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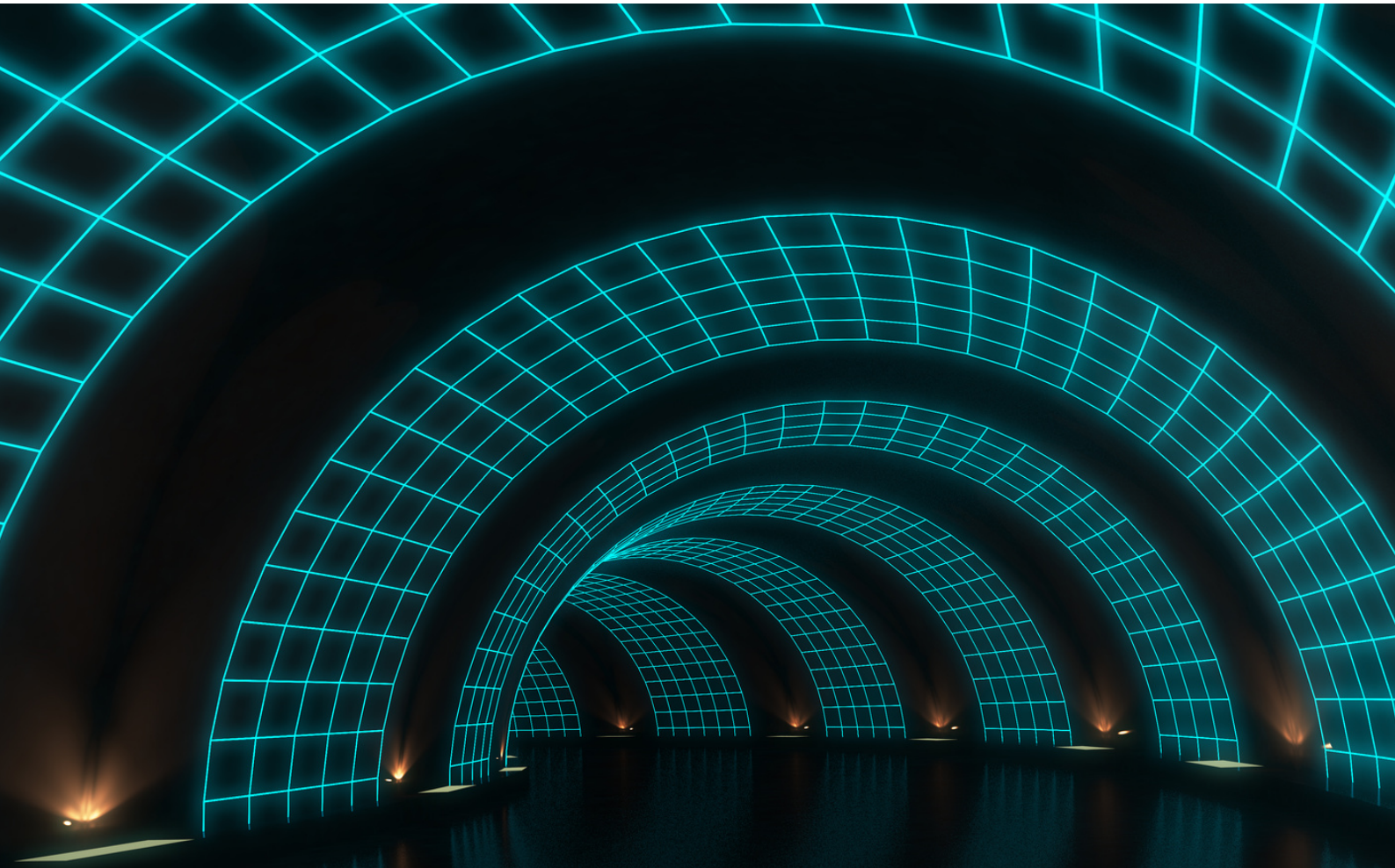

UPDATES TO THE FRENCH EARLY ACCESS SCHEME FOR DRUGS

REFINEMENT OF CRITERIA FOR INNOVATIVENESS IN THE AUTORISATION TEMPORAIRE D'UTILISATION (ATU) SCHEME

2022

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1. BACKGROUND

- The French law for temporary authorization for use (ATU) for early access to medicines has been active since 1992.
- The ATU scheme provides early access to medicines and carries several advantages when preparing launch of a new treatment:

1. Access to medicines for patients with immediate unmet needs.
2. Enhanced patient monitoring and evidence generation for French clinical settings
3. Opportunities for physicians to familiarize themselves with new innovative treatments.

