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Report of the pilot on parallel regulatory-health technology assessment scientific advice

Summary

In 2010, the European Medicines Agency (EMA) established, with Health Technology Assessment Bodies (HTABs), a pilot on parallel scientific advice where developers could receive simultaneous feedback from both regulators and HTABs on their development plans for new medicines. This report provides an EMA assessment of the pilot:

- Parallel regulator-HTA scientific advice procedures have increased over time. Levels of alignment between HTABs and regulators following parallel scientific advice indicate that the evidence needs of different stakeholders can be met within one trial design or one development programme in most cases without blurring of remits between regulators and HTABs. Safeguards for data confidentiality are in place.
- Contributions submitted in response to the public consultation on the draft Best Practice Guide (BPG) for the pilot showed a high level of support for the concept and provided constructive suggestions for changes in the medium and longer term.
- The Best Practice Guide has been agreed between regulators and participating HTA Bodies. Publication of the best practice guide, and collated HTA body information will ensure that all stakeholders can have up-to-date guidance on the procedure, and should help applicants access parallel advice. The guidance is based on the experiences of more than fifty procedures under Best Practice Guide, four parallel regulatory-SEED[1] procedures, and the public consultation of the draft best practice guide.
- The report makes observations for a final sustainable model of parallel scientific advice whereby the regulator-HTAB interactions through parallel advice can be developed beyond what can be achieved in the current framework; such observations are for consideration when the final sustainable model is being designed.

Conclusion: The pilot of parallel regulatory-HTA advice under the draft Best Practice Guide has demonstrated positive outcomes and should now continue on an operational basis. Further

[1] Shaping European Early Dialogues for health technologies (SEED) consortium

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

development of this procedure, in conjunction with stakeholders, will take Joint Action 3 into account, until a final sustainable model of parallel regulatory-HTA scientific advice is firmly established.

Parallel Advice between regulators, HTA bodies and other relevant stakeholders offers a key platform in which to discuss the development of important new medicines, in order to pre-plan and maximise efficient, good quality and appropriate data collection that meets the needs of all stakeholders across the medicines lifecycle and thus, to facilitate timely access to these medicines. Parallel advice forms one element of the support tools available to foster medicines development for the benefit of patients in the EU.

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1. Introduction and background

The European regulatory system for medicines is based on a network of all national medicines regulatory authorities from Member States in the European Union and European Economic Area, united in the Heads of Medicines Agencies (HMA), and the European Medicines Agency (EMA), working closely together in an integrated fashion. For scientific advice, the European Medicines Agency (EMA) coordinates the existing scientific resources put at its disposal by 31 European Economic Area (EEA) countries for the provision of scientific advice for regulatory ends. The marketing authorisation is based on the benefit/risk assessment, requiring evaluation of quality, non-clinical and clinical data, excluding any economic considerations but frequently including data comparisons for clinical evaluation[2]. Following regulatory approval, subsequent decisions on coverage (reimbursement) and price of an authorised drug are made at the national level in each Member State. In countries where Health Technology Assessment (HTA) is in place, third-party payers, pricing and reimbursement agencies/HTA bodies (HTABs) rely upon HTA mainly to determine the reimbursement status, to inform about benefits and harms of new treatments compared to available treatment options of a drug and to support the price negotiation process.

Parallel scientific advice between regulators and HTABs is necessary to learn about data requirements at an early stage in a medicine's development process, and to learn about divergent data requirements between regulators and HTABs, and between participating HTA bodies. Stakeholders recognise that different frameworks drive the data needs for regulators and HTA bodies. To facilitate more efficient data collection, there is a need to understand data requirements and levels of alignment or divergence, and how data can be best collected if data requirements are different. Since 2010, the EMA has established a pilot project of parallel scientific advice with HTA bodies that allows developers to receive simultaneous feedback from both regulators and HTABs on their development plans for new medicines.

This pilot has taken place on the background of interaction between EMA and HTABs on a number of fronts. The initial focus of the collaboration was a project looking into how the information on the benefits and risks of a medicine contained in European Public Assessment reports (EPAR) could better address the needs of HTABs. This started following recommendations by European high level Pharmaceutical Forum in 2008 to improve the way data published by regulators contribute to relative-effectiveness assessments by HTABs. Other areas of collaboration include providing mutual input on methodological and disease-specific guidelines. The Agency and EUnetHTA also agreed the development of a joint three-year work programme in May 2013 outlining key areas of collaboration.

Furthermore, the pilot has also taken place in the context of the need recognised since 2005 to establish a sustainable European network of HTA bodies. To this end, the European Commission (EC) oversaw the setting up of the EUnetHTA Project, a network of HTA bodies with the objective of working together in order to develop reliable, timely, transparent and transferable health technology assessment scientific information across Europe. The project facilitated a number of work packages leading up to the Joint Action 1 in 2010. HTA bodies have performed several collaborative multi-HTA-body early dialogues within the framework of the EUnetHTA Joint Actions 1 and 2, and the EMA was invited to participate as an observer in the multi-HTA-body early dialogues of EUnetHTA Joint Action 2. EMA was also associated with the Shaping European Early Dialogues for health technologies (SEED) project - a consortium of HTA bodies - financed by the European Commission to explore a number of scenarios for conducting collaborative early dialogues. EMA took part in 4 parallel EMA regulatory SEED procedures.

The EC also established the HTA Network (HTAN) under Directive 2011/24 (article 15) and it gathers together all Member States, Norway and Iceland. EMA is also associated to the network. The network has published a strategy paper setting out its strategic vision, including long term sustainability. See Box 1.

[2] See Documents reference nos; EMEA/119319/04, EMEA/17424/01

In relation to scientific advice, the HTAN

- Commits to further strengthen interaction between HTA bodies and the EMA, building on ongoing cooperation within the EUnetHTA Joint Action.
- Calls for stronger synergies and closer interaction between developers of health technologies, regulators, HTA bodies and decision makers whilst respecting remits of different players.
- Calls for improving timely exchange of information and data through the life cycle of health technology.
- Calls for cooperation on defining phase IV studies and observational data collection and research (post-marketing phase).
- Calls on the Commission to facilitate exchange of information with the Network, as appropriate. For example, when implementing relevant legislative and non-legislative measures which can contribute to strengthening synergies between regulators and HTA bodies.

This will contribute to:

- Facilitating patients' safe, sustainable and timely access to innovative, effective technologies.
- Reducing duplication of efforts for clinical studies, data generation and analysis, faced by all actors along the pathway.
- Improving business predictability for developers of health technologies.
- Providing for a more seamless transition of technologies from development to regulatory and implementation stages.

Box 1: HTAN Strategy relevant to parallel scientific advice

The HTA Network will be supported by a scientific and technical cooperation mechanism, a function which will be fulfilled by Joint Action EUnetHTA until the end of 2015. Next steps are under consideration. Joint Action 3 will keep up building on these initiatives "to increase the use, quality and efficiency of joint HTA work at European level". This is part of the European Commission Public Health programme.

In 2015, the HTAN has published a reflection paper on Reuse of Joint Work in National HTA Activities which recommends:

- Maintaining and possibly clarifying the different options for scientific advice that meets the needs and the capacities of both HTA bodies and technology developers
- Strengthening interactions with regulators
- Defining one single framework/process to perform early dialogue (ED) involving both HTA bodies and regulators at European level, building on existing experiences (pharmaceuticals)
- Other aspects espoused include capacity building, involving any necessary additional expertise, appropriate stakeholder involvement, feeding the results of advices into the future disease specific guidelines, exploring possible funding and organisational models to make these activities self-sustainable, including the possibility of collecting fees and paying attention to the specific needs and concerns of some national/regional realities and to SMEs.

Lastly, the draft EU Medicines Agencies Network Strategy to 2020 aims to ensure timely access to new beneficial and safe medicines for patients and to strengthen collaboration with other key bodies such

as HTA, pricing and reimbursement bodies and patient and healthcare groups to enable appropriate decision making and sharing of information to this end. This builds on the EMA Roadmap 2010 to 2015 wherein the Agency stated that it would engage with HTA bodies in the early stages of development of a medicine (to avoid as far as possible the appearance of two different medicine-development programmes) and throughout the medicinal product's lifecycle, in terms of alignment of regulators' and HTA bodies' evidence requirements.

2. Analysis of activities in pilot

The pilot started in July 2010. This report is based on procedures completed by and experience gained from the start of the pilot up to December 2015. The pilot is now closed with the finalisation of the analysis and review of these data, as of the date of this report.

