

Smart Pharma
CONSULTING

Orphan Drug Access in Euro-5

Country-specific
Access & Ecosystem

November 2026

Pharma companies should adopt an integrated, country-specific launch strategy built around three priorities: Secure access – Protect value – Drive uptake

Five key takeaways

WHAT MATTERS ACROSS THE FIVE MARKETS

1 APPROVAL ≠ PATIENT ACCESS
Regulatory approval, national funding and treatment delivery are distinct milestones

2 CLINICAL EVIDENCE DRIVES VALUE
Comparative benefit, unmet need and uncertainty shape HTA[1] and price outcomes

From January 2028, orphan drugs will be subject to EU-level Joint Clinical Assessments (JCA)*

3 PROTECT SUSTAINABLE NET PRICING
Anticipate rebates, expenditure controls, reassessments and evidence commitments

4 LOCAL DELIVERY DRIVES UPTAKE
Diagnosis, referrals, expert centers and hospital capacity determine real access

5 INTEGRATE LAUNCH FUNCTIONS EARLY
Align Market Access, Medical, Regulatory and Commercial from development

COUNTRY-SPECIFIC PRIORITIES

HAS[2] SMR[3] / ASMR[4] – CEPS[5] terms – AAP[6] – FSMR[7] / CRMR[8] networks

AMNOG[9] evidence – €30M threshold – Specialist uptake

AIFA[10] P&R[11] and innovativeness – Regional implementation

2026 HTA framework – National P&R – CSUR[12] pathways

NICE[13] TA[14] / HST[15] value case – NHS[16] commissioning readiness

THREE PRIORITIES FOR SUCCESSFUL LAUNCH & GROWTH

SECURE ACCESS	PROTECT VALUE	DRIVE UPTAKE
Regulatory – HTA – Funding	Pricing – Evidence strategy	Referral – Treatment capacity

**** National authorities will retain responsibility for assessing overall therapeutic value and making pricing and reimbursement decisions***

Sources: Smart Pharma Consulting analysis of Euro-5 regulatory, HTA, P&R and rare disease access frameworks

[1] Health Technology Assessment – [2] French National Authority for Health – [3] Clinical Benefit – [4] Clinical Added Value – [5] Economic Committee on Healthcare Products – [6] Early Access Authorization – [7] Rare Diseases Healthcare Networks – [8] Rare Diseases Reference Centers – [9] German Pharmaceutical Market Reorganization Act – [10] Italian Medicines Agency – [11] Pricing & Reimbursement – [12] National Health System Reference Centers, Services and Units – [13] National Institute for Health and Care Excellence – [14] Technology Appraisals – [15] Highly Specialized Technologies – [16] National Health Service

In France, HAS[1] assesses clinical and economic value, CEPS[2] negotiates prices, and national authorities determine reimbursement and funding conditions

Market access in France (1/2)

Timelines (months)

~22*

Marketing Authorization

- EU centralized application, evaluation by the EMA and approval by the European Commission
- ANSM[3] controls drug safety aspects and plays a key role in early access authorizations[4]

Health Technology Assessment

By the French National Authority for Health (HAS)

Economic and Public Health Assessment Committee (CEESP)

- Conducts health economic assessments for innovative drugs…
- … claiming ASMR[5] I, II, III with estimated 2nd-year sales > €20M
- The CEESP conclusions inform CEPS price negotiations

Transparency Committee (CT)

Assessment of:

- Medical benefits (SMR[6]) driving reimbursement rates
- Improvement in medical benefits (ASMR) driving price negotiations
- Target population driving price-volume agreements

Pricing & Reimbursement Decision

National Union of Health Insurance Funds (UNCAM)

- Determines statutory reimbursement rate for outpatient drugs, based on the SMR assessment

CEPS (Economic Committee for Healthcare Products)

- Sets[7] ex-factory prices for reimbursable drugs, incl. confidential rebates, price-volume arrangements and expenditure-control mechanisms
- Sets[7] applicable prices and tariffs for hospital drugs excluded from the diagnosis-related group funding system (T2A)

Ministry of Health (MoH)

- Formal reimbursement and hospital-listing decisions…
- … and publication in the Official Journal

** Note: Average time to availability as of January 5, 2026, for orphan drugs approved by the European Medicines Agency (EMA) between 2021 and 2024*

Sources: HAS 2025 activity reports and French Social Security Code – EFPIA Patient WAIT Indicator Survey, IQVIA (May 2026) – Smart Pharma Consulting analyses

[1] French National Authority for Health – [2] Economic Committee on Healthcare Products – [3] French National Agency for Medicines and Health Products Safety, under the responsibility of the Ministry of Health (MoH) – [4] HAS grants early access authorizations, with ANSM assessing the presumed efficacy and safety of medicines that have not yet received marketing authorization – [5] Clinical Added Value – [6] Clinical Benefit – [7] Based on HAS assessments

If orphan drugs are not automatically reimbursed, many patients with rare diseases benefit from full statutory coverage through the ALD[1] scheme or specific hospital funding arrangements

Market access in France (2/2)