- The ANSM performed all evaluations between 1992 and 2021.

2. CHANGES

- In July 2021, the HAS took on the responsibilities of implementing the ATU schemes.
- In May 2022, the HAS and ANSM concluded a performance review of the early access schemes and based on this review, updates to the criteria for presumption of innovation were made.
- Applicants for early access to innovative medicines will now need to show context to current therapeutic practice and unmet clinical need in addition to existing criteria about new modalities with substantial clinical benefits.

3. IMPACT

Advantages for Manufacturers

- Associated expedited HTA assessment by HAS
- Additional evidence generation supporting HTA in France
- Early familiarization in the health system supporting access in a competitive setting

Drawbacks for Manufacturers

- Potential delays and additional costs for inclusion of French clinical trial sites to fulfill innovativeness criteria related to local therapeutic context and to show strong unmet need

AAP = Autorisation d'accès précoce; AAC = Autorisation d'accès compassionnel; ANSM = Agence nationale de sécurité du médicament et des produits de santé; CPC =cadre de prescription compassionnel; HAS = Haute Autorité de Santé

References: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000042665373; https://ansm.sante.fr/actualites/autorisation-dacces-precoce-aux-medicaments-un-premier-bilan-positif-et-des-principes-devaluation-affines; https://www.insideeulifesciences.com/2021/07/06/new-early-access-and-off-label-use-rules-in-france/

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DEFINITION

Early Access is commonly understood as controlled mechanisms of access to investigational drugs outside of the main clinical trial space, often with evidence collection and before the commercial launch of the drug. In some situations the manufacturer is reimbursed for the treatment and some schemes have criteria associated, such as early access programs only for patients with life-threatening diseases having no treatment options available.

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WHAT IS THE EARLY ACCESS SCHEME IN FRANCE ?

The Early Access schemes (autorisation temporaire d'Utilisation, ATU) were launched originally in 1992, at the time of the AIDS pandemic. They comprised of 6 separate schemes for named patients, patient cohorts, post/pre authorization access, new therapeutic indications and off label usage.

KEY FEATURES OF THE 6 SCHEMES (1992 to 2021)

Scheme	Scope
ATU	Main scheme for temporary use authorization (i.e. Early access)
ATU nominative	Early access for named patient
ATU cohort	Early access for a patient cohort
RTU	Off-label temporary use of authorized products
Post-ATU	Continued access after marketing authorization
Direct access to Post-ATU	Access for authorized products without previous ATU
ATU for new indication	Access for authorized products in new indication

Overview: history of Early Access Schemes in France

1992 — Launch of ATU, ATU nominative and ATU de cohorte

2011 to 2014 — Off label use of authorized products (RTU)

2014 to 2019
- Post-ATU
- Direct access to post-ATU
- ATU for new therapeutic indication

2021
- Early access authorization (AAP)
- Compassionate access (AAC and CPC)

2022 — Further refinement of innovative medicine evaluation criteria

References: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000042665373; https://ansm.sante.fr/actualites/autorisation-dacces-precoce-aux-medicaments-un-premier-bilan-positif-et-des-principes-devaluation-affines; https://www.insideeulifesciences.com/2021/07/06/new-early-access-and-off-label-use-rules-in-france/

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WHAT HAPPENED TO THE EARLY ACCESS SCHEMES IN 2021 ?

In July 2021, the 6 different early access schemes were replaced by 2 key programs for Early Access and Compassionate Use.

KEY FEATURES OF THE 2021 SCHEMES

Scheme	Scope	What did it replace ?
Early Access Autorisation d'accès précoce (**AAP**)	Innovative medicines prior to authorization Innovative medicines post-authorisation	ATU, ATU cohort and post-ATU schemes
Compassionate Use	Compassionate access authorization Autorisation d'accès compassionnel (**AAC**)	ATU nominative scheme
	Compassionate access framework cadre de prescription compassionnel (**CPC**)	RTU scheme

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HOW DID THE EARLY ACCESS CRITERIA CHANGE IN 2021 ?