2.1. Number of procedures

By the end of December 2015, the overall number of completed procedures for all types of parallel regulatory-HTA scientific advices is 63. At the time of writing, 14 procedures are registered in 2016. This report is based on procedures completed by and experience gained up to December 2015. Of the overall 63 completed procedures, 4 were conducted under the framework of the Shaping European Early dialogue (SEED) Consortium, 6 were very first multi stakeholder consultations with third party facilitation, while the remainder were under the best practice guide (BPG) procedure. Four BPG procedures followed on from Adaptive Pathways discussions.

The overall number of parallel advices has been increasing over time since its launch in 2010 (Figure 1). There was a clear step change in take up of procedures in 2015, more than doubling the number of procedures in the previous year.

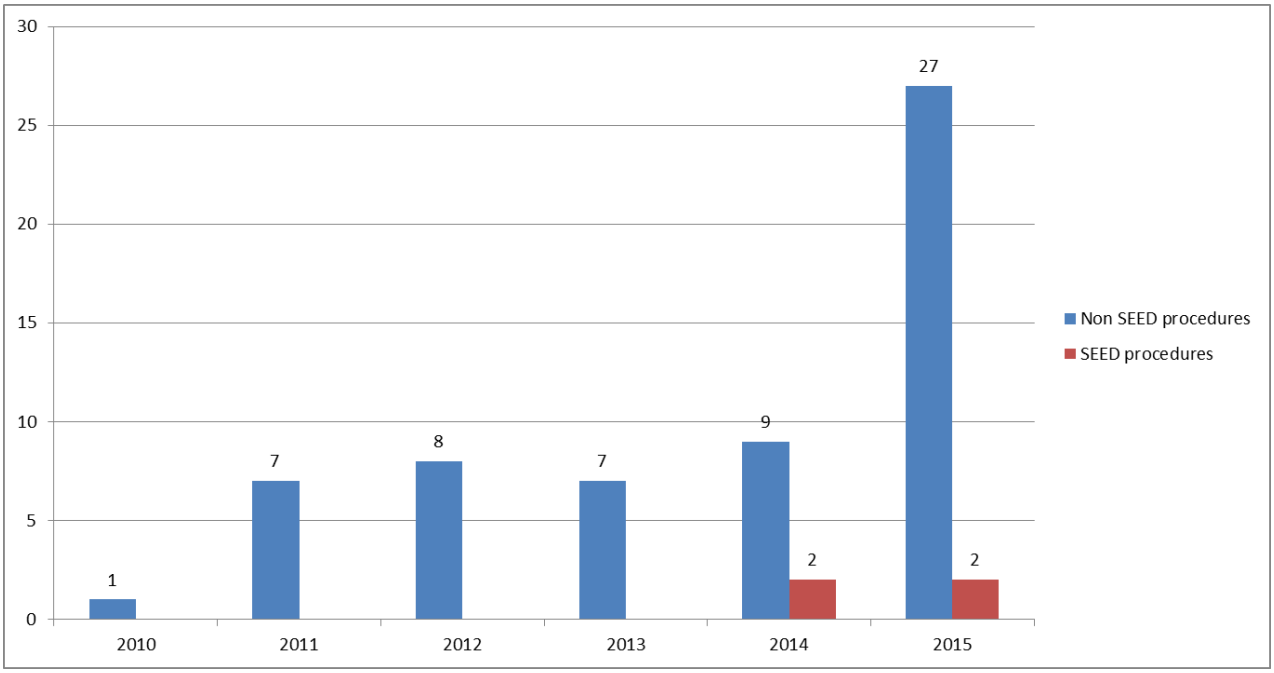

Figure 1**:** Number of completed parallel Regulatory HTA scientific advice procedures per year to end 2015.

2.2. Number of participating HTABs

The median number of HTA bodies involved per procedure in-non-SEED parallel regulatory advice procedures was 3, ranging between 1 and 5. (See also Figure 2, and Table 3).

HTABs in parallel Regulatory HTA scientific advice (Excluding parallel SEED procedures)
AIFA: Italian Medicines Agency (Italy)
AEMPS Spanish Medicines Agency (Spain)
CAHIAQ: Catalan Agency for Health Information, Assessment and Quality (Spain)
G-BA: German Federal Joint Committee (Germany)
HAS: Haute Autorité de santé (France)
HVB: Main Association of Austrian Social Security Institutions (Austria)
IQWiG: Institute for Quality and efficiency in Healthcare (Germany)
NOMA: Norwegian Medicines Agency (Norway)
NICE: National Institute for Health and Care Excellence (UK)
TLV: Swedish Dental and Pharmaceutical Benefits Agency (Sweden)
ZIN (formerly CVZ)**:** Dutch National Health Care Institute (The Netherlands)
INAMI: National Institute for Sickness and Invalidity Insurance (Belgium)
AOTMit Agency for Health Technology Assessment and Tariff System (Poland)

Table 1: HTA bodies taking part in at least one parallel scientific advice procedures under the best practice guide procedure. See also Figure 2.

HTABs in Parallel Regulatory SEED procedures
AETSA: Andalusian Agency for Health Technology (Spain)
AIFA: Italian Medicines Agency (Italy)
AVALIA-T: Galician Agency for Health Technology (Spain)
ASSR: Regional Agency for Health and Social Care (Italy)
G-BA: German Federal Joint Committee (Germany)
GYEMSZI: National Institute for Quality and Organizational Development in Healthcare and Medicines (Hungary)
HAS: Haute Autorité de santé (France)
HVB: Main Association of Austrian Social Security Institutions (Austria)
INAMI: National Institute for Sickness and Invalidity Insurance (Belgium)
IQWiG: Institute for Quality and efficiency in Healthcare (Germany)
KCE: Belgian Healthcare Knowledge Centre (Belgium)
NICE: National Institute for Health and Care Excellence (UK)
TLV: Swedish Dental and Pharmaceutical Benefits Agency (Sweden)
ZIN (formerly CVZ): Dutch National Health Care Institute (The Netherlands)

Table 2: For completeness-HTA bodies involved in parallel scientific advice procedures under SEED

EUnetHTA and SEED have performed in total 19 EDs on drugs in 3 years with a cooperative approach to optimise interaction and seek convergent views whenever possible. Four SEED procedures were

conducted as parallel regulatory SEED procedures.[3] A median of 9 HTA bodies were represented in each of the 4 Parallel EMA SEED procedures.

[3] ISPOR 2015: poster PHP275 Shaping European Early Dialogues. The SEED project.

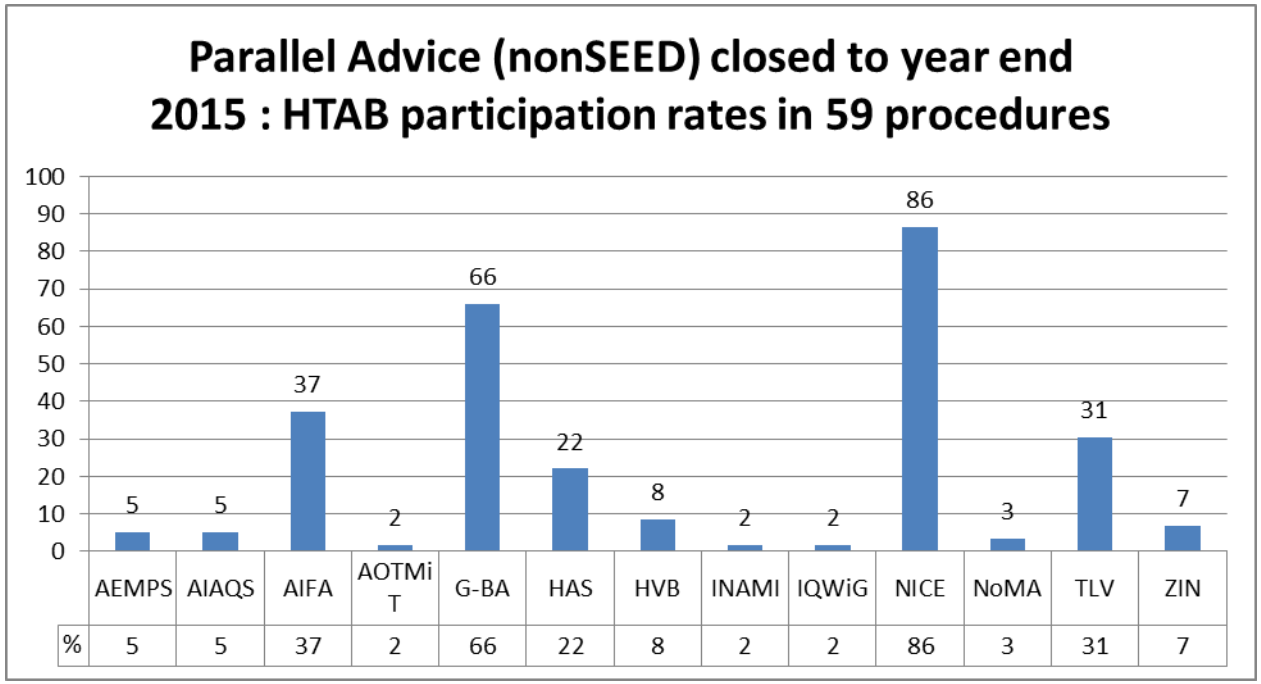

Figure 2: Rate of participation of HTA bodies in Parallel Scientific advice, parallel advice procedures (n=59) excluding SEED

Legend: NoMA; Norwegian Medicines Agency. NICE: National Institute for Health and Care Excellence, G-BA: German Federal Joint Committee, AIFA: Italian Medicines Agency, TLV: Swedish Dental and Pharmaceutical Benefits Agency, HAS: French National Authority for Health, HVB: Main Association of Austrian Social Security Institutions, AIAQS: Catalan Agency for Health Information, Assessment and Quality, ,IQWiG: Institute for Quality and efficiency in Healthcare, ZIN (formerly CVZ): Dutch National Health Care Institute, , INAMI: Belgian National Institute for Sickness and Invalidity Insurance, AEMPS: Spanish Medicines Agency, AOTMiT: The Agency for Health Technology Assessment and Tariff System.