Reimbursement procedure by the National Health Insurance Fund

- Drug expenditure is largely funded through the statutory health insurance system, funded by social contributions and taxation, which provides coverage to almost the entire population
- The public healthcare resources are completed with private health insurances to insure the co-payment of the healthcare system
- In parallel with the pricing dossier, a reimbursement dossier is sent to the Transparency Committee (CT) after Marketing Authorization has been granted
- Reimbursement status and rate (100%, 65%, 30%, 15%, 0%) are decided on the basis of the product's perceived medical benefit, calculated taking into account the following criteria:
  - Severity of the disease
  - Product efficacy and safety
  - Importance of the drug in the treatment strategy
  - Intention for curative, preventive or symptomatic treatment
  - Benefit in terms of public health
- Orphan drugs are not automatically reimbursed, and even when they are, the reimbursement rate is not necessarily 100%

Pricing procedure by the CEPS[2]

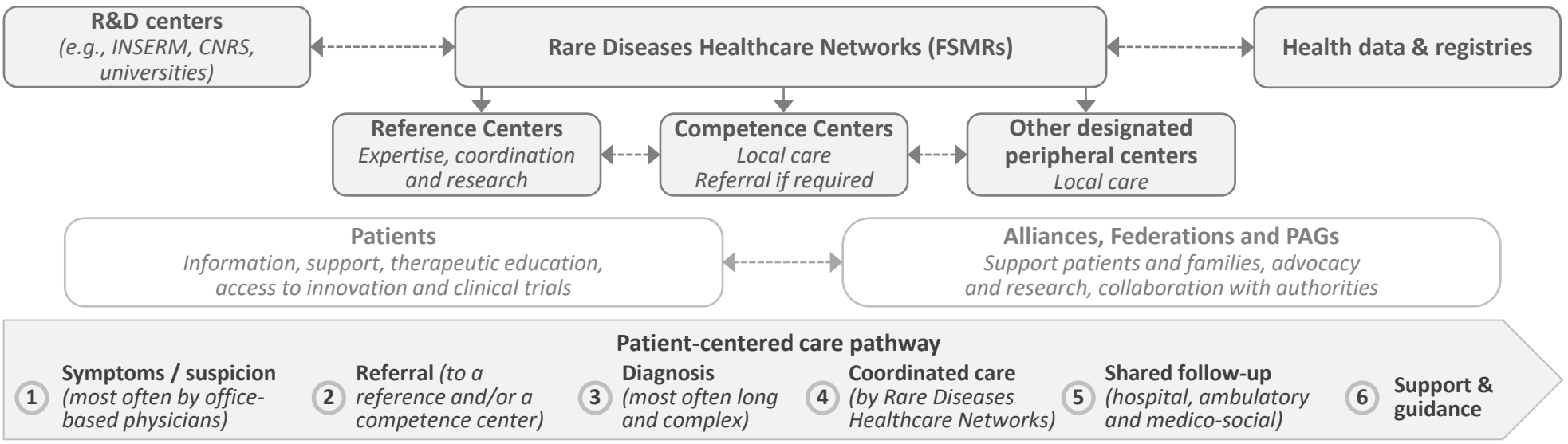
- The pricing dossier submitted by pharmaceutical companies to the CEPS is designed to justify the price requested for the orphan drug
- Price-review provisions, durations and reassessments depend on the applicable CEPS framework and negotiated product-specific terms, considering:
  - Product profile (MA, orphan designation, reimbursement)
  - Clinical value & unmet medical needs (CT opinion, comparators)
  - Target population (epidemiology, patient funnel, likely uptake)
  - Pricing rationale (requested price, treatment costs, prices of drugs of the same class, EU price comparisons)
  - Economic value & budget impact (cost-effectiveness, Budget Impact Analysis)
  - Sales forecast (volumes, revenue, scenarios and rebate strategy)
  - Implementation & post-launch commitments (supply security, RWE plans and follow-up evidence)
- The CEPS dossier translates the CT clinical value into a justified price, forecast expenditure and negotiated financial conditions

Sources: CEPS and pharmaceutical industry associations, Framework Agreement (September 2026) – Smart Pharma Consulting analyses

[1] Long-Term Condition – [2] Economic Committee for Healthcare Products

The rare diseases ecosystem is highly patient-centric, with dedicated pathways designed to shorten complex diagnoses and ensure coordinated care across specialized networks

Rare disease ecosystem in France



- France has 23 Rare Diseases Healthcare Networks (FSMRs) which coordinate stakeholders involved in rare disease care. They bring together national Rare Diseases Reference Centers (CRMRs) and regional Rare Diseases Competence Centers (CCMRs), facilitating diagnosis, patient referrals, specialized treatment and coordinated follow-up
- PNDSs[1] are standardized, expert-developed guidelines for the diagnosis, treatment and follow-up of specific rare diseases. Developed and disseminated by the relevant CRMRs, in collaboration with CCMRs, they aim to harmonize and improve patient care nationwide
- Healthcare networks and expert centers are becoming more specialized, registries and R&D centers more data-driven and collaborative
- PAGs are becoming key co-decision partners, creating opportunities for pharma companies to engage early and co-develop initiatives to drive access and adoption

Sources: Smart Pharma Consulting analyses

[1] *National Diagnostic and Care Protocols*

Orphan drugs benefit from a simplified initial AMNOG* assessment, but exceeding €30M in annual SHI[1] expenditure triggers a full comparative evaluation, potentially impacting prices

Market access in Germany (1/2)

Timelines (months)

~4*

Marketing Authorization

- EU centralized application, evaluation by the EMA and approval by the European Commission
- BfArM[2] controls drug quality, safety, efficacy, and oversees early access programs[3]

AMNOG Early Benefit Assessment

- G-BA[4] is responsible for the AMNOG Early Benefit Assessment (EBA)
- G-BA determines the extent[5] of additional benefit, relevant patients, requirements for appropriate use, may mandate post-launch data collection for subsequent assessments
- G-BA may commission IQWiG[6] to perform scientific assessments vs. a defined comparator and cost-benefit assessments

Pricing Scenarios

A – SHI expenditure ≤ €30M p.a.

