Medicines Access Group

Horizon scanning terminology

Like all specialist areas, horizon scanning involves the use of terminology with specific meanings: it is necessary to understand the meaning of this in order to ensure New Drugs Online (NDO) is as up-to-date and relevant as possible.

The EMA has produced a user friendly brief overview of the EU process – The European regulatory system for medicines and the European Medicines Agency.

Further information on how to get a licence in the UK can be found via the MHRA, see www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk

The table below lists horizon scanning terminology mentioned in horizon scanning resources; the implications for updating NDO are also included.

Terminology	Brief definition / explanation
Accelerated approval	US process that allows drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate or intermediate endpoint, which should be a marker or endpoint that is reasonably likely to predict clinical benefit. Confirmatory trials (Phase 4) will normally be required. Similar to EU Conditional authorisation.
Accelerated assessment	EMA procedure that reduces the time required for an application review from the standard 210 days (excluding 'clock-stops') to 150. A pre-submission meeting is offered to ensure that the applicant's data package is likely to be sufficient. Eligible products will be of major interest for public health and therapeutic innovation. Equivalent to US Priority Review.
Adaptive pathway	EMA project aimed at improving access to new medicines in areas of high unmet need; combines several existing processes to allow iterative development with additional evidence-gathering through real-life use, and early involvement of patients and health technology-assessment bodies.
Advanced Therapy Medicinal Product (ATMP)	EU designation for medicinal products based on genes, cells, or tissues. The definition encompasses any medicinal product for human use that is a gene therapy medicinal product, or a somatic cell therapy medicinal product, or a tissue engineered product. There is a similar definition for veterinary products.
ANDA	See NDA.
Application	Submission of a dossier by a company to a regulatory authority for consideration for licensing. Summarised by the FDA as "The documentation required in [a regulatory submission] is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged."
Approved	Granted a product licence or 'marketing authorisation'.
Authorised	Another name for approved. See also marketing authorisation.
BLA	Biologics License Application (US).

Terminology	Brief definition / explanation
Breakthrough therapy	US programme to expedite development and review of medicines for serious or life-threatening conditions with preliminary evidence of substantially improving at least one clinically significant endpoint over available therapy. Breakthrough therapies are eligible for fast track benefits including accelerated approval and priority review, and more intensive FDA guidance on efficient drug development.
CAT	EMA's Committee for Advanced Therapies. CAT is responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs). Main responsibility is to prepare a draft opinion on each ATMP application submitted to EMA, before the CHMP adopts a final opinion on the marketing authorisation of the medicine concerned. Companies can ask the CAT to confirm if the product they are developing meets the scientific criteria for defining an ATMP – see CAT recommendations on the classification of advanced therapy medicines.
Centralised procedure	European Union-wide procedure for authorisation of medicines, where there is a single application to the EMA, a single evaluation and a single authorisation throughout the EU and European Economic Area. Once a licence has been obtained via this route the medicine is simultaneously licensed in all participating EU countries. Mandatory for some products and optional for some others; some are ineligible and will follow the decentralised route: see www.ema.europa.eu/about-us/what-we-do/authorisation-medicines
CHMP	The Committee for Medicinal Products for Human Use, the advisory committee to the EMA that reviews product applications and gives an 'opinion' on suitability for approval. There is a similar Committee for Veterinary Medical Products (CVMP).
Clinical trial	Broadly, a research study intended to examine interventions aimed at improving health; in NHS horizon scanning, a study in humans to determine whether a new treatment intervention is safe and effective. After preclinical studies *in vitro* and in animals, most drugs go through at least three clinical trial phases (some have four), usually quoted with Roman numerals as PI, PII, etc. The usual phases are: **Phase I** - 'first in humans': no comparison intervention, involves small numbers (in the 10s) and usually in healthy volunteers, although in serious or rare illnesses the drug may be offered to volunteer patients; intended to determine human pharmacokinetics, likely effective dose, ensure there are no major safety issues, and sometimes to find out whether it has any therapeutic benefits. **Phase II** – the 'proof of concept' stage and usually the first trials in patients with the condition that the intervention is intended to treat (healthy volunteers if the trial is a preventive intervention). Number involved usually in the low 100s; the study will be double-blind (if feasible) and randomised with a comparison arm, usually placebo: all participants will receive usual standard care. PII trials in very rare diseases may depart from this standard, but only as much as necessary. **Phase III** – the 'effectiveness' stage, confirms efficacy and tolerability in a larger group of patients to clarify potential effectiveness in practice. Number involved usually the high 100s to 1,000s or more; again double-blind and randomised with a control arm, which may be placebo (plus standard therapy if ethically required) or a standard therapy. Usually multi-centre and often multi-national; essential for licensing application except for rare diseases and regulators will often require at least two in different populations. **Phase IV** – post-licensing study or studies to confirm effectiveness or study a different patient group; may be mandated by a regulatory agency (see Conditional authorisation) or may be instituted by the company to extend the licensed indications.