HTABs	Number of Parallel Advice (nonSEED) closed to year end 2015:	% Procedures
AEMPS	3	5
AIAQS	3	5
AIFA	22	37
AOTMiT	1	2
G-BA	39	66
HAS	13	22
HVB	5	8
INAMI	1	2
IQWiG	1	2
NICE	51	86
NoMA	2	3
TLV	18	31
ZIN	4	7

Table 3 HTAB participation rate in 59 procedures

2.3. Therapeutic areas, SMEs, advanced therapies, rare diseases (orphans)

The therapeutic area of all the 63 procedures was derived from the anatomical, therapeutic and chemical (ATC) classification code of the product. A wide variety of therapeutic areas was evident. antineoplastic/ immunomodulating agents (ATC code L) represented 38% of the total, whereas neurology (ATC code N) and anti-infective agents (ATC code J) accounted for 13% and 12% respectively (Figure 3). There were a total of 9 orphan drugs procedures, and of these, 3 requested advice on significant benefit.

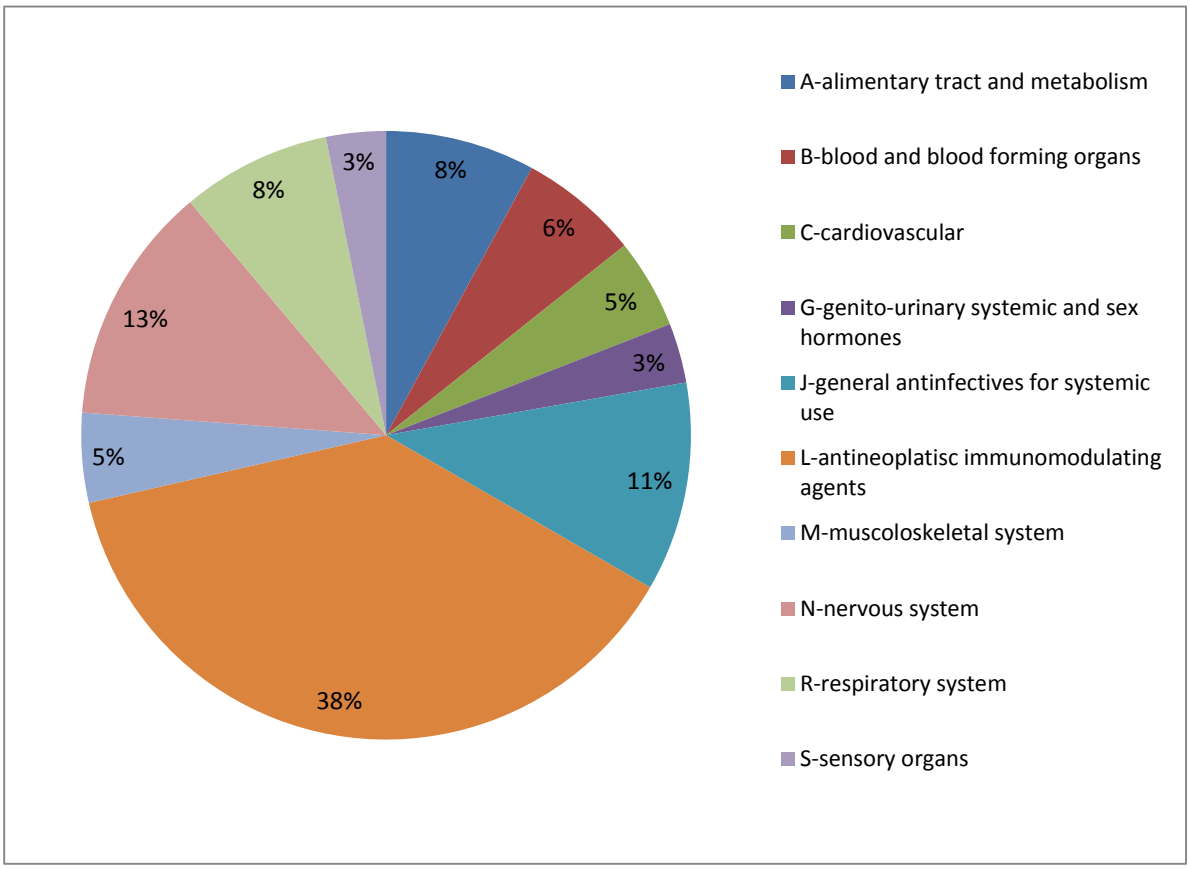

Figure 3: Procedures per ATC (n=63)

Of all the finalised procedures (n=63), 5 (8%) were advanced therapies, 27 (43%) were bio(techno)logical products and the remaining 31 (49%) were chemical entities (Figure 4).

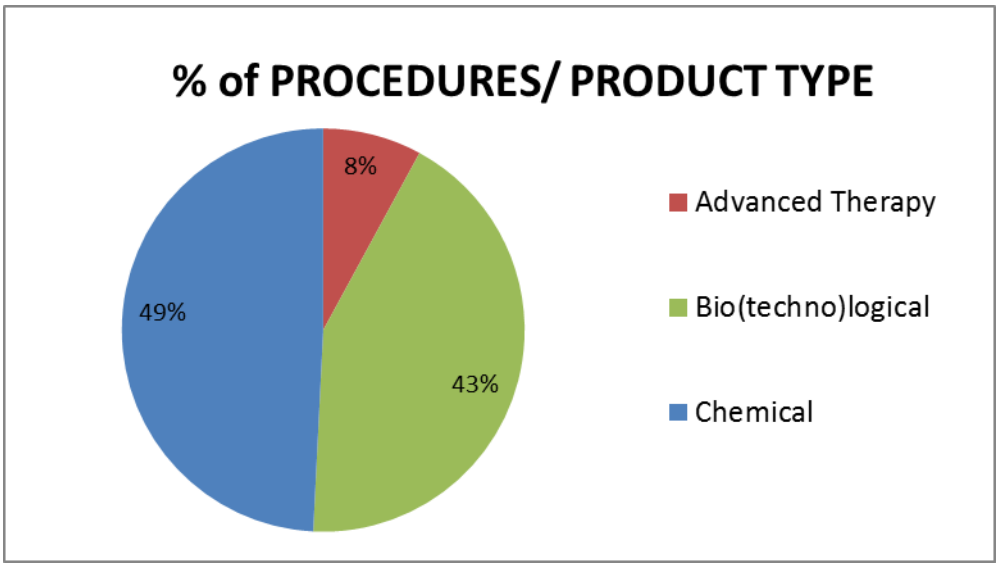

Figure 4: Procedures per type (n=63)

A single procedure was for paediatric use only, however 14% (n=9 out of 63) had Paediatric Committee involvement. Seven procedures out of 63 (about 11%) were submitted by small or medium enterprises (SME), three of which were related to orphan drugs.

With/without quality/nonclinical

Virtually all of the analysed procedures requested advice on clinical aspects (62 out of 63), although one was a follow-up procedure requesting advice on quality only. The number of procedures covering questions on quality and preclinical aspects were 8 and 16 respectively. Questions on clinical aspects covered pharmacokinetics, statistics and risk management plans.

2.4. Patient representative participation rate

Overall patient representatives participated to about 40% of the finalised procedures (25 out of 63). Patient representative were routinely invited from December 2014. Indeed a steep increase was reported in the last two years, when patient participation rose from 18% in 2014 (2 out of 11 finalised procedures) to almost 60% in 2015 (17 out of 29 finalised procedures) (Figure 5).