- Additional benefit is legally presumed based on marketing authorization
- The GKV-SV[7] negotiates the reimbursement price using the G-BA assessment[5] and other statutory pricing criteria but…
- … no formula converting it into a price
- Pharma companies retain some negotiation flexibility, but no premium is guaranteed

B – SHI expenditure > €30M p.a. with demonstrated added benefits

- A full benefit dossier, incl. comparative evidence vs. comparator is required and IQWiG may be asked to assess evidence
- The GKV-SV uses the G-BA conclusions as the foundation for negotiations
- A recognized added benefit does not guarantee a premium price

C – SHI expenditure > €30M p.a. without demonstrated added benefits

- A full benefit dossier, incl. comparative evidence vs. comparator is required
- If not demonstrated added benefit, the GKV-SV normally applies a comparator cost-based approach or…
- … assign a reference pricing where applicable

** AMNOG: Arzneimittelmarktneuordnungsgesetz (German Pharmaceutical Market Reorganization Act) links the reimbursement price of innovative medicines to their demonstrated added therapeutic value*

** Note: Average time to availability as of January 5, 2026, for orphan drugs approved by the European Medicines Agency (EMA) between 2021 and 2024*

Sources: G-BA, AMNOG Benefit Assessment (§35a SGB V) – GKV-Spitzenverband, Reimbursement Price Negotiations (§130b SGB V) – EFPIA Patient WAIT Indicator Survey, IQVIA (May 2026) – Smart Pharma Consulting analyses

[1] Statutory Health Insurance – [2] Federal Institute for Drugs and Medical Devices – [3] For chemical drugs. For vaccines and biological drugs, it is under the responsibility of the PEI (Paul-Ehrlich-Institut) – [4] Federal Joint Committee – [5] Six levels of additional benefits: major, considerable, minor, not quantifiable, non, inferior – [6] Institute for Quality and Efficiency in Health – [7] National Association of Statutory Health Insurance Funds

Orphan drugs can be reimbursed from commercial launch, but negotiated prices apply retrospectively from Month 7, with additional statutory rebates and expenditure controls

Market access in Germany (2/2)

AMNOG reimbursement and pricing timeline

Month 1

- Newly authorized orphan drugs can generally be marketed and reimbursed by SHI immediately after commercial launch, at price freely set by the manufacturer

Months 1-6

- The G-BA conducts the AMNOG early benefit assessment, with special provisions for orphan drugs. Reimbursement continues during the assessment

Months 7-12

- The manufacturer and GKV-SV negotiate the reimbursement amount, based on the G-BA decision and applicable statutory pricing criteria

Months 13+

- The reimbursement amount is implemented; if no agreement, arbitration[1] determines it. The amount generally applies retrospectively from Month 7

Mandatory discounts and financial agreements

Standard statutory rebate	Generally, 7% for applicable drugs in 2026, subject to exemptions[2] and specific arrangements
Additional statutory rebate from Jan. 2027	An additional 8.5%, bringing the total to 15.5% for applicable patented drugs, subject to exemptions[3] or qualifying replacement arrangements
Price-volume agreements	AMNOG agreements must address expenditure-related volume provisions. Where no specific arrangement is negotiated, statutory price-adjustment mechanisms can apply from the fourth year following launch
Confidential reimbursement price option	An optional mechanism under §130b(1c), subject to a further 9% reduction in the agreed reimbursement amount when elected
Individual SHI rebate agreements	Additional agreements may be negotiated with health insurers, including volume-related rebates, expenditure caps or outcomes-based arrangements

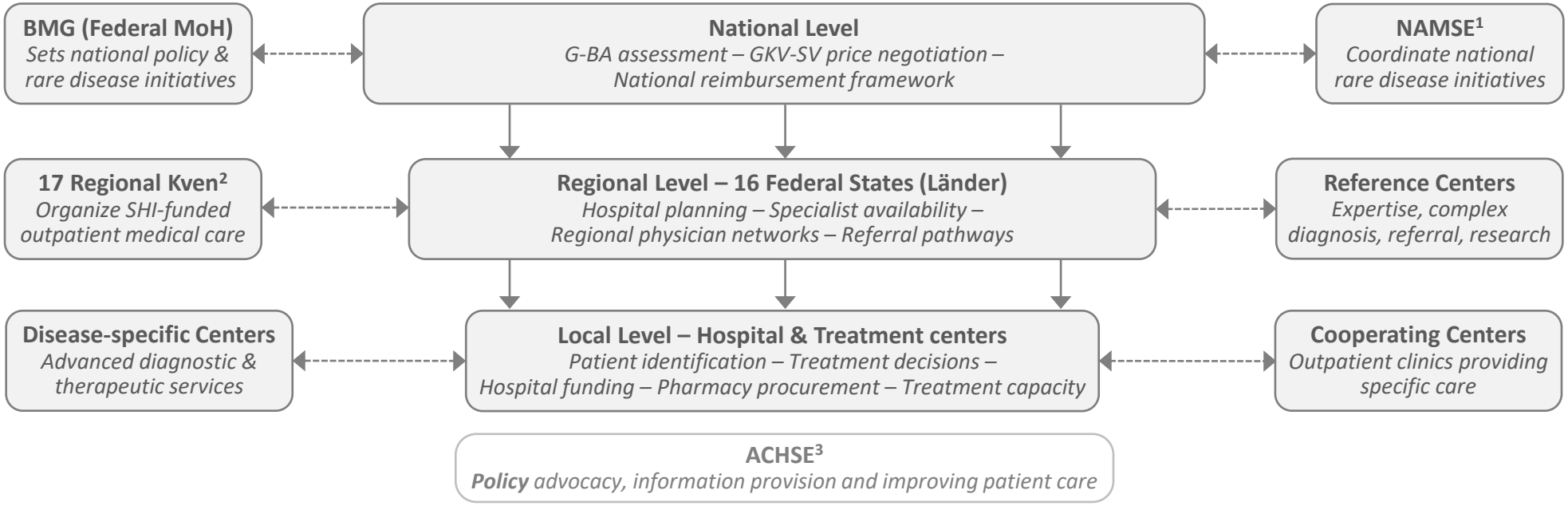
Reimbursement does not guarantee immediate patient access which depends on specialist identification, referral pathways, hospital funding and procurement, prescribing processes, qualified treatment capacity and treatment-center readiness