Terminology	Brief definition / explanation
Compassionate use	EMA procedure that provides recommendations, through CHMP, for use of an unauthorised medicine by suitable patients who cannot enter clinical trials. Note that CHMP only provides recommendations: compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures. Similar to US expanded access.
Complete response letter	Sent by the FDA to companies to indicate that the review of product application is complete and it is considered not ready for approval. The letter describes specific deficiencies and may outline recommended actions.
Concerned member state (CMS)	See decentralised system.
Conditional marketing authorisation	EMA mechanism to grant temporary approval before comprehensive quality, safety, and efficacy data can be provided, but where these are expected to become available. Applies in cases where there is a significant unmet medical need and the benefit of immediate availability outweighs the risks. Available data must indicate a positive benefit to risk balance, but will not be sufficient for full approval. Similar to FDA Accelerated approval. In both cases, approval may be withdrawn if confirmatory studies do not verify clinical benefit.
DAC	Drugs Advisory Committee (US). Independent panel of experts that reviews product applications and advises the FDA on approval decisions. The FDA is not bound by their recommendations.
Decentralised procedure	An EU procedure intended to simplify the process where a company wishes to market a medicine in more than one member state; allows medicines to be assessed and approved at European level by two or more Member States. Applies when the product has not previously received an authorisation in any EU/EEA member state. One Member State acts as Reference Member State (RMS) and will assess the application and provide the other Member States with an assessment report, SPC, labelling and package details. The RMS will liaise with the Concerned Member States (CMSs), i.e. the other member states where the applicant wishes to market the product. When agreement is reached the application is approved by the individual Member States concerned in the procedure and national marketing authorisations are granted. If the RMS and CMSs cannot reach agreement the matter is referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which may further refer to the CHMP. See also Mutual Recognition.
Discontinued development	The company has taken a decision to discontinue development for that indication.
EAMS	Early Access to Medicines Scheme – voluntary UK scheme that allows the NHS to supply medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Companies can use evidence collected in the scheme in support of their NICE appraisal submission. MHRA issues an EAMS scientific opinion on the benefit/risk balance of the medicine. This may be around the same time the company files for a licence. The opinion lasts for a year, can be renewed and is provided after a 2-step evaluation process: 1. the promising innovative medicine designation (see PIM designation below) 2. the EAMS scientific opinion