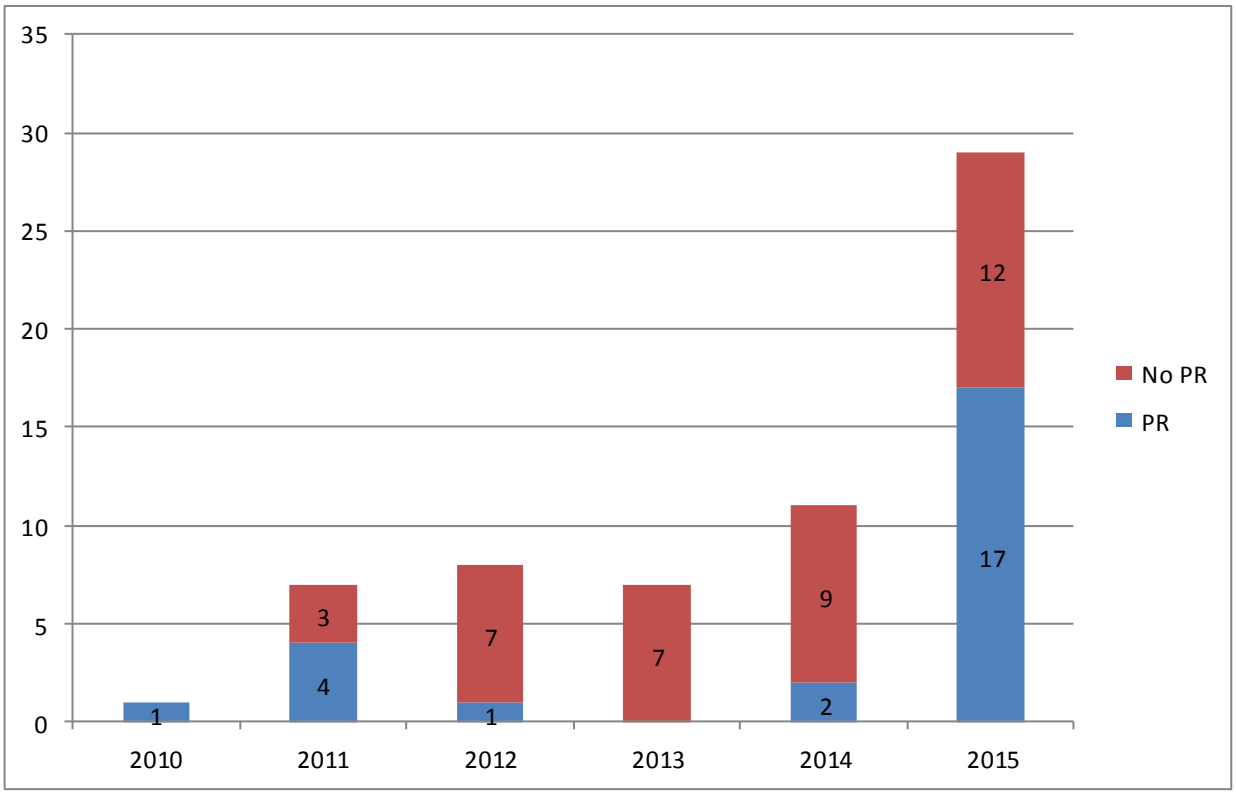

Figure 5: Rate of participation of patient representatives per year (n=63 procedures).
Legend: **PR**: patient representatives involved, **No PR**: patient representatives not involved

Reaction

The top three therapeutic areas are in line with standard scientific advice where in 2013 corresponding numbers for oncology, neurology and anti-infectives were 32%, 11% and 11%.

Small and medium enterprises are significantly under-represented in EMA parallel regulatory-Health Technology Assessment scientific advice comprising only 11% of the sample compared to 27% within standard scientific advice. However, this under-representation appears to be declining with more SMEs now coming forward. Products with orphan designation also appear to be under-represented 14% vs 29%. Advanced therapies appear to be as frequent and standard scientific advice ~5-7%.

Patient participation rate in 2015 appears no less successful than with standard scientific advice. Significant efforts are made to identify procedures that would benefit from patient participation, to and identify and support patients in their contribution in line with the revised EMA framework for patient participation.

3. Content analysis

Summary

To explore how the parallel scientific advice system was working, a retrospective blinded comparative analysis was undertaken on 31 procedures under the draft best practice guide between 2010, and May 2015. This pragmatic analysis indicated that there was a high level of full or partial alignment between regulators and HTAB across all domains at the culmination of the procedure. Alignment was highest for the domain of population (77% full agreement, 14% partial agreement) and lowest for the domain of comparator (44% full agreement, 25% partial agreement). Agreement on the domains Endpoints, Other study design characteristics and Overall package were in between these values.

Examination of 7 cases with remaining nonalignment on comparator was conducted. In four cases, these could potentially be addressed with indirect comparisons. In one of these cases, a redesigned trial was needed to address the issues related to the comparator but also other dimensions of the trial 2) in two cases, a three arm trial was the most obvious solution, potentially acceptable to both the Regulator and the HTABs.

Examination of a random sample (15%) of cases where there was full or partial alignment between regulators and HTABs on comparators confirmed that the choice of the comparator for regulators was firmly anchored in an expected regulators' rationale. The argument for absence of blurred remits is further strengthened in the 7 remaining comparator disagreements discussed above where regulators retained a complete regulators' based choice of comparator e.g needing to understand the placebo or vehicle response, or the proposed comparator was an acceptable licensed alternative based on the current state of the art from a scientific and clinical perspective.

Reaction

Whilst it is recognised that different decision makers have different objective to address, and thus may have different evidence requirements, through the process of parallel scientific, understanding is reached on what these different requirements may be, the level of commonality in the evidence requirements between decisions makers, and whether there are different trial designs, or amendments to the development plans that would mean a single development plan or trial is possible to meet potentially disparate evidence needs.

The retrospective study shows that at the culmination of the parallel scientific advice, the level of commonality in the evidence requirements between participating decisions makers on issues like comparator and study endpoints is relatively high. Future research should validate this analysis prospectively. In the long term the impact of parallel advice on the success factors of MAA and market access needs to be examined.

A detailed joint publication of the analysis summarised above is planned in a peer reviewed journal.

There is no blurring of remits. Roles and remits of different stakeholders are respected. The regulatory criteria for Marketing Authorisation approval remain unchanged; there is no intention to change these.

4. Best practice guide for pilot parallel regulatory-health technology assessment scientific advice procedures

4.1. Public consultation

The European Medicines Agency (EMA) published on the 8 May 2014 the draft best practice guidance for pilot parallel scientific advice procedures in the pilot involving the regulators and Health-Technology-Assessment (HTA) bodies for a three month public consultation. Annex 1.

The document was a key outcome of the Regulatory-HTA workshop on parallel scientific advice, which took place in November 2013 and brought together over 280 representatives from, amongst others, the European Commission, European regulators, HTA bodies, the European Network for Health Technology Assessment (EUnetHTA), the pharmaceutical industry, payers, patients and healthcare professionals. The report of the workshop was also published. See Annex 2.

The draft guidance set out the different phases of the process for regulatory-HTA parallel scientific advice and highlighted ideal timelines and actions for all parties, including HTA bodies, the EMA and applicants undertaking a parallel advice procedure. The document was drafted in collaboration with HTA bodies based on the experience gained so far with parallel scientific advice and on the input provided by stakeholders during the November 2013 workshop. Specifically, a process working group comprising representatives from EMA, SAWP and HTA Bodies (AIFA, G-BA, NICE, TLV) met frequently to discuss and review the procedure, the consultation contributions, and revisions. EUnetHTA representation was also invited.

Stakeholders were invited to provide comments on the proposed process by 14 July 2014, using the online form accessible via the draft guidance document. It was noted in the consultation document that the EMA was also associated with the Shaping European Early Dialogues for health technologies (SEED) consortium, to explore a number of scenarios for conducting early dialogues. The document also stated that the outcome of the pilot, the public consultation on the draft process, as well as the results from the SEED project, would be taken into consideration to in formulating the next steps to best meet the objective of the early dialogue for health-technologies exercise at the EU level.

Frame of consultation and received contributions

Twenty four questions were posed for consultation under the EMA Specific Privacy Statement for Public Consultations EMA/310325/2012. In case of contributions submitted by individuals on behalf of a legal person, only the identity of the latter will be published.

Received contributions are summarised in the report text below. A full line listing of all text answers is provided in Annex 3 classified by question. A full line listing of all text answers classified by area of procedure together with detailed EMA responses is provided in Annex 4. Note that changes to the process are considered at 2 levels; those proposed for an interim model of the pilot best practice guide, and secondly observations are made for a final sustainable model.