Sources: G-BA, AMNOG Benefit Assessment (§35a SGB V) – German Social Code V, §§130a–130b – BMG, 28 August 2026 – Smart Pharma Consulting analyses

[1] By an arbitration board. Pharma companies and GKV-SV can also ask for a cost-benefit assessment prepared by the IQWIG (Institute for Quality and Efficiency in Health), if not satisfied with the arbitration decision, and price discount may be renegotiated – [2] If rebates prevent the company from financing R&D costs of the drug – [3] For new API (Active Pharmaceutical Ingredient), when at least 5% of relevant clinical-trial participants were enrolled at German sites

Germany offers early reimbursement after launch, but sustainable pricing depends on the AMNOG assessment and uptake on specialist networks and treatment-center readiness

Rare disease ecosystem in Germany



Pharma companies' priorities should vary by type of therapy

- **Outpatient orphan drugs**: disease awareness, specialist identification and education, diagnosis, referral networks and long-term adherence
- **Hospital-administered orphan drugs**: Hospital reimbursement pathways, pharmacy logistics, budgets and treatment protocols
- **Gene and cell therapies:** qualified treatment centers, capacity, referral process, patient eligibility, long-term monitoring and RWE

Sources: Smart Pharma Consulting analyses

[1] National Action League for People with Rare Diseases – [2] Regional Associations of Statutory Health Insurance Physicians – [3] Alliance for Chronic Rare Diseases (National patient umbrella organization)

AIFA[1] integrates clinical and economic evaluation with national price negotiations, while reimbursement terms, innovativeness status and managed entry agreements shape access

Market access in Italy

Timelines (months)

~15*

Marketing Authorization

- EU centralized application, evaluation by the EMA and approval by the European Commission
- AIFA[1] oversees national pharmacovigilance, inspections and early access schemes (Law 648/96 and the 5% Fund), newly authorized drugs pending P&R[2] decisions are classified as C(nn)

Pricing & Reimbursement process

1. AIFA – Orphan fast-track

- Orphan P&R filing starts after a positive CHMP[3] opinion
- Priority review with a target timeline of 100 days
- AIFA reviews evidence and budget impact

2. CSE[4] – Dossier assessment

- **Clinical assessment**: Therapeutic value, place in therapy, innovativeness
- **Economic assessment:** Treatment costs, budget impact on the SSN[5], economic evidence supporting P&R negotiations and potential MEAs[6]

CSE adopts technical-scientific opinions and supports P&R negotiations

3. AIFA – Formal approval and determination

- Following the applicable approval process, AIFA issues the formal P&R determination

4. Official gazette – National P&R effectiveness

- Publication of the national decision, incl. reimbursement classification[7], agreed price and applicable prescribing or monitoring conditions

Five key components of the CSE assessment for orphan drugs

1. Unmet medical needs: severity of the disease, alternative treatments
2. Clinical evidence & uncertainty: the company must substantiate the clinical relevance and robustness of the available data
3. Therapeutic innovativeness: based on a) unmet medical need, b) added therapeutic value and c) quality of evidence
4. Economic value & budget impact: eligible population, treatment cost, economic rationale, consequences for SSN expenditure
5. Management of uncertainty: where appropriate, negotiations may address financial or outcome-based MEAs, supported by monitoring arrangements or additional evidence collection

