A survey to gather developers' view on challenges and opportunities in ATMP development

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SURVEY Features

Platform: EUSurvey

Launch: 23 Oct 2024

Target: ATMP developers

Objective: to get feedback on

- perceived **challenges and potential opportunities** to improve ATMPs development and early access
- **awareness and experience** of the available EU regulatory **support tools**
- expectations on **regulators' role** in EU public and public-private **funded projects**

Cut-off: 10 Nov 2024 (N_{resp} = 38)

Survey open at the link https://ec.europa.eu/eusurvey/runner/EUInnovation

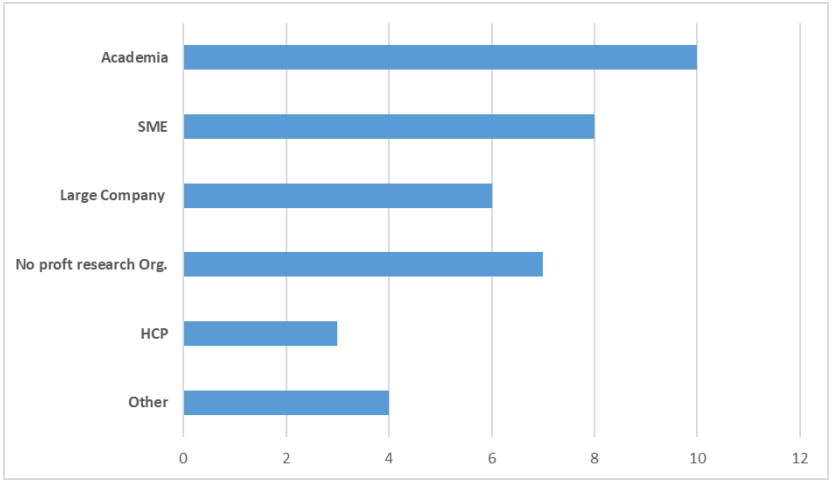
Your feedback matters!

SURVEY Features

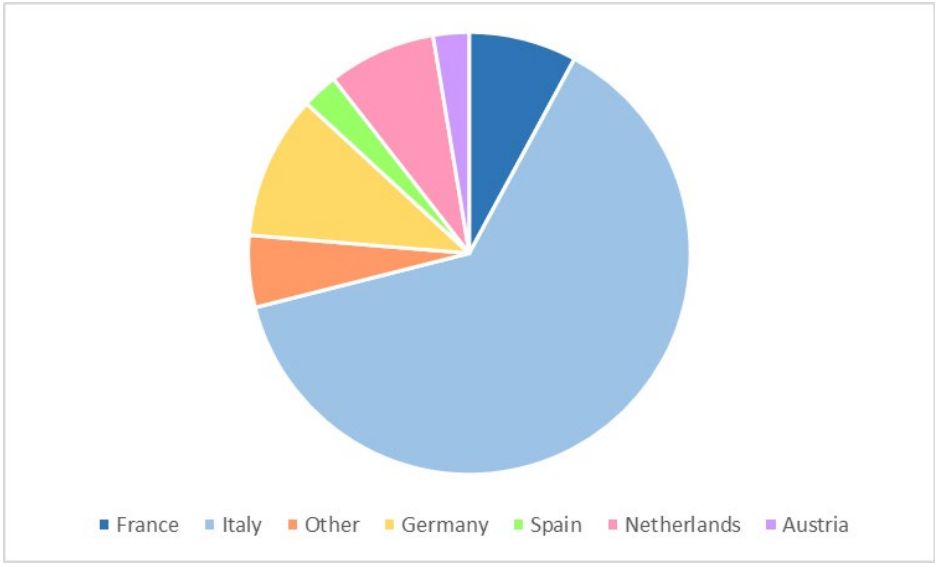
Structure: 4 sections

- **Profile** (category, country, ATMP type, etc)
- **Challenges & Opportunities** in
  - GMP/Manufacturing
  - Nonclinical aspects
  - Early access & Clinical development (Hospital Exemption, Combined ATMPs, GMO)
- **Awareness & Experience** in **Regulatory support tools** (e.g. Scientific advice, Innovation meetings)
- **Expectations on regulator's role in public/public-private funded projects**

Responder's category



Responder's country



GMP / Manufacturing

N = 20/38 (52.6%)

Based on your experience, provide your feedback on the following aspects:

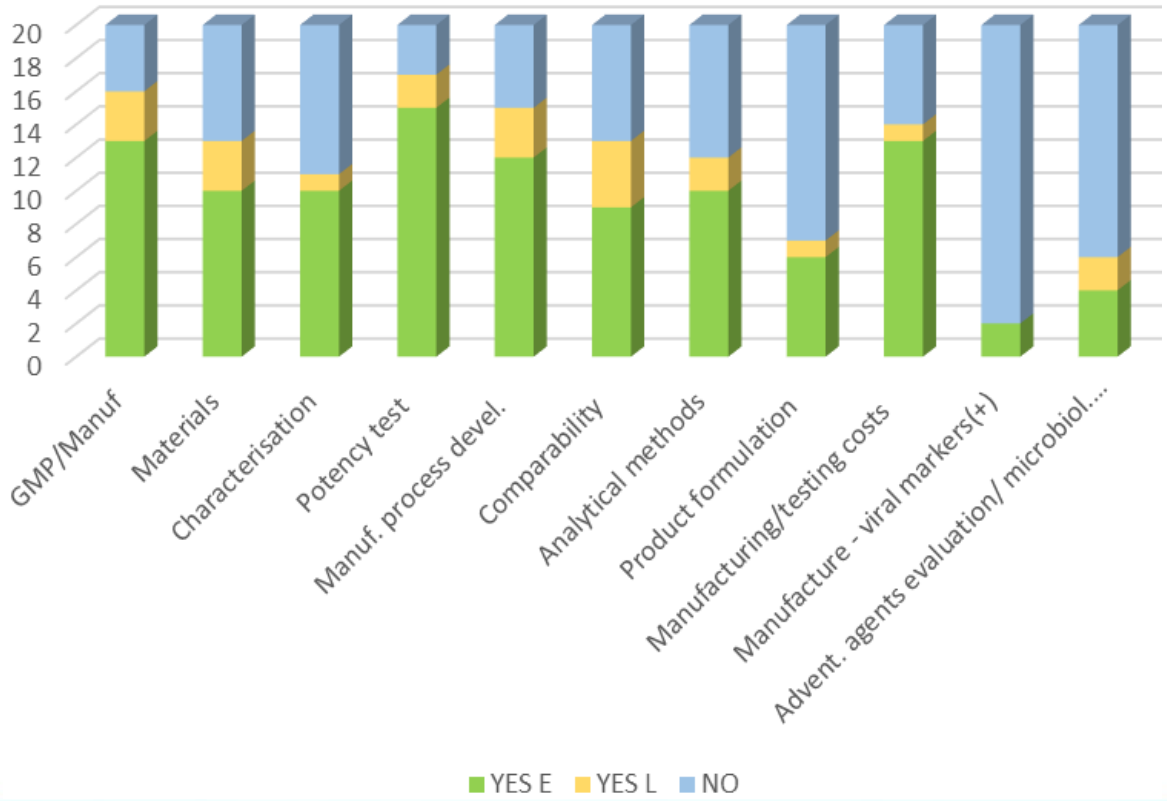
- GMP compliance
- Materials' quality grade and supply
- Product characterisation
- Potency testing development
- Manufacturing process development
- (characterization/validation/scale-up)
- Comparability
- Analytical test methods (development, validation and/or transfer)
- Product formulation
- Manufacturing/testing costs
- Product manufacture in case of viral markers positivity
- Adventitious agents safety evaluation and microbiological control.

Indicate if and in which development phase you experienced challenges.	Provide more details to describe the encountered challenges.	Suggest potential opportunities for improvement.
* *Between 1 and 2 selections* ☐ Yes, early/exploratory clinical development ☐ Yes, late/confirmatory clinical development ☐ No	Details *Text of 1 to 500 characters will be accepted*	Suggestions *Text of 1 to 500 characters will be accepted*

GMP / Manufacturing

Challenges / Development Phase

(Yes Early/Exploratory - Yes Late / Confirmatory - No)



GMP / Manufacturing

Challenges:

- **GMP compliance**
- **Materials** quality grade
- **High costs** (materials, outsource ext labs)
- **Long times** to start a CT or early GMP production
- Develop a **potency assay and setting specs**
- **Lack of knowledge**

Opportunities for improvement:

- **Global convergence** for requirements
- **Guidance**
- **Prior knowledge**
- **Differentiated costs** for academia/no-profit
- **Training**
- **Discussion with Regulators**
- **Knowledge sharing**
- **Flexibility**