Questions 1-5 inclusive were questions pertaining to contact details and affiliation.

EMA received 18 submissions in response to the questionnaire with supplementary letters submitted from 4 participants, 3 of whom also submitted questionnaire responses. These were from a variety of affiliations. See Figure 7 and Table 5. The majority were from Industry but included Small and Medium Enterprises as well as individual big companies and industry representative organisations. Contributions were received from 1 disease patient organisation and 1 joint response from 4 advocacy groups who classified their affiliation as 'other'. There was a single contribution from one individual and written contributions from 2 HTABs.

Participating HTABs were fully and continuously involved in the preparation of the draft best practice guide and consultation document, the review of contributions and consequential change to the best practice guide.

Stakeholder Number	Name of the organisation or individual
1	National Institute for health and Care Excellence (NICE)
2	Teva Europe
3	The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE AISBL)
4	F.Hoffmann - la Roche Ltd.
5	GSK
6	Biogen Idec International GmBH
7	Alexion Pharma International Sàrl
8	Association Internationale de la Mutualité (AIM) Health Action International (HAI) Europe, The Medicines in Europe Forum (MiEF) The International Society of Drug Bulletins (ISDB)
9	European Federation of Pharmaceutical Industries and Associations (EFPIA) EuropaBio and Vaccines Europe (joint comments)
10	International Patient Organisation for Primary Immunodeficiencies (IPOPI)
11	European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) Health Technology Assessment (HTA) Special Interest Group (SIG)
12	Plasma Protein Therapeutics Association (PPTA)
13	Novartis Europharm Ltd.
14	Janssen Pharmaceutical Companies of Johnson and Johnson
15	Boehringer Ingelheim
16	Novo Nordisk A/S
17	RIZIV-INAMI Brussels
18	Individual
19*	Plasma Protein Therapeutics Association (IPFA)

* No questionnaire response submitted

Table 4: List of contributors

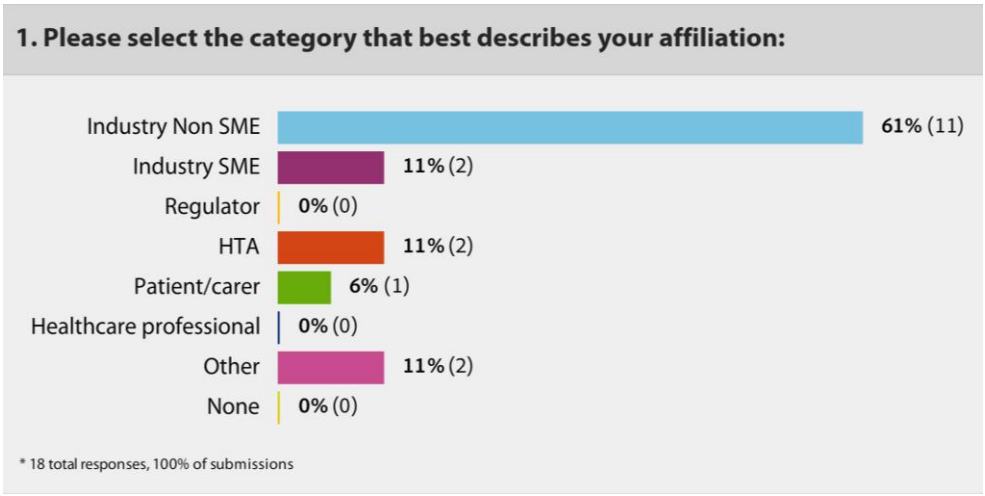

Figure 6: Affiliation of contributors

Two thirds of contributors had not undertaken parallel scientific advice. As a public consultation, a broad response is solicited and there is no requirement for participants to have undertaken the procedure in order to be able to comment on the procedure. The absence of participation also is not considered to undermine the responses from these applicants and all responses are considered valid.

Model of parallel regulatory-health technology assessment scientific advice and general principles

Overall, there was broad agreement with the principle of multi-stakeholder parallel scientific advice where 71% agreed with the model presented. Collaboration between stakeholders was seen as extremely important, that this can help decisions on development plans and aligns evidence requirements both pre- and post-approval, and that the end goal was to ensure that patients have access to a new therapeutic option. See figure 8.

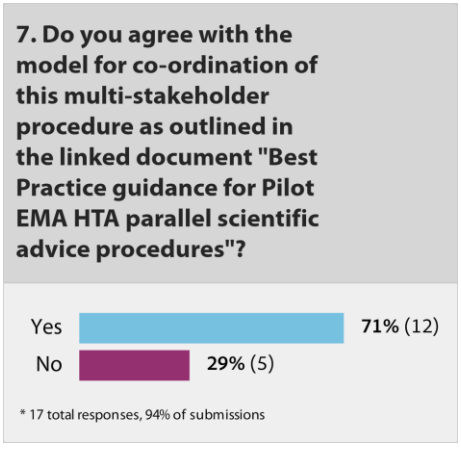

Figure 7: Support for the model of parallel regulatory-Health Technology Assessment scientific advice

Of those, who did not agree, there was only one fundamental objection to the principles of the parallel scientific advice; this was from a joint advocacy group on the grounds that this constituted 'regulatory capture', that the process was opaque and that those involved in decision making should not be part of those giving advice. See 'reaction' below.

Of the remainder of 'No' not agreed, the issue was that the model could be improved further such as with: a common HTAB output, joint advice with a consolidated regulatory HTAB output clearly identifying divergences, greater HTAB involvement, greater efforts to align HTAB positions, that all experience from all related pilots should be considered in drafting a final sustainable model. There

were also calls for a single point of contact and administration driving the clarity, logistics and organisation of the procedure. It was stated that the procedure also should remain optional.

Other general principles emphasised were inclusion of good governance, scientific excellence, a concise process (no more than 6 months from first contact to advice output), appropriate expertise, use of nonHTA public bodies in the case of vaccines, metrics to measures success, inclusion of other stakeholders such as healthcare professionals and payers. The EMA was proposed by one company as the single central administrative structure, and there was a request for simplification of the agreements and fees for HTAs e.g. the applicant could pay one fee to EMA which covers EMA and HTA fees. Two contributors were concerned about capacity of HTABs to undertake such procedures, with one reflecting on whether this would lead to prioritisation of products. One contributor remarked that small markets should not be neglected. One contributor asked if closer alignment would lead to a change in marketing authorisation criteria.

Reaction

EMA agreed that the draft parallel advice procedure as released for public consultation could be amended further with greater clarity on coordination, a common or coordinated HTAB output, more comprehensive and EU wide HTAB involvement. As this is a multi-stakeholder procedure, it is for HTA bodies to decide how they themselves are organised within the procedure and the nature of HTAB outputs. Thus, all such elements were comprehensively discussed with participating HTABs in the process working group, and a multi-lateral agreement was reached on an interim model as laid out in the best practice guide. EMA agrees that all experience from all related pilots should be considered in drafting a final sustainable model of parallel advice, and that a single point of administration and contact would drive the clarity, logistics and organisation of the procedure. Content (HTA scientific) coordination can be differentiated from logistical coordination as in the current standard regulator scientific advice procedure. Broader HTA engagement in the medium term is foreseen, and thus the method of recruiting HTA bodies may change. At the time of writing, the current method, where industry makes requests to individual HTA bodies, will continue until an alternative method is further discussed, agreed and communicated.

Furthermore, a final sustainable model would have a clear and common conflict of interest policy for all members and experts. Transparency on the selection process for all experts is also needed. It is also agreed that the a final sustainable model would also espouse good governance, scientific excellence, a concise process (no more than 6 months from first contact to advice output), appropriate expertise, use of nonHTA/other bodies in the case of vaccines or other cases as needed, and inclusion of other stakeholders such as healthcare professionals and payers. The resource model could also be considered together with how HTAB are incorporated into the procedure.

To address the fundamental objection to the provision of scientific advice, the Agency provided the following response. Scientific advice is an important tool used by the EMA, EU Member States and other international regulators to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients. Scientific advice helps the applicant to make sure that it performs the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing-authorisation application. It is important to avoid failure at marketing authorisation because of poor or inadequate trial design. The coalition of the European medicines advocates (HAIE, ISDB, MEF and AIM[4]) imply that scientific advice is "unnecessary if scientific data are robust, if guidelines are acceptable or if clinical trials are designed to address legitimate public health needs". Each of these cases is refuted below, together with clarification of the scientific advice process and its purpose.

Regulation 726/2004 foresees that the Agency must provide the best possible scientific advice to applicants. Scientific advice is prospective in nature; it focuses on development strategies rather than pre-evaluation of data to support a marketing-authorisation application, and it is not legally binding on

[4] Health Action International Europe (HAIE), International Society of Drug Bulletins (ISDB), Medicines in Europe Forum (MEF), Association Internationale de la Mutualite (AIM).

the Agency or on the sponsor. Scientific advice can be given to any legal or natural person seeking advice on the undertaking of clinical trials on medicinal products for use in humans.