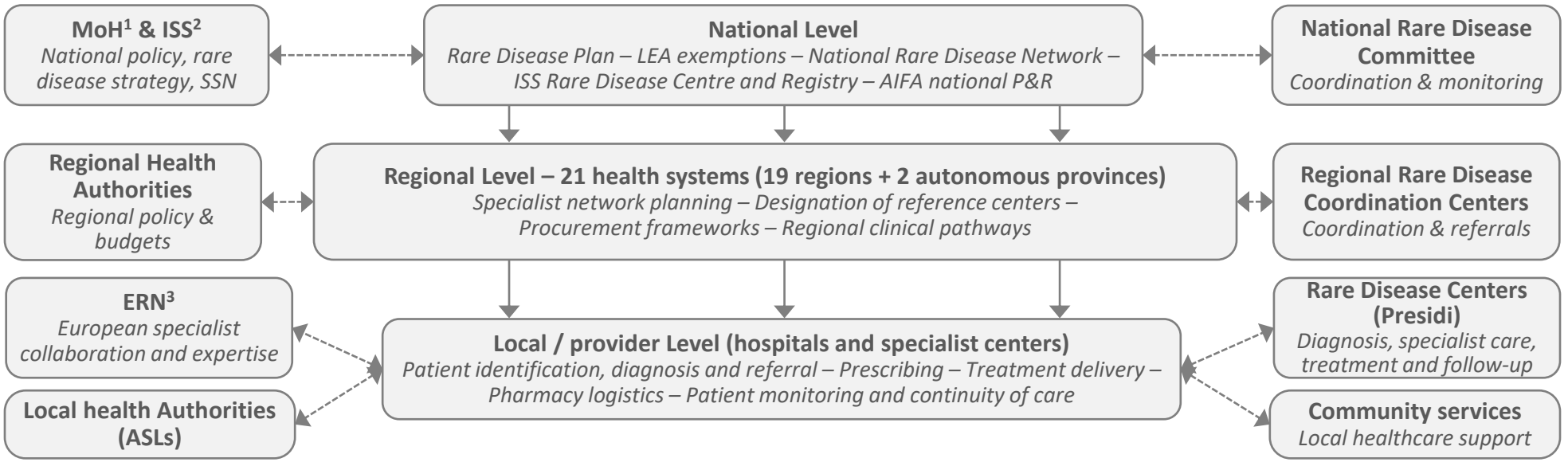
** Note: Average time to availability as of January 5, 2026, for orphan drugs approved by the European Medicines Agency (EMA) between 2021 and 2024*

Sources: AIFA, CSE responsibilities (2024–2026) – AIFA P&R dossier guidelines (2026) – Determination Pres/966/2025 – EFPIA Patient WAIT Indicator Survey, IQVIA (May 2026) – Smart Pharma Consulting analyses

[1] Italian Medicines Agency – [2] Price and reimbursement – [3] Committee for Medicinal Products for Human Use – [4] Scientific & Economic Committee for Medicines – [5] National Health Service – [6] Managed Entry Agreements – [7] Class A: reimbursed (essential drugs), Class H: reimbursed (hospital-only drugs), Class C: non-reimbursed and free pricing drugs, Class C (nn): authorized medicine pending P&R

AIFA establishes national P&R conditions, while regional health authorities, local health services and specialist centers determine how treatment is delivered to patients

Rare disease ecosystem in Italy



- **Regional Health Authorities:** Implement national reimbursement decisions, organize networks, budgets and procurement frameworks[4]
- **Regional Coordination Centers:** Coordinate rare disease networks, referral pathways and collaboration among expert centers
- **Local Health Authorities (ASLs):** Organize local care, community services and drug distribution arrangements according to regional rules
- **Hospitals / Presidi:** Confirm diagnoses, prescribe or administer treatments, and monitor outcomes
- **UNIAMO[5] / PAGs**: Advocate for patient needs, treatment access, information and improved care pathways

Sources: Smart Pharma Consulting analyses

[1] Ministry of Health – [2] Italian National Institute of Health, the leading public institution for scientific research, public health surveillance and technical expertise which operates under the supervision of the MoH – [3] European Reference Network – [4] Regional implementation and formulary requirements are subject to national provisions applicable to orphan drugs – [5] Italian Federation of Rare Diseases

Spain's 2026 HTA reform strengthens orphan drug evidence-based evaluation, while the Ministry of Health and CIPM[1] retain pricing and reimbursement authority

Market access in Spain

Timelines (months)

Marketing Authorization

- EU centralized application, evaluation by the EMA and approval by the European Commission
- AEMPS[2] controls drug quality, safety, efficacy, may grant early access authorizations and defines commercialization eligibility

~19*

Pricing & Reimbursement Assessment

1. AEMPS – Medicines HTA Office

- The AEMPS is the lead authority responsible for the health technology assessment of drugs, including orphan drugs:
  - Clinical assessment: comparative effectiveness, safety, added clinical value and evidence uncertainty
  - Non-clinical assessment: economic, organizational, ethical and other relevant dimensions

2. HTA Adoption Group

- Integrates assessment findings and other relevant evidence to inform subsequent national P&R decisions, but does not determine them

3a. DGCYF[3]

- Decides if the drug should be reimbursed based on its technical evaluation after the IPT[4] and the pharma company's value dossier

3b. CIPM

- Interministerial decision (incl. national and regional public authorities) which sets the national reimbursed industrial price

4. MoH – Formal P&R Resolution

- Once the price and the applicable conditions of use within the Spanish National Health System (SNS) has been agreed upon at the CIPM, the decision to reimburse the drug is formalized by an express resolution of inclusion or no inclusion in the provision
- The responsibility for the provision and funding is decentralized to the 17 autonomous communities

The Royal Decree 415/2026, which separates scientific HTA from subsequent pricing and reimbursement decisions, is expected to be implemented progressively