Non Clinical (NC)

N = 23/38 (60.5%)

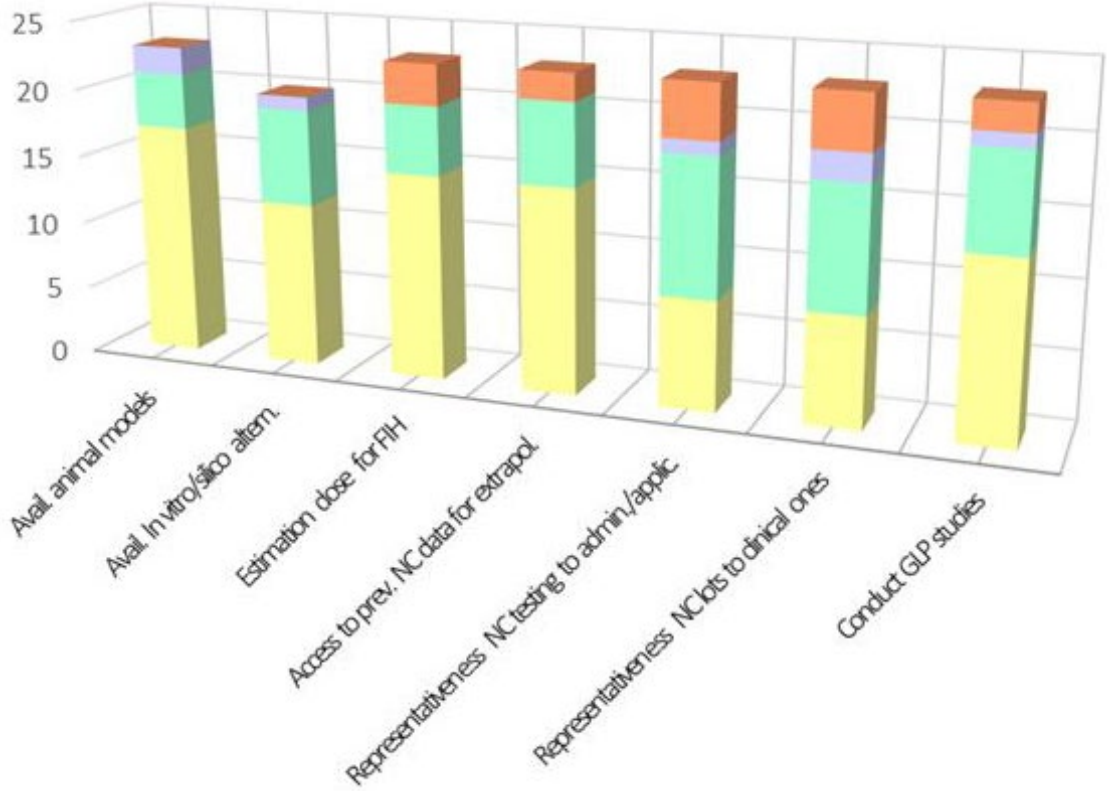
Based on your experience, to what extent the following aspects impact an ATMP(s) development. Please, rate the impact.

- Availability/identification of relevant suitable **animal models**
- Availability of **in vitro/in silico alternatives** to animal testing predictive of human tox.
- Estimation of safe and effective **dose** to be used in first in human trial (FIH)
- Access to **previously generated NC data** for extrapolation between similar types of ATMPs
- **Representativeness of NC testing** to the ATMP clinical administration procedures and application devices
- **Representativeness of NC lots** to the clinical ones
- Conduction of **GLP** compliant studies

SURVEY Results - Non Clinical (NC)

Extent of impact an ATMP(s) development

High – Low – Not at all – Not Known



Non Clinical (NC)

Challenges

- Missing/not predictive **animal models**
- Lack of **platform and/or "prior knowledge"** approach
- Uncertainty on In vitro / in silico alternatives **acceptance** for FIH trials
- Uncertainty on **predictivity** of in vitro/in silico tests, need for standardization
- Lack of **knowledge/awareness** (e.g. when use GLP test)

Opportunities for improvement

- **Global harmonization** of in vitro /in silico alternatives
- **Platform and/or `prior knowledge`**
- Flexibility with old toxicology concepts
- Acceptability extrapolation data from literature
  e.g. on administration risks of the procedure
- Accept minimal packages and risk-based approach
- **Infomation sharing**

Clinical development & Early access - Hot topics

N = 24/38 (63%)

Investigate developers' view on challenges & potential opportunities for improvement on selected topics related to:

- Early access through **Hospital Exemption (HE)**
- **Combined developments** of ATMPs with Medical Devices (MD) and In Vitro Diagnostics (IVD)
- **Genetically Modified Organism (GMO)** requirements**.**

Hospital Exemption (HE)

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What would you consider the most **appropriate use and desirable aim** of HE?