Terminology	Brief definition / explanation
EMA	The European Medicines Agency (formerly the EMEA) is a decentralised agency of the European Union (EU) responsible for scientific evaluation, supervision and safety monitoring of medicines in the EU. It coordinates and supports interaction between national competent authorities in the EU and EEA.
EC - European Commission	The EU executive body; for medicines, it acts as the licensing authority responsible for granting marketing authorisations submitted through the centralised procedure and some others.
EUA	Emergency Use Authorization (US). FDA allows unapproved medical products or unapproved uses of approved medical products to be used in an emergency when there are no adequate, approved, and available alternatives. Company is expected to continue ongoing trials and work towards submission of a BLA as soon as possible.
Exceptional circumstances	Allows products to be approved in cases where comprehensive quality, safety and efficacy data cannot be provided, e.g. where the disease in question is very rare, or scientific knowledge is insufficiently advanced, or normal trials would be unethical. Note differences from Conditional Approval (EU).
Expanded access	US procedure that allows investigational drugs to be used in special circumstances outside of a clinical trial. EU equivalent is compassionate use.
Fast track	US programme to expedite development and review of medicines for serious or life-threatening conditions, where non-clinical or clinical data indicate they fill an unmet medical need. It allows a company to file an application on a rolling basis and permits the FDA to review the filing as it is received; this speeds the approval process. Takes account of the seriousness of the disease and lack of alternative treatments. Fast track drugs are potentially eligible for accelerated approval and priority review.
FDA	Food and Drug Administration. US regulatory authority for medicines; also regulates medical devices and veterinary products, and supervises safety of foods and many other products.
Filed	The company has submitted an application for a licence to the regulatory authority. Once accepted, the product will enter the pre-registration development stage.
Filing withdrawn	The company has taken the decision to withdraw the licence application for whatever reason.
IDMB / IDMC	Independent data monitoring board / committee. Established to assess the progress of a clinical trial and if necessary recommend stopping the trial before the planned duration on the basis of safety (harms detected outweigh potential benefits), futility (data already available indicate that there is no significant difference between the treatments – except in non-inferiority trials) or rarely, efficacy (data already available show clear superiority). Primary remit is patient safety.
IND	Investigational New Drug application (US). Technically, a mechanism by which a drug trial sponsor can legally ship an unlicensed drug across state lines. In practice, IND approval is almost essential before clinical trials can begin in the US.
Launched	A product is marketed and available for prescribing.

Terminology	Brief definition / explanation
List of questions (CHMP)	At day 120 from validation of a MAA, the CHMP reviews progress to date, makes a provisional recommendation, and produces a List of Questions to the applicant. These address any issues that the Committee consider are not adequately addressed in the application and may cover any aspect. The CHMP timeline clock stops and the company has three (exceptionally six) months to respond. There may be a further request after a secondary evaluation at day 180 (excluding clock-stop).
MAA	Marketing authorisation application, same meaning as 'filed' in the EU and is often used with reference to the EU.
Marketing authorisation (MA)	Given by the licensing authority to the company to allow marketing of the product.
Marketing Authorisation extension (EU)	The term 'extension' has specific meaning within the overall EMA process, and indicates a variation to the MA that alters the active substance in the medicinal product or its strength, dose form or route of administration. These are considered to be fundamental changes to the product.
Marketing Authorisation variation (EU)	The term for a wide range of changes to a product's MA that are not considered to alter the product itself fundamentally. Has two levels: level I involves minor changes (e.g., minor changes in the manufacturing process, packaging, product compositions and appearance, etc.); level two covers any major changes to the product and its manufacture, and includes addition of new indications. Thus, a new indication that requires a new dose form could involve a level II variation and an extension.
MHRA	Medicines and Healthcare products Regulatory Agency, the national UK regulatory agency.
Mutual recognition procedure	An EU procedure intended to simplify the process where a company wishes to market a medicine in more than one member state; allows medicines to be assessed and approved at the European level by two or more Member States. Similar to the decentralised procedure but applies where the product has already received a marketing authorisation in another member state.
NDA	New Drug Application (US); equivalent to European MAA. (An ANDA is an Abbreviated NDA: used for new generic medicines - not for licence extensions, which require a Supplementary NDA, or sNDA.)
Negative opinion	Not recommended for approval by CHMP (EU), or the Drug Advisory Committee (US) or the FDA has issued a Complete Response letter. CHMP / DAC recommendations are rarely ignored by the EC or FDA.
Non-inferiority trial	A trial design that aims to show that the efficacy of a new treatment is not unacceptably worse than an existing one. It may be useful if the new treatment is expected to have other advantages that would outweigh potential loss of efficacy. Not easy to design and interpret, and may have significant disadvantages in some settings. Can be useful in a regulatory context, but are less helpful for health technology assessment purposes. [1,2]
Not approved	In the EU this means that the product has not been granted a licence, generally follows a negative opinion.