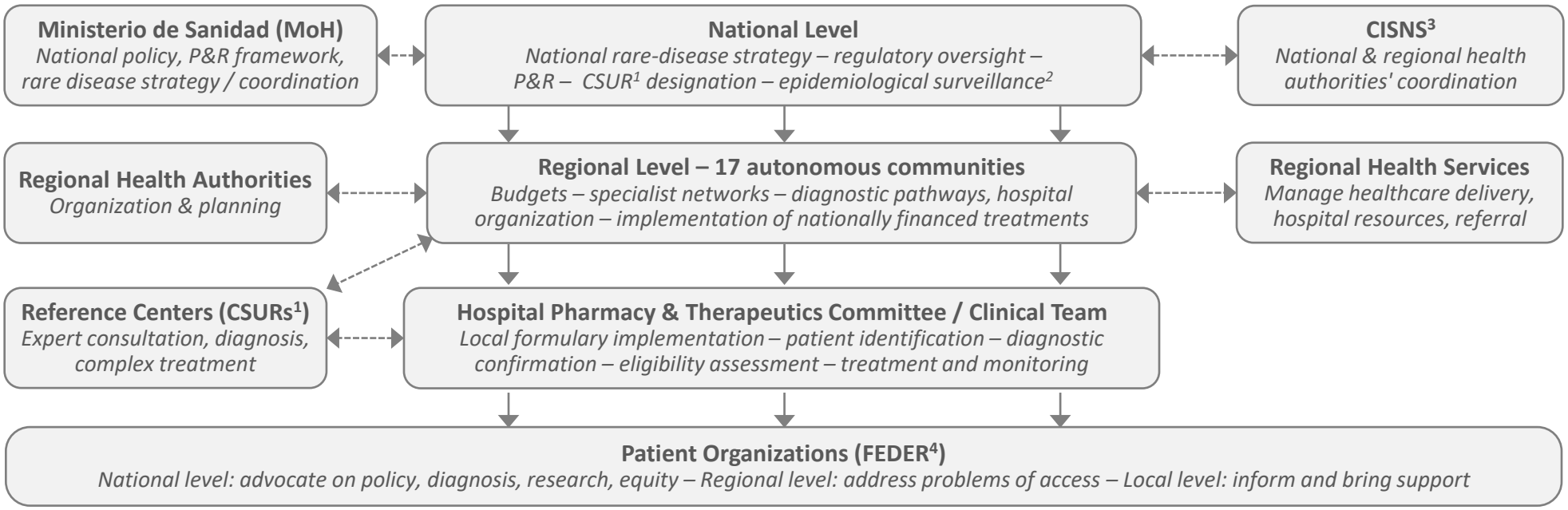
** Note: Average time to availability as of January 5, 2026, for orphan drugs approved by the European Medicines Agency (EMA) between 2021 and 2024*

Sources: Royal Decree 415/2026 (BOE, 29 May 2026) – AEMPS, New HTA System (17 July 2026) – Ministry of Health – EFPIA Patient WAIT Indicator Survey, IQVIA (May 2026) – Smart Pharma Consulting analyses

[1] Interministerial Commission on Medicine Prices – [2] Spanish Agency for Medicines and Medical Devices – [3] Directorate-General for the Common Services Portfolio of the National Health System and Pharmacy – [4] Therapeutic Positioning Report

National reimbursement applies across Spain, but effective orphan drug access depends on regional healthcare organization, specialist-center readiness and patient referral pathways

Rare disease ecosystem in Spain



- **CSURs** are critical enablers of access to complex orphan drugs, providing specialized expertise and supporting referrals across autonomous communities. They provide multidisciplinary diagnosis, complex treatment, expert consultation, training and coordination with other hospitals for one or several rare conditions and participate in the European Reference Networks (ERNs), where applicable
- **The use of orphan drugs** having received national SNS financing is governed by the nationally established conditions
- The main **bottleneck to access** is the difficulty of identifying patients and guiding them to the appropriate specialist center

Sources: Spanish Ministry of Health, Rare Disease Strategy and CSUR framework – Royal Decree 1302/2006; Order SND/433/2026 – FEDER – Smart Pharma Consulting analyses

[1] National Health System Reference Centers, Services and Units – [2] Rare-disease registry, which aggregates epidemiological information supplied by regional rare-disease registries – [3] Interterritorial Council of the SNS – [4] National federation representing rare-disease patient organizations

UK commercialization requires MHRA[1] marketing authorization, while NHS[2] funding depends on HTA recommendations and commissioning arrangements that differ across the 4 nations

Market access in the UK

Timelines (months)

9*

Marketing Authorization – MHRA

- Marketing authorizations granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) apply across the four UK nations
- UK orphan status is assessed by the MHRA, alongside the marketing authorization application
- Several MA fast-track pathways exist (e.g., IRP Route B[3], ILAP[4], EAMS[5])

Health Technology Assessment (4 Nations)

England

- The NICE[6] assesses the clinical and cost-effectiveness of new medicines
- It issues recommendations on NHS reimbursement through TAs (Technology Appraisals) and HST (Highly Specialized Technologies) evaluations
- Positive NICE recommendations normally trigger NHS funding within three months, subject to applicable exceptions

Wales

- NICE recommendations apply to NHS Wales for most new drugs
- The AWMSG[7] assesses selected medicines not evaluated by NICE, where a specific Welsh clinical need or NHS benefit is identified
- The AWMSG Scrutiny Panel determines which drugs require assessment
- The New Treatment Fund supports timely implementation of recommended treatments

Scotland

- The Scottish Medicines Consortium (SMC) evaluates the clinical and cost-effectiveness of newly licensed medicines
- It advises NHS Scotland Health Boards on which medicines should be accepted for routine use
- A dedicated ultra-orphan pathway supports access and additional evidence collection for eligible medicines

Northern Ireland

- The Department of Health (DoH) reviews and endorses NICE technology appraisals for Northern Ireland
- Endorsed NICE recommendations are implemented through the Health and Social Care (HSC) system
- Local endorsement and implementation procedures must be considered when planning patient access