Please rate (1- 5most appropriate/desirable)

1. Treatment of **individual patients** with unmet medical need (UMN) and for whom the clinical trial is not an option, on a case-by-case basis, ***following availability of clinical data*** *for the concerned ATMP*
2. Treatment of patients with UMN and for whom clinical trial is not an option, on a **case-by-case** basis, ***before availability of clinical data*** *and supported by rationale/proof of concept*
3. Treatment of an **undefined number of patients** under a **temporary "National authorisation for use"** of an ATMP in a specific indication with UMN, ***following availability of supportive clinical trial data***

Hospital Exemption - Comments

Large company/ SME
Stick to the current HE definition, not an alternative to centrally authorised products

Academia/No profit
one does not automatically exclude the other

Large company/ SME
HE should remain an exception in case of UMN. No routine use

Academia/No profit
Depends on the clinical situation of the patient and data available

*HE very useful for (ultra) **orphan** indications, products which will not picked up by industry*

***Differences** in the interpretation of HE in the EU members. A clearer central policy would be desiderable.*

Hospital Exemption (HE)

In your view, please indicate to what extent this aspect impact ATMP development (Rate high, low, not at all, not known)

- **cost coverage and funding** impact the ATMP access via the HE framework. **75% high**

- increased **transparency and data sharing** is needed toimprove the HE framework. **79% high**

Agreement across all responders

Combined ATMP development

Please, indicate to what extent the following aspects could **impact** the ATMP-device combinations development. Rate the impact

Coordination between assessment of CTAs for ATMP and clinical investigation/performance studies for MD/IVD (e.g. common IT infrastructure, unique submission, alignment timelines/documents)	**High = 62.5%** Low = 4.2% Not at all = 0% Not known = 33.3%
Harmonisation across EU Member states and Ethics Committees (e.g. national legislation, interpretation of legislation, procedural aspects)	**High = 70.8%** Low = 0% Not at all = 0% Not known = 29.2%
Availability of **guidance** for Applicants	**High = 66.7%** Low = 8.3% Not at all = 0% Not known = 25%
Availability of dedicated coordinated **support tools** (e.g. scientific advice)	**High = 66.7%** Low = 8.3% Not at all = 0% Not known = 33.3%

Genetically Modified Organism (GMO)

GMO framework refers to the need of clinical trials (CTs) with investigational medicinal products containing or consisting of GMO to be compliant with Directives 2001/18/EC & 2009/41/EC as regards the environmental risk assessment (ERA) and consent by the competent authority of a Member State.

High variability in terms of national requirements and procedures.

Genetically Modified Organism (GMO)

QUESTION	RATE
How relevant do you consider the **assessment of GMO aspects** in relation to the risks posed by ATMPs containing or consisting of GMOs?	**Relevant = 41.7%** **Rel. in some cases = 37.5%** Not rel. = 8,33% Not known = 12.5%
Please indicate to what extent the **lack of harmonization** across EU Member states of the application of GMO framework implementation impact the ATMP development.	**High = 62.5%** … Not known = 33.3%
Please indicate to what extent the **lack of alignment** and coordination between evaluation of the GMO aspects and of clinical trial applications impact the ATMP development.	**High = 75%** … Not known = 20.8%
How relevant do you consider the application of the current "**crop-tailored**" GMO legislation to ATMPs containing or consisting of GMOs?	**Relevant = 29,1%** **Rel. in some cases = 12,5%** Not rel. = 16,7% Not known = 41,7%
Have you ever used the **common application forms** and consulted the **good practice** documents on the GMO aspects as developed by the European Commission?	**Yes= 54,2%** No**, not aware = 20.8%** No, but aware = 25%%

GMO - Comments

Where a GMO has been assessed before or is of a **low risk** class (e.g. BSL-1), expedited / abridged assessments or even complete **waivers** should be made possible

GMOs that are not expected to be shed (eg. genetically modified cells) do not pose a risk and should get a class **waiver**