The criteria for Early access (AAP) schemes in 2021 included a new, **'presumption of innovative product'** clause. The compassionate use criteria included a new '**absence of clinical commercial research**' clause.

What were the criteria for Early Access (AAP) ?

- Serious, rare, disabling disease indication
- No appropriate treatment option
- Access to treatment cannot be delayed
- Medicine **presumed to be innovative**, in particular with regard to a relevant clinical comparator

What criteria did innovative products need to fulfill ?

- New modality with substantial benefits
- No significant unknowns related to safety or other important data
- Development plans to show clinical benefit to patients

What were the criteria for Compassionate Use (AAC and CPC) ?

- The medicinal product is not part of clinical research for commercial purposes
- No appropriate treatment is available
- Safety and efficacy are presumed on the basis of available clinical data and for a rare disease condition based on work and data collected by clinical professionals

Exceptions to the above criteria

- CPC (i.e. off label use) may be granted even when appropriate treatment exists, if it responds to patient needs 'just as well' as the authorized treatment (allows economically viable options to be put to use)
- Very early compassionate use may be permitted to meet urgent, unmet patient needs and the company will need to submit a AAP application along with AAC request.

AAP = Autorisation d'accès précoce; AAC = Autorisation d'accès compassionnel; CPC =cadre de prescription compassionnel

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A NEW ROLE FOR THE HAS SINCE 2021

Since July 2021, all decisions regarding early access to medicines in France are made by the Haute Autorité de Santé (HAS) with input from ANSM.

Two routes for early access (AAP)

Pre-MA Applicant

1. ANSM assesses benefits vs safety risks of the new drug

2. ANSM issues favorable opinion

3.HAS evaluates if the following criteria are met:

- Serious, rare, disabling disease indication
- No appropriate treatment option
- Access to treatment cannot be delayed
- Medicine presumed to be innovative, in particular with regard to a relevant clinical comparator

HAS must complete its evaluation within 90 days of the application

4. Applicant must:
- Submit MA application within 2 years of grant of AAP
- Make product accessible to patients within 2 months of grant of AAP
- Register product for reimbursement within 1 month of MA

Post-MA applicant

1.HAS evaluates if the following criteria are met:

- Serious, rare, disabling disease indication
- No appropriate treatment option
- Access to treatment cannot be delayed
- Medicine presumed to be innovative, in particular with regard to a relevant clinical comparator

HAS must complete its evaluation within 90 days of the application

2. Applicant must:
- Make product accessible to patients within 2 months of grant of AAP while negotiations with Economics committee may continue about pricing

AAP = Autorisation d'accès précoce; ANSM = Agence nationale de sécurité du médicament et des produits de santé; HAS = Haute Autorité de Santé
MA = Marketing Authorization

References: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000042665373; https://ansm.sante.fr/actualites/autorisation-dacces-precoce-aux-medicaments-un-premier-bilan-positif-et-des-principes-devaluation-affines; https://www.insideeulifesciences.com/2021/07/06/new-early-access-and-off-label-use-rules-in-france/

WHAT WERE THE KEY FEATURES OF AAP, AAC AND CPC IN 2021 ?

The AAP, AAC and CPC all require patient monitoring and data collection protocols. Data collection requirements may be waived for CPC if sufficient evidence is already available or a comparable authorized product exists

Integrated data collection

- Compulsory clinical protocols for patient monitoring and data collection
- Data collection for efficacy, adverse effects, real conditions of use and patient characteristics
- Defined patient reported outcome measures (PROMS) are developed by company and patient organisations

Key decision makers

HAS	ANSM
Administers the AAP	• Evaluates efficacy and safety for pre-authorization AAP • Administers the AAC and CPC

Pricing and reimbursement

Early Access (AAP)

Provided free of charge or for a freely-set maximum fee (indemnité).

Two types of price rebates are applied:

1. Annual rebate according to sales volume
2. Retrospective rebate calculated as difference between net reference price and the sales amount billed during the early access period

Compassionate Access (AAC and CPC)

- If product is reimbursed in another indication, then the same rate will be applied for AAC or CPC schemes
- An annual flat rate may be defined
- The company may set a fee, which will be subject to a rebate based on sales volumes

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REVIEW AND UPDATES IN 2022

In May 2022, the HAS and ANSM conducted a review of performance of all early access and compassionate use schemes in France. Following the review, the **"presumption of innovative product"** clauses were updated.