** Note: Average time to availability in England as of January 5, 2026, for orphan drugs approved by the European Medicines Agency (EMA) between 2021 and 2024*

Sources: MHRA – ILAP and EAMS guidance (2026) – NICE, Technology Appraisal and HST guidance – SMC – AWMSG –HSCS – EFPIA Patient WAIT Indicator Survey, IQVIA (May 2026) – Smart Pharma Consulting analyses

[1] The MHRA is an executive agency of the department of health (DoH), which controls the efficacy and safety of drugs – [2] National Health Service – [3] International Recognition Procedure Route B follows a qualifying assessment by a reference regulator (e.g., EMA, FDA) – [4] Innovative Licensing and Access Pathway supports transformative medicines development by coordinating MHRA, HTA and NHS to accelerate authorization and subsequent patient access – [5] Early Access to Medicines Scheme to accelerate patient access to life-changing treatments – [6] National Institute for Health and Care Excellence – [7] All Wales Medicines Strategy Group

NICE evaluates cost-effectiveness using a standard £25,000 – £35,000/QALY[1] threshold, with severity adjustments and a dedicated pathway for selected highly specialized technologies (HST)

NICE cost-effectiveness assessment

- Economic evaluation is usually conducted in the form of a cost-effectiveness analysis, with the health effects being measured using an appropriate non-monetary outcome indicator
- The NICE evaluates new treatments by comparison with current NHS (National Health Service) care, assessing:
  - Incremental cost to the NHS
  - Incremental benefits in Quality-Adjusted Life Years (QALYs)
  - Incremental Cost-Effectiveness Ratio (ICER)
- The NICE uses QALYs as the primary outcome for quantifying the expected health benefits associated with a given treatment regimen
- When combined with the relative cost of treatment, QALY can be used to estimate the ICER[2], which is considered in relation to NICE's threshold willingness-to-pay value

ICER = Incremental cost ÷ Incremental QALYs

- From April 2026, the standard NICE threshold range per QALY is comprised between £25,000 and £35,000
- An ICER < £ 25,000 is likely to be accepted while an ICER > £ 35,000 will require strong justifications



Below £25k
Generally, more favorable for a positive recommendation

£25k–£35k
Greater scrutiny of uncertainty and other decision factors

Above £35k
Stronger justification or additional flexibility required

- Example:
  - Existing care: 1 year x 0.4 quality score = 0.40 QALYs
  - New treatment: 1.25 year x 0.6 quality score = 0.75 QALY
  - Incremental benefit: 0.75 – 0.40 = 0.35 QALY

Additional cost £7,000 ÷ 0.35 = £20,000/QALY

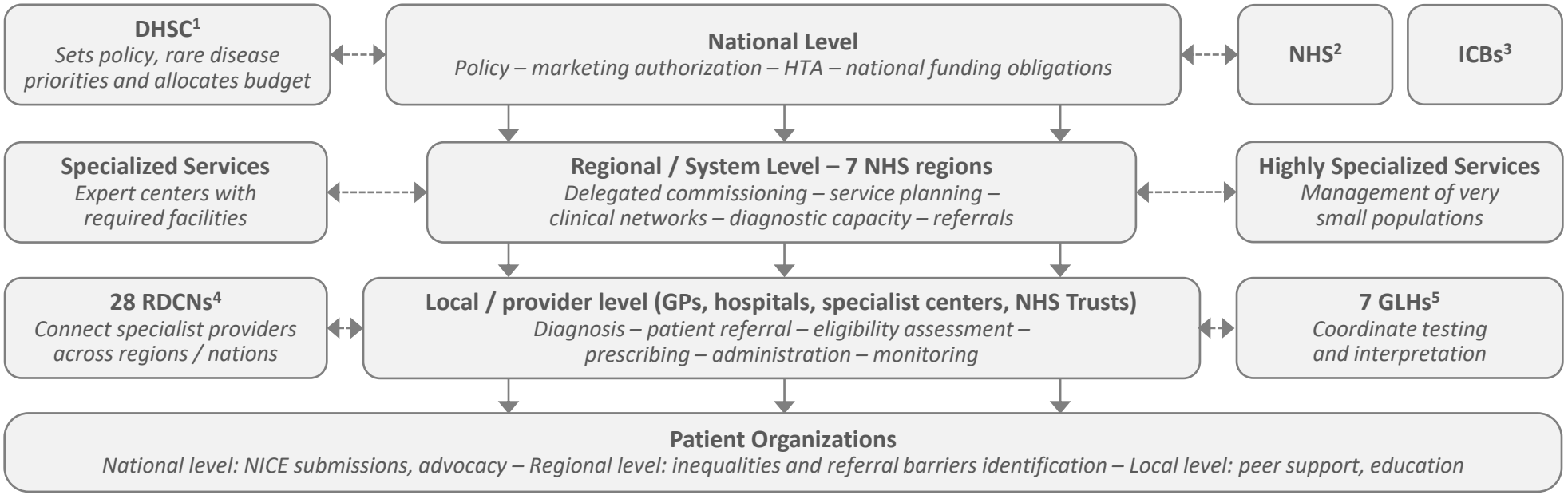
- These are appraisal reference thresholds, not automatic approval or refusal cut-offs
- Rare diseases exceptions[3]:
  - **Severity modifier:** qualifying diseases may receive QALY weights of ×1.2 or ×1.7 in standard appraisals, giving greater weight to the clinical benefits of drugs treating particularly severe diseases
  - **HST** is a separate evaluation route for innovative treatments for very rare and severe conditions, applying a higher cost-effectiveness threshold (£100,000/QALY), potentially reaching £300,000/QALY through additional weighting-based lifetime QALY gains