By giving an opinion on the appropriate and necessary study designs before such studies are conducted, it means that patients will not be entered into inappropriate clinical trials, and resources for scientific research will not be wasted doing the wrong studies. The clinical trial methods in a particular marketing application require detailed considered in any event. It is too late to provide this feedback on trial design at the time of MAA, if the wrong studies have been done or done inadequately or inappropriately as this will lead to inordinate delays while the correct studies are performed. In particular, it is stressed that according to the declaration of Helsinki "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects." Therefore, enrolling patient in regulatory trials that will likely not be deemed conclusive by regulators violates the principles of ethical trial conduct, may expose trial patients to an unjustified risk, and may delay or prevent access for patients to potentially beneficial therapies. To be effective, early engagement has to involve those who collectively and ultimately judge the quality of the development program at the time of marketing authorisation applications.

Guidelines do not address all research scenarios, in particular for innovative areas of research, and can become rapidly out of date, where science is advancing rapidly. Even within existing guidelines, advice is often needed on how to implement particular aspects.

The coalition states that advice is unnecessary if clinical trials are designed to address legitimate public health needs. The question is posed as to how these trials are to be designed? The design of a clinical trial is a specific therapeutic area is a complex and difficult issue and the wrong design choices can invalidate the trial. Scientific advice is best place to guide the appropriate clinical trial designs. There is a responsibility to future patients to ensure that trials are done are up to the standard as required by the opinion makers which is why the current EMA advice model is pursued. Therefore, it is not supported that scientific advice should be disconnected from those formulating the final opinion on the marketing authorisation application (Committee for Medicinal Products for Human Use (CHMP)). The Final Decision on the marketing authorisation application is granted by the European Commission. . The relationship of advice with CHMP is not a conflict of interest but is in the interests of patients.

Scientific advice procedures include patient representatives as individuals rather than organisations. All individuals taking part must adhere to the EMA conflict of interests policy. EMA has a robust conflict of interest policy in place to avoid any financial conflict of interest of committee or working party members or experts. Furthermore, Applicants are unable to exercise any choice in the allocation of which regulatory National Competent Authority provides such advice.

One contributor asked for clarification that closer alignment between regulators and HTA would not lead to a compromise or change of the criteria for Marketing Authorisation approval based on safety and efficacy. As stated above in the section on Content Analysis, there is no blurring of remits. Roles and remits of different stakeholders are respected. The regulatory criteria for marketing authorisation approval remain unchanged; there is no intention to change these. Evidence from the content analysis also bears this out.

HTAB information, pre-requisites and dossier circulation

There was overwhelming support that information on HTAB contact details and pre-requisites should be available at a central location. The remaining dissenting voice also did not agree with the concept in principle. More than two thirds wished this to be available on the EMA website, two (nonHTAB) contributors wanted it available only on request, and the remainder wanted it available on the EMA and EUnetHTA website, or had not clear preferences as long as the information remained up to date. See figure.

Included in the requests for information was transparency as to how the HTAB advice would be implemented at the national level.

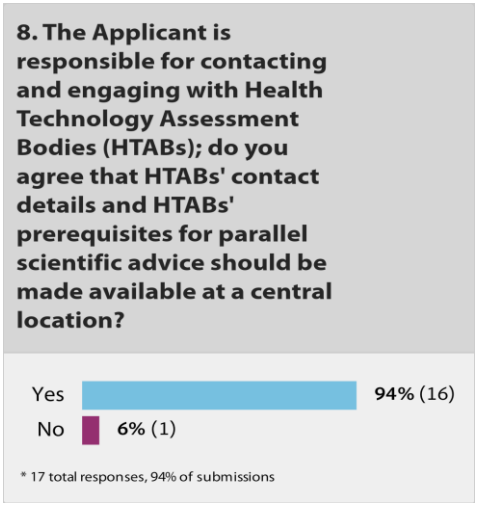

Figure 8: Availability of HTAB information

Reaction

It is agreed that collated information on HTAB contact details and pre-requisites should be available at a central location such as the EMA and HTAB associated websites. This should include for information was transparency as to how the HTAB advice would be implemented at the national level.

The final sustainable model would ensure the experts included are abreast of authorities' general direction and policies, scientifically prepared, empowered to adapt discussions, and that internal processes are adapted to be able to consider the impact of face to face discussions to ensure that the outcomes of advice processes are useful to minimise regulator HTAB divergences where possible and reusable in future national discussions.

Most contributors considered that the applicant should still send the documents to the HTABs. Those who did not agreed and wished the EMA or 1 coordinating both to circulate documents were of mixed affiliations with no clear pattern.

Reaction

The applicant should continue to circulate the documents directly to all involved HTABs and regulators as in standard scientific advice as this is applicant's responsibility and is also resource and time efficient.

Confidentiality, communication, coordination

The majority of contributors agreed that there were elements of communication that needed to be clarified or strengthened. There were requests to separate communication and coordination in the guidance, to have clearer responsibilities for specific actions and logistics, that confidentiality should be respected, and that a confidentiality agreement should be implemented between HTABs and EMA. One contributor fundamentally did not agree that the process should be confidential. There were requests for feedback from pre face to face meetings to the Applicant concerning divergences as well as requests for preliminary HTAB views. Project timelines, use of a secure system of sending documents, and EMA to collate HTA comments were also requested.

Reaction

To address the fundamental objection that "scientific advice should not be confidential", the following response is provided from the regulators' perspective. Scientific advice is a procedure in which the Agency, upon a voluntary request from the drug developer, provides guidance on issues relevant for the generation of the best possible data on quality, efficacy and safety of medicines. This is done in a

confidential environment given the fact that drug development is carried out in a competitive manner by different sponsors. It is also given prospectively before the trials are designed and years before the final marketing authorisation application is submitted to the EMA or reimbursement requests are submitted to HTABs.

The advice given guides developers on how to generate the best possible evidence in support of a future marketing authorisation. It contributes to the best possible use of resources for drug development, including patient involvement in clinical trials, avoiding futile or inadequate developments; agreeing on the best clinical trial design is of particular importance for patients and public health.

Upon finalisation of the assessment procedure of the marketing authorisation, EMA includes details of the Scientific Advice that have been given to the applicant in the European Public Assessment report (EPAR) published on the Agency's website. This provides transparency on the advice given to the applicant and how this was taken into account (or not) during development and product assessment.

Untimely or inadvertent disclosure of the details of the scientific advice given may discourage applicants to request scientific advice from EMA and may as such result in failing to develop and bring to patients potentially good drugs because companies do not use the right methodology to test them. Furthermore, scientific advice letters invariably contain information that is commercially confidential, such as future development plans, multiple or broader indications, only 1 of which may be finally authorised (the final indication is only concluded upon by the CHMP at the last stage of the authorisation process), or details of production processes. Therefore maintaining the confidentiality of the scientific advice prior to grant of marketing authorisation is important in order to encourage applicants to seek such advice with a view to optimising drug development and favouring patients' timely access to innovative treatments.

To contribute to the scientific knowledge on product development and providing scientific guidance, learnings from regulators' scientific advice is distilled in an anonymised and generalised way in the form of specific guidelines when sufficient experience on the area has been gained and general principles can be formulated.

Therefore, commercially confidential Information provided to the EMA within the context of scientific advice will not be shared with any party preauthorisation in the absence of a signed confidentiality undertaking or the consent of the sponsor as per the European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043, and Art. 4(2) of Regulation (EC) No 1049/2001. Scientific advice or protocol assistance outcomes will not be shared with other applicants. Nevertheless, sharing of relevant documents (e.g. Lists of Issues and Final advice letter) with HTA bodies is needed within the parallel advice procedure to achieve the stated aims of the activity and will respect these data safeguards. At the time of writing, no current confidentiality framework exists between the EMA/EC and HTA bodies, therefore sponsor's consent to any document sharing between EMA and HTA bodies will be sought by EMA with regard to sharing of documents in these parallel advice procedures.

A final sustainable model of parallel advice would have a clear confidentiality framework for all regulators and HTA bodies to facilitate collaboration and exchange of relevant documentation in a protected way in order to meet the objectives of parallel advice.

It is agreed to separate communication and coordination in the best practice guide, to have clearer responsibilities for specific actions and logistics, that confidentiality should be respected within applicable frameworks, and that feedback from pre face to face meetings to the applicant concerning divergences should be given as well preliminary HTAB views in the form of HTAB list of questions.

Project timelines, use of a secure system of sending documents, and EMA to collate HTA comments are all possible revisions.