2021

What were the criteria for Early Access (AAP) ?

- Serious, rare, disabling disease indication
- No appropriate treatment option
- Access to treatment cannot be delayed
- Medicine **presumed to be innovative**, in particular with regard to a relevant clinical comparator

What criteria did innovative products need to fulfill ?

- New modality with substantial benefits
- No significant unknowns related to safety or other important data
- Development plans to show clinical benefit to patients

2022

What are the criteria for Early Access (AAP) ?

No changes to AAP criteria

- Serious, rare, disabling disease indication
- No appropriate treatment option
- Access to treatment cannot be delayed
- Medicine **presumed to be innovative**, in particular with regard to a relevant clinical comparator

What criteria do innovative products need to fulfill ?

Changes to innovativeness criteria

- New modality with substantial benefits
- **Fulfill an unmet medical need**
- Plans to show clinical benefit **in the context of currently available therapies**

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EXAMPLES

- A total of 40 new early access approvals have been awarded since July 2021

After July 2021, several drugs have fulfilled the criteria for early access in France. Two key examples are illustrated below.

Drug	Indication and type of application (Pre/Post-MA)	Meeting criteria	Would new criteria introduced in 2022 be fulfilled ?
Trodelvy (sacituzumab govitecan)	Monotherapy treatment of patients with unresectable or metastatic triple-negative breast cancer, who received 2 or more previous treatments (atleast one at advance stage) • **ATU nominative (compassionate use) granted previously** • **Pre-MA Application for Early Access**	• Serious and disabling disease indication • No appropriate treatment option (limited efficacy of current monotherapies) • Access to treatment cannot be delayed • (especially as treatment is of curative intent and median survival time with disease is 14 months) • Strongly presumed safety and efficacy evaluation by ANSM • New modality with substantial benefits • No significant unknowns related to safety or other important data • Development plans to show clinical benefit to patients	✓ Fulfill an unmet medical need ✓ Show clinical benefit in the context of currently available therapies (1 currently ongoing clinical trial with data collection sites in France)
Kaftrio (ivacaftor/ tezacaftor/ elexacaftor) + Kalydeco (ivacaftor)	Patients with cystic fibrosis aged 6 to 11 years heterozygous for the F508del mutation of the gene CFTR (cystic fibrosis transmembrane conductance regulator) and carriers of a minimal function CFTR gene mutation [Part of MA indication] • **ATU nominative (compassionate use) granted previously** • **Post-MA Application**	• Serious, rare and disabling disease indication • No clinically relevant comparator available for the treatment of this patient population • Access to treatment cannot be delayed as no appropriate treatment is available • New modality with substantial benefits • No significant unknowns related to safety or other important data • Development plans to show clinical benefit to patients Clinical data was available in a larger population than that claimed for early access, however the company did not submit a request for early access in its entire MA.	✓ Fulfill an unmet medical need ? Show clinical benefit in the context of currently available therapies (no available treatment for the indication)

MA = Marketing Authorization

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IMPACT

How will the changes impact future applicants for innovative medicines and early access in France? How will the HAS decide and weigh each criterion?

- After May 2022 and announced in 2021, two additional criteria for **'presumption of innovativeness'** have been introduced - (1) requirement to show clinical benefit in the context of currently available therapies and (2) demonstrate fulfillment of an unmet medical need. These may require additional attention from manufacturers planning AAP applications in the future.

Potential challenges for manufacturers

- **Planning an AAP will require plans for comparative assessments to establish benefit over currently available therapy, a potential added risk to successful launch of a new drug.**
- **Increased investments may be needed for executing the AAP**
- **Lack of appropriate comparators for non-pharmaceutical treatment options.**
- **Introduction of selection bias when choosing appropriate comparator treatments.**
- **Physicians will need to be convinced of the efficacy of new innovative treatment options over long established therapy regimens.**
- **A high unmet clinical need for innovative treatments must be demonstrated for approval.**

What will be the impact to the changes given that now HAS decides on the applications?

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