Sources: NICE, Health Technology Evaluation Methods Manual (updated March 2026) – NICE, Changes to cost-effectiveness thresholds (April 2026) – UK Parliamentary Office of Science and Technology (2026) – Smart Pharma Consulting analyses

[1] Quality-Adjusted Life Year – [2] Incremental Cost-Effectiveness Ratio – [3] These weights and the HST pathway do not automatically apply to orphan drugs

In England, positive NICE recommendations mandate NHS funding, while commissioning, specialist service capacity and referral pathways determine effective patient access

Rare disease ecosystem in England



- **NHS commissioning** is the process of planning, funding, contracting and monitoring healthcare services to ensure that appropriate treatments are available to eligible patients
- **Highly Specialized Services (HSS)** which treat very small populations with exceptionally concentrated expertise and infrastructure, are commissioned nationally by NHS England, while ICBs have delegated responsibility for many other specialized services
- A **patient** can be eligible for a nationally reimbursed treatment but experience delay because the specialist center is not ready, diagnostic confirmation is outstanding or the referral pathway is inefficient

Sources: NHS England, Specialized Commissioning Framework (2025/26) – Direct Commissioning Update (March 2026) – UK Department of Health and Social Care, Health Bill Factsheet (September 2026) – Smart Pharma Consulting analyses

[1] Department of Health and Social Care, equivalent to the MoH – [2] National Health Service: National & regional health authorities' coordination and implementation of priorities – [3] Regional Integrated Care Boards: commission healthcare services, including many delegated specialized services – [4] Rare Disease Collaborative Networks – [5] Genomic Laboratory Hubs

The five Euro-5 markets present distinct opportunities and challenges, requiring tailored strategies to optimize orphan drug launch and growth

Strategic market access comparison

Countries	Main opportunities	Main challenges	Strategic imperatives
FRANCE	▪ Early access and structured rare-disease networks	▪ HAS[1] value demonstration, CEPS[2] negotiations and expenditure controls	▪ Integrate early access, evidence generation and expert networks
GERMANY	▪ Early statutory reimbursement	▪ AMNOG[3] reassessment and net-price pressure	▪ Secure initial uptake while anticipating comparative evidence requirements
ITALY	▪ Established national P&R system and specialist networks	▪ National negotiation and regional implementation	▪ Align AIFA[4] strategy with regional execution
SPAIN	▪ National funding decisions and CSUR[5] expertise	▪ HTA[6] uncertainty during reform implementation and regional delivery differences	▪ Prepare robust evidence and coordinate with regional health systems
UK / ENGLAND	▪ Defined NICE[7] decision framework and national funding obligations	▪ Cost-effectiveness, clinical uncertainty and specialist service capacity	▪ Optimize NICE value arguments and NHS[8] implementation readiness

Sources: Smart Pharma Consulting analyses

[1] French National Authority for Health – [2] Economic Committee on Healthcare Products – [3] German Pharmaceutical Market Reorganization Act – [4] Italian Medicines Agency – [5] National Health System Reference Centers, Services and Units – [6] Health Technology Assessment – [7] National Institute for Health and Care Excellence – [8] National Health Service

Successful orphan drug launches require an integrated European evidence and value strategy, combined with country-specific pricing, reimbursement and patient access execution

Country-specific key success factors

FRANCE

- Secure favorable HAS[1] assessment (SMR/ASMR)[2] and CEPS[3] pricing conditions
- Leverage early access (AAP) when eligible and plan RWE generation
- Mobilize FSMRs[4], CRMRs[5] and hospital centers to accelerate diagnosis, referral and treatment

GERMANY

- Prepare comparative evidence for AMNOG[6] / G-BA[7] assessment and GKV-SV[8] negotiations
- Anticipate the €30M orphan-drug threshold and price-adjustment mechanisms
- Engage specialist networks and ensure hospital/treatment-center readiness

ITALY

- Optimize AIFA[9] P&R negotiations and assess eligibility for innovativeness status
- Anticipate registries, managed entry agreements and evidence commitments
- Engage regional health systems and reference centers to ensure treatment availability

SPAIN

- Build robust clinical and economic evidence for HTA[10] and national P&R
- Prepare engagement with national authorities and autonomous-community health systems
- Mobilize CSURs[11] and hospital teams to strengthen diagnosis, referral and adoption

UK / ENGLAND

- Optimize NICE[12] clinical/economic evidence, severity weighting and HST[13] eligibility where relevant
- Secure positive HTA recommendations and align NHS[14] commissioning arrangements
- Prepare specialist services, diagnostic pathways and treatment-center capacity

Sources: Smart Pharma Consulting analyses

[1] French National Authority for Health – [2] Clinical Benefit / Clinical Added Value – [3] Economic Committee on Healthcare Products – [4] Rare Diseases Healthcare Networks – [5] Rare Diseases Reference Centers – [6] German Pharmaceutical Market Reorganization Act – [7] Federal Joint Committee – [8] National Association of Statutory Health Insurance Funds – [9] Italian Medicines Agency – [10] Health Technology Assessment – [11] National Health System Reference Centers, Services and Units – [12] National Institute for Health and Care Excellence – [13] Highly Specialized Technologies – [14] National Health Service

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Best regards

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