introducing a priority review voucher (PRV) mechanism, similar to the US model, with transferable vouchers awarded to developers in the pathway. However, interest in PRVs should be tested more widely prior to implementation as it may not be as attractive in the UK compared to US market.

Furthermore, the success of the pathway will also depend on the predictability of regulatory decisions, and the speed and quality of interactions.

14. In your view, will the pathway achieve its aim of supporting innovation while safeguarding patients and maintaining confidence in regulatory decision-making?

- **Strongly agree**
- **Tend to agree**
- **Undecided**
- **Tend to disagree**
- **Strongly disagree**

Please add any further comments here and if you don't think this aim will be achieved please explain why. (optional)

The framework has the potential to support innovation while safeguarding patients and maintaining confidence in regulatory decision-making. Its emphasis on early engagement, flexible evidence generation, and iterative approvals aligns with the needs of rare disease therapies, particularly for conditions with high unmet need.

However, there are areas where the framework could be improved to fully achieve its aims and provide further clarity on the mechanics and likelihood for a company to achieve a return on investment, including through reimbursement and incentives. This is crucial to ensuring the framework is effective in supporting innovative medicines and improving patient access to new treatments.

15. In your view could this framework reduce barriers to patient access, including time and cost, and in turn help reduce overall treatment costs?

- **Strongly agree**
- **Agree**
- **Neither agree or disagree**
- **Disagree**
- **Strongly disagree**

Please add any further comments here and if you don't think this aim will be achieved please explain why.

While the framework has the potential to reduce development timelines and enable faster patient access, it is unlikely that this will tangibly impact the cost of development. While it has the potential to reduce some upfront development costs, developers could incur greater maintenance costs for many years, especially if there is not sufficient support for data collection.

Moreover, products will not be developed just for the UK market, so international regulatory alignment is critical in enabling development costs to be reduced.

As set out in previous answers, faster access for NHS patients will only be achieved if there are appropriate mechanisms for reimbursement for products with an IMA, which will require a different approach from HTA bodies and the NHS. The framework references managed access as a potential route to reimbursement, and while this may be appropriate in some cases, we are concerned that it will not provide a viable route to access for all medicines in this pathway. Managed access still requires treatments to demonstrate cost-effectiveness at the end of the managed access, which is

challenging for many innovative rare disease medicines due to unavoidable evidential uncertainty. Moreover, previous managed access agreements for rare disease medicines have demonstrated challenges with real-world data generation and its acceptance by NICE committees.

The BIA has set out a proposal for an alternative assessment pathway for rare disease medicines which does not use cost-effectiveness-based assessment, instead adopting a budget impact-based approach which considers the clinical and socioeconomic value of the treatment.[5] This proposal should be considered by system partners as part of the solution in enabling an end-to-end pathway for rare disease therapies which can actually deliver faster and broader patient access.

About the BIA

The BioIndustry Association (BIA) is the voice of the innovative life sciences and biotech industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation.

We have over 600 members spanning human health and non-health biotech, including start-ups, scale-ups and established global companies. Our membership also encompasses the full UK ecosystem, including non-commercial research institutions and service providers.

[5] BIA report https://www.bioindustry.org/static/1dd67412-3ae4-4817-989afa4e1b18a0fc/BIA-RDIG-Unlocking-patient-access-to-innovative-rare-disease-medicines.pdf