Pre-validation phase

The majority of contributors agreed that the pre-validation teleconference between HTABs, regulators and the applicant should be optional. Views were split as to whether the pre-validation phase could be streamlined in any other way. Those who considered that further streamlining could take place identified the following; HTAB and regulators' comments at the pre-validation stage should be shared between regulators and HTABs with clear deadlines and collation. EMA comments at this stage should also include scientific as well as 'regulatory' comments.

Other comments were related to: changes to the EMA letter of intent specific to the procedure, that patient representatives should be invited from the start of procedures, that there should be a conference call possibility offered also when in the shortened pre-validation stage of option 2 (i.e without pre-validation TC) and there should be a choice of face to face or TC for the pre-validation meeting.

Reactions

It is agreed that the pre-validation TC continues to be optional. This can be understood to be needs-based and an efficient use of resources of all stakeholders. A pre-validation TC option would be recommended when applicants are very inexperienced, the technology is very novel or controversial or the applicants otherwise consider this necessary.

It is agreed that HTAB and regulators' comments at the pre-validation stage should be shared between regulators and HTABs with clear deadlines and collation. EMA comments at this stage should also include scientific as well as 'regulatory' comments. The term 'regulatory' in this context refers broadly to activities pertaining to safety, quality and efficacy as opposed to reimbursement and HTA. It is acknowledged that in a narrower context regulatory refers to non-scientific matters regarding the rules within medicines development; there is thus potential for misunderstanding. Changes to the EMA letter of intent specific to the procedure area also agreed.

In principle, there is no opposition to inclusion of patient representatives as early as possible in the procedure. In practice, despite early and repeated attempts with a dedicated unit, there are often difficulties in identifying available patients with a particular disease until later in the procedure.

It is not agreed a conference call can be routinely offered also when in the shortened pre-validation stage of option 2 (i.e without pre-validation TC). It is also not practical or resource efficient to offer a choice of face to face or TC for the pre-validation meeting.

In response to global drug development timeframes, scientific advice has shortened the lead-in timetables for all scientific advice procedures including parallel advice and biomarkers. Currently, it could be a short as 4 months from time of first contact with EMA to request a date for theface to face meeting date, to the face to face meeting if no presubmission meeting is needed. A draft briefing package should be submitted together with the letter of intent to allow quicker start of procedure. The final briefing package is expected in the week prior to the start as per current procedure.

The term pre-validation will be replaced by pre-submission in common with standard EMA scientific advice.

Meeting phase, list of issues and advice format

When asked if all applicant's questions should be discussed during the face to face meeting, two thirds agreed that this should be the case. There was support for an HTA list of issues, one contributor wanted the Applicant to decide the issues, and one contributor wanted to base the meeting only on divergences. Two thirds of contributors agreed that the EMA regulators' list of issues should always be

sent to the HTABs with the remainder only with Applicant consent. Two thirds of contributors supported HTAB written answers. See figure.

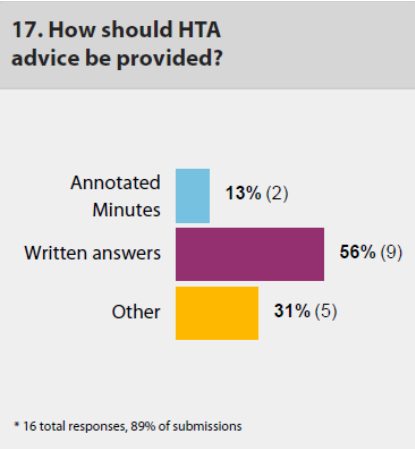

Figure 9: Format of advice

Reaction

The best practice guide consulted on this question in the frame of the practice at that time which was that HTABs only gave feedback during the face to face meeting. HTAB written answers mean that the face to face meeting can be more focused on exploring specific issues if interest for HTABs and EMA, and areas of divergence. This is time efficient and more productive for the aims of the procedure. HTAB written answers for all participating HTABS and a HTAB list of issues is essential to facilitate such a focused meeting approach. This means also that HTAB and regulator meeting participants can reflect upon the meeting interaction and update final advice as needed.

It is agreed that the EMA regulators' list of issues is sent to participating HTABs; the letter of intent will expressly request applicant consent on document exchange between EMA and HTABs in the procedure. In the absence of consent, exchange of confidential documents is not possible.

If divergences are not resolved, or a development plan that can accommodate such divergences is not mooted during the face to face discussion meeting, opportunities to further consider these scenarios could include parallel regulatory HTA qualification procedures, parallel regulatory HTA broad advice, workshops or follow up parallel regulatory HTA advice.

Amended development plans and follow-up procedures

There was very strong support in the public consultation for the possibility of submitting amended development plans, emphasising the need to take account of changes such as FDA feedback. In general, the time frame for such submission was supported but a preference was for 10 days before the face to face meeting rather than 2.5 weeks, and consistent with the timing of the responses submission. All parties must be notified of coming changes as soon as this is known, with a comparative documents showing what has changed and why. See figure. There was very strong support for the possibility of a follow up advice.

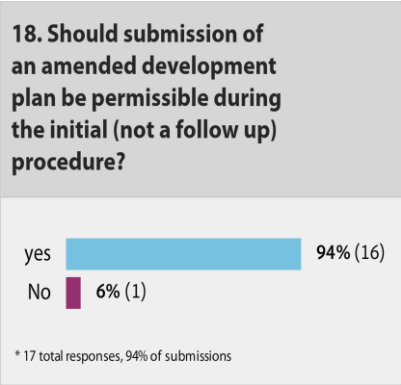

Figure 10: Amended development plan

Reaction

It is clear from experience that requesting submission of the presentation so early prior to the face to face meeting is not optimal. Presentations are invariably changed causing confusion and frustration on behalf of assessors. It is proposed to leave the presentation submission until an absolute deadline of 4 full working days prior to the face to face meeting. This leaves more flexibility in scheduling the pre face to face interaction between regulators and HTABs. Applicants must respect the requirements for amended development plans such that of assessors to have sufficient time available to provide informed views.

Duration of procedure

There was strong support for a procedure that lasts no more than 6 months from pre-notification until final letter.

Reaction

This is agreed. Now, it could be a short as 4 months from time of first contact with EMA to request a date for theface to face meeting date, to the face to face meeting itself if no presubmission meeting is needed.

4.2. Comparison of best practice guide with final parallel regulatory SEED procedure

During the SEED project, efforts were made to align regulator and HTAB procedures. There were 4 regulatory SEED parallel advice procedures during this project, each testing a new iteration of the procedure, changing timings and actions according to accruing experience. The process for 4th iteration is below see Box 2.

Comparing the 4th iteration of the parallel regulatory SEED procedure and the consolidated best practice guide (BPG) procedure, some remarks can be made. Both have a lead in pre-submission period before the procedure starts. The BPG procedure is more flexible in allowing a longer (42 day with presubmission TC) or shortened (21 day without presubmission). A flexible approach here is required according to the consultation comments.

Both procedures set out day 30 list of issues for HTABs and regulators. Both procedures set out a day 60 face to face meeting with written answers by about day 80. Three weeks for finalisation of the letters seems ample.

The main timing issue appears to be the end loading of the parallel regulatory SEED procedure where a 3 hour closed face to face meeting between the SEED HTABs only, followed by a closed SEED EMA regulatory face to face meeting of 1 hour all occurs on the same day of the 3-4 hour face to face meeting. This closed SEED meeting at day 60 considers the draft answers pre-meeting provided by the

HTABs at Day 49. This full day meeting approach appears not sustainable with increasing throughput for parallel advice. If draft written answers were provided by HTABS by day 22, that would still allow 3 weeks full assessment time to prepare draft HTAB answers pre-meeting, and would mirror the day 22 SAWP first reports. This means that the closed HTAB only e-meeting which already occurs at day 30 could also consider draft HTA answers and reduce the number of meetings, resources and costs per procedure.

Regarding coordination, in each parallel regulatory SEED procedure, there were 2 logistic coordinating bodies (EMA and SEED) and an applicant. This led to the position where the applicant was triangulating between the 2 coordinating bodies when submission timetables were being discussed. With 2 coordinating bodies, there is duplication of time and resources when running the procedure. It also means that there is no clear single contact point for the procedure, and the applicant emerges as a go-between which is not desirable for a regulatory-type procedure. Another potential disadvantage of 2 coordinating bodies is the missing out on potential efficiency gains that could be harnessed from common IT, patient organisation support, potential sharing of clinical experts or other support platforms.

As well as shaping evidence generation for HTA appraisal and post-launch, it is observed that HTA body involvement in parallel advice could aid horizon scanning, capacity building, the better understanding of regulators' thinking, the building on synergies between regulator and HTA expertise (much in common on scientific principles of clinical trials, real-world evidence generation, and evidence based decision making), and is a good practical basis on which to build and strengthen the collaboration between regulators and HTA bodies.