Terminology	Brief definition / explanation
NIHR portfolio adoption	See https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/crn-portfolio.htm A clinical trial programme has to meet a number of eligibility criteria to be 'adopted'. Once adopted the programme is offered support and resources from NIHR that could speed access to market.
Orphan drug	Orphan status is designated to new drugs for diseases affecting small numbers of people (≤5 in 10,000 in the EU or <200,000 in the US). It provides a period of market exclusivity (10 years in the EU, 7 in the US) for the indication following approval. In the EU, if a drug is used in both orphan and non-orphan indications, the orphan medicine will be a different medicinal product with a separate MA and a different brand name. If a non-orphan indication is added to an orphan medication, it automatically loses orphan status.
Patent Term Restoration	US equivalent of the EU SPC, gives a maximum of 14 years market exclusivity. Calculated as half the time from patent date to FDA submission plus the time taken for FDA approval, excluding any time where the company was not acting 'with due diligence' and subject to a maximum added time of five years and the 14 year maximum exclusivity.
PDUFA	The US Prescription Drug User Fee Act; sets a time frame for FDA decisions on approval following filing (10 months for a standard review and 6 months for a *Priority Review).*
Phase (clinical trials)	Stage of a clinical trial – see Clinical trials entry for more.
PIM designation	Promising Innovative Medicine, the UK's fast track programme for allowing patients to access medicines sooner, before they are marketed or have been appraised by NICE The PIM designation will give an indication that a product may be eligible for the Early Access to Medicines Scheme (based on early clinical data). The PIM designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed.
PIP	Paediatric investigation plan
Pivotal trial	A clinical trial, usually phase III, which is specifically intended to provide data for a licensing application.
Positive opinion	Recommended for approval by CHMP or the FDA Drug Advisory Committee.
Pre-registration	A licence application has been submitted (or filed) and accepted by the regulatory agency.
Priority Medicine (PRIME)	EMA scheme intended to increase support for the development of medicines that target an unmet medical need; gives access to enhanced interaction and early dialogue between the EMA and the medicine developer. Would be expected to lead to accelerated assessment once filed (see above).
Priority review	US – the FDA makes its approval decision within 6 months (rather than the usual 10- to 12-month review period); for medicines with potentially significant advances over existing therapies. Equivalent to EMA Accelerated Assessment.
Rapporteur	The CHMP member who prepares a scientific assessment report on an application on behalf of the CHMP. May be supported by a co-rapporteur, who prepares an assessment independently. They are supported by assessment teams that can include outside experts.

Terminology	Brief definition / explanation
Recommended for approval	Recommended for approval by CHMP or the FDA Drug Advisory Committee (see also 'positive opinion').
REMS	Risk Evaluation and Mitigation Strategy (US).
RMS	Reference Member State (EU). The EU member state that evaluates a licence application using the decentralised or mutual recognition procedure on behalf of other states in the EU (see Decentralised system).
RMAT	Regenerative Medicine Advanced Therapy (US). An award from the FDA that allows for faster, more streamlined approvals of regenerative medicine products within the US, such as cell and gene therapies and tissue engineered products. Includes all benefits of fast track and breakthrough therapy programs. Unlike breakthrough therapy, RMAT status does not require evidence to show the drug may offer a substantial improvement over available therapies.
RMP	Risk management plan (EU).
Rolling review	One of the regulatory tools that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency. CHMP reviews data as they become available from ongoing studies, before a formal application is submitted. Also used in the US, but differently. A company can submit completed sections of its BLA or NDA for review by FDA, rather than waiting until every section is complete. BLA or NDA review usually does not begin until the entire application has been submitted.
sBLA	Supplementary BLA – application for a licence extension for a biological product (US).
sNDA	Supplemental NDA – application for a licence extension (US).
SPA	(US) Special Protocol Assessment – Company and FDA agree in writing on the design and size of a trial that will form the primary basis for an efficacy claim in the regulatory submission.
Suspended development	Progress through the licensing systems has been suspended. Usually follows identification of serious side effects which may signal closer monitoring.
Ultra orphan	Ultra-orphan medicines are orphan drugs that are licensed for treatment of diseases with a prevalence of less than 1 in 50,000 persons in the EU at the time of licence submission.

References

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2. Dunn, D.T., Copas, A.J. & Brocklehurst, P. Superiority and non-inferiority: two sides of the same coin?. Trials 19, 499 (2018). https://doi.org/10.1186/s13063-018-2885-z (open access - https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2885-z)