Derogations

Different forms, language, submission procedures, fees, review times etc… **the common form is a drop in the ocean**

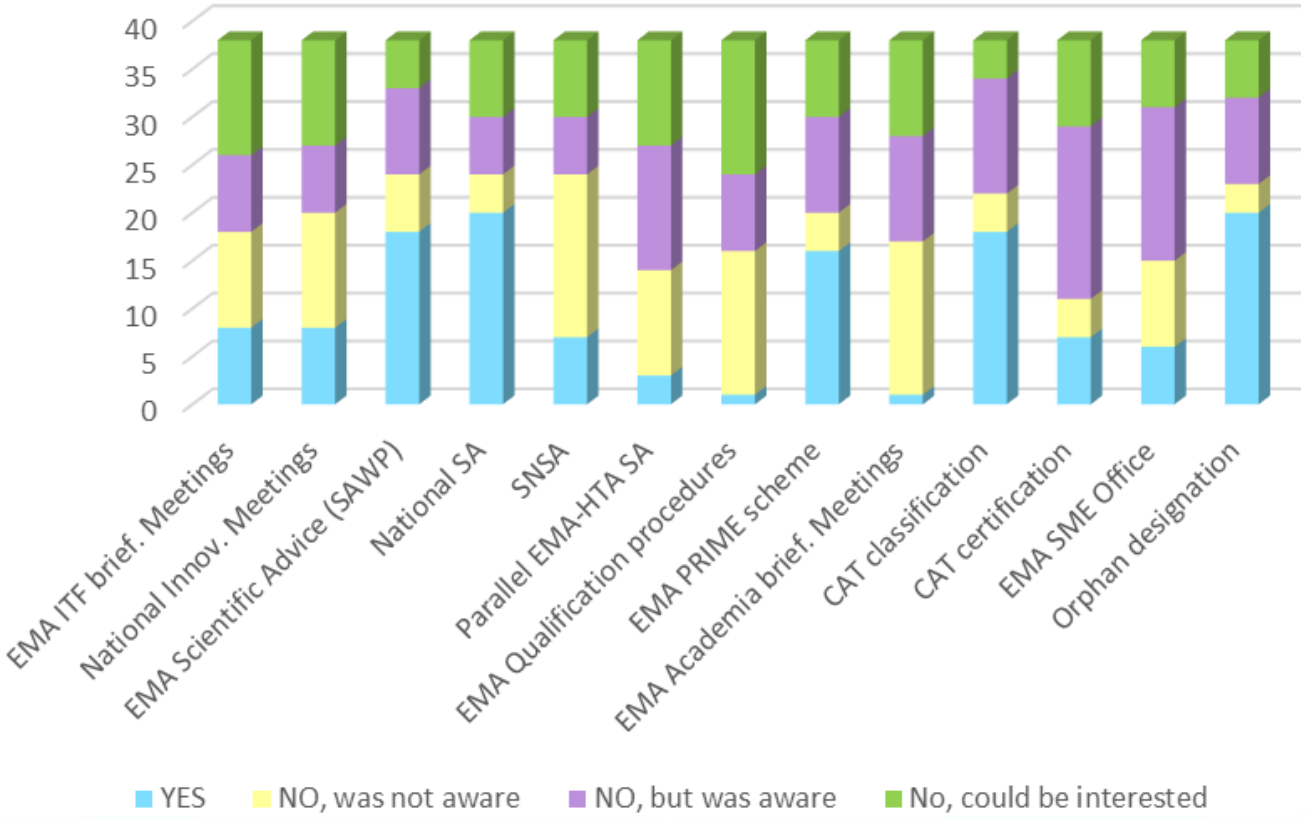
Multiple stakeholders /applications per country, lots of **different documents** to consider. Time-consuming, cumbersome and a major hurdle when considering e.g. study feasibility in a country

Request for **harmonization** across EU

Harmonization!

Regulatory Support Tools

Developers' **awareness and experience** of the currently available **EU regulatory support tools**.



Public and Public-Private funding

This question aim to investigate developers' expectations on **regulators' role** in EU public and public-private funded projects.

Accounting for regulatory requirements during planning and conduction of public or public-private funded projects could **facilitate translation** of research/innovation into clinical practice.

Which of the following **roles for regulatory authorities** would you consider **desirable**?

- ❑ Advice to public funders on strategic **priorities for future calls**, also based on regulatory science needs
- ❑ Support funding bodies in **drafting calls** to account for regulatory requirements
- ❑ Support funding bodies in **assessing applications** to check for regulatory acceptability of the submitted proposals
- ❑ Provide regulatory support to applicants **before submission of project proposal** to funding calls
- ❑ Provide regulatory support **during the project** (with fundings ad hoc allocated to this aim)
- ❑ Involvement in funded, non-commercial, regulatory-science related **research projects**, which do not relate to the development of specific products

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Conclusions

Regulators are in listening mode

Don’t miss the survey:
https://ec.europa.eu/eusurvey/runner/EUInnovation

Your feedback matters!

Thank You!

BACK UP SLIDES

SURVEY Results - GMP / Manufacturing

- Challenges:

- **GMP compliance** (definition SMs), awareness of relevant GMP expectations, difficulties in trasfer from lab to GMP / Clinical grade. Lack of GMP grade reagents (hard to find right quality grade & costs)
- **High costs** (materials, outsource ext labs)
- **Long times** to start a CT or early GMP production
- Develop a **potency assay and setting specs** (e.g. when transgene encode a structural protein)
- **Lack of knowledge,** not familiar with regulations (academia)

Opportunities for improvement:

- **Changing critical materials** could have an impact on the process and could require comparability. A **Q&A** could help
- **Guidance** to develop a potency matrix for a structural protein with no activity
- **Global convergence** for requirements
- Use **prior knowledge**, small scale or one-step comparability studies, with only one late stage overall comparability at full scale
- Accept **alternatives** to standard validation protocols
- **Differentiated pricing** for academia/no-profit + accessible SA
- **Guidance** for less experienced developers
- **Training /discussion with Reg/knowledge sharing/more flexibility**

Hospital Exemption (HE)

Manufacture of an ATMP on a **non-routine basis**, in compliance with **GMP** and according to specific quality standards, for use under the exclusive responsibility of a medical practitioner, to comply with an **individual** medical prescription.
ATMP access via the HE is meant to address **unmet medical needs**. Divergences across EU in terms of intended purpose, clinical evidence for authorisation, duration, patients' eligibility, definition of "non-routine", etc.

What would you consider the most **appropriate use and desirable aim** of HE?

Please rate (1- 5most appropriate/desirable)

1. Treatment of **individual patients** with unmet medical need (UMN) and for whom the clinical trial is not an option, on a case-by-case basis, ***following availability of clinical data*** *for the concerned ATMP*
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N = 24/38 (63%)

Hospital Exemption (HE)

What would you consider the most **appropriate use and desirable aim** of HE? Please rate (1- 5most appropriate/desirable)

Use/Aim of Hospital Exemption	Rate (1 -5)
Treatment of individual patients with unmet medical need and for whom the clinical trial is not an option, on a case-by-case basis, *following availability of clinical data for the concerned ATMP.*	**83% rate 4+5** 1 = 8,3% 2 = 4,2% 3 = 4,2% 4 = 29,2% 5 = 54,2%
Treatment of patients with unmet medical need and for whom clinical trial is not an option, on a case-by-case basis, *before availability of clinical data and supported by rationale/proof of concept.*	**50% rate 4+5** 1 = 12,5% 2 = 16,7% 3 = 20,8% 4 = 16,7% 5 = 33,3%
Treatment of an undefined number of patients under a temporary "National authorisation for use" of an ATMP in a specific indication with unmet need, *following availability of supportive clinical trial data.*	**62% rate 4+5** 1 = 29,2% 2 = 0% 3 = 8,3% 4 = 8,3% 5 = 54,2%

RESULTS – Regulatory Support Tools

N = 38/38 (100%)

Developers' **awareness and experience** of the currently available **EU regulatory support tools**.

- EMA Innovation Task Force (ITF) briefing Meetings
- National Innovation meetings
- EMA Scientific Advice (SAWP)
- National Scientific Advice
- Simultaneous National Scientific Advice (SNSA)
- Parallel EMA-HTA body scientific advice
- EMA Qualification of novel methodologies and biomarkers
- EMA PRIME scheme – eligibility and enhanced support
- EMA Academia Briefing Meetings
- CAT classification
- CAT certification
- EMA SME Office
- Orphan designation

Indicate if you ever used it

- **Yes**
- **No, because I was not aware of it**
- **No, but I was aware of it**
- **No, I could be interested in the future**