One major advantage of the parallel regulatory SEED procedure seen from the regulators' stand-point, is the coordination of HTA bodies on content, making it easier for each sector to appraise the scientific views of the other. The broader inclusion of HTABs is also welcomed. EMA supports these elements being brought forward in the interim and final models of parallel advice.

Phase	Actions of HTABs in parallel Regulatory SEED procedure	Actions of Regulators in Parallel Regulatory SEED procedure
Day – 33	Draft Briefing Book (BB) send partners, check for completeness (ALL)	Draft BB send to all regulators, check for completeness (ALL)
Day -18	TC EMA, Applicant, SEED Coordinator	TC EMA, Applicant, SAWP Coordinator
Day -18	Written List of points for clarification sent by HTA bodies to the coordinator	List of comments EMA sent to Applicant
Day 0	Final BB received	Final BB received
Day 18		First reports SAWP
Day 29	List of key issues discussion (E-meeting) between HTAB only	SAWP only discussion
Day 29	TC Closed Joint exchange EMA Regulators HTA	TC Closed Joint exchange EMA Regulators HTA
Day 30	List of Key issues to Applicant	
Day 32		Regulators' List of issues to the company
Day 45	Applicant's answers to key issues	
Day 49	SEED draft written answers	
Day 64	HTA only closed meeting	
Day 64	Closed Joint exchange EMA Regulators HTA	Closed Joint exchange EMA Regulators HTA
Day 64	Face-to-face meeting EMA Regulators HTA Applicant	Face-to-face meeting EMA Regulators HTA Applicant

Phase	Actions of HTABs in parallel Regulatory SEED procedure	Actions of Regulators in Parallel Regulatory SEED procedure
Day 64	Closed Joint exchange EMA Regulators HTA	Closed Joint exchange EMA Regulators HTA
		Regulator's draft Joint report
Day 84		Regulator's Final advice letter sent
Day 87	Final SEED written answers	

Box 2 Parallel EMA Regulatory SEED procedure at 4th iteration

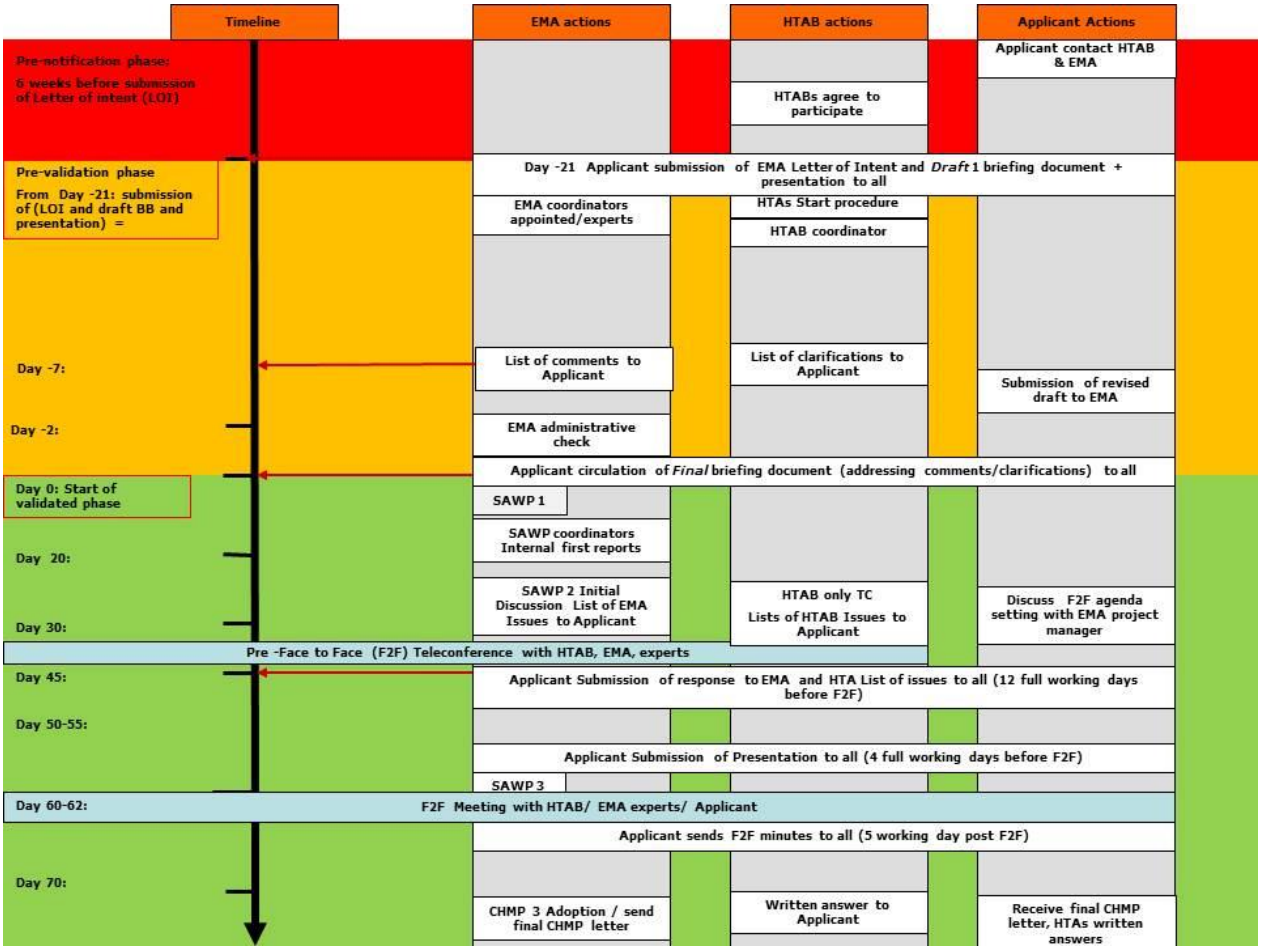

Figure 11; Best Practice Guide revised procedure without pre-submission TC

5. Recommendations

5.1. Best practice guide consolidated as an interim model

Following the experience of parallel advice in the pilot, consideration of public consultation comments on the draft best practice guide, and the parallel regulatory SEED experience, the draft best practice guide procedure was reviewed and revised through the process working group. All participating HTABs were then consulted on the draft revision. Additional amendments were made by this group, and taken into account in the update.

This best practice procedure is now consolidated and provides applicants with up-to-date guidance on the current procedure. This will update the best practice shared between participating HTABs and regulators, implementing what can be done within the current framework. This includes a HTAB coordinator, HTAB lists of issues, HTAB written answers, a more flexible duration for the face to face

meeting depending on the range of issues to be discussed. An earlier pre face to face closed discussion between HTAB and regulators is recommended. A closed HTAB only TC beforehand is implemented together with later submission of the presentation by the applicant. See Annex 5.

However, this revision is considered an interim model of parallel scientific advice, and further evolutions of the parallel advice procedure are foreseen taking Joint Action 3[5] on EU HTA cooperation into account. In the long term, a single final sustainable model is foreseen based on learnings and input from all relevant stakeholders.

Parallel advice with regulators and HTAs is positioned to have a key role in bringing medicines to patients. With the advent of PRIME (a scheme for priority medicines (PRIME), to optimise the development and accelerated assessment of medicines of major public health interest), applicants with medicines so designated as potentially breakthrough medicines are strongly encouraged to pursue parallel advice with regulators and HTA bodies to start thinking early about the data requirements of all stakeholders. In particular where Applicants are considering conditional marketing authorisation or accelerated assessments, for such cases, it is essential that forethought is entertained about the implications and data packages for HTA.

Likewise with innovative content or development plans such as Adaptive Pathways (involving iterative expansions of indications, multi-stakeholder interactions and use of real world data), or proactive planning of additional evidence generation, and use of registries, a formal parallel regulatory HTA scientific advice is strongly recommended as a platform to shape evidence plans for all stakeholders. This can be sought at a very early strategic stage as a broad advice (not necessarily indication specific to discuss possible approaches in more general terms) or later as indication specific advice.

Therefore it is important that this procedure is supported and developed in the interests of patients in the EU. . Parallel advice forms one element of the regulatory support tools (EMA/531801/2015) available to foster medicines development for the benefit of patients in the EU.

5.2. Observations for a final sustainable model of parallel regulatory HTA advice

Standard EU scientific advice is a networked model of National medicines Competent Authorities giving EU level advice coordinated at the EMA as a single point of contact and administration. Content (scientific) coordination and assessment is provided by National Competent Authorities.

With regard to parallel scientific advice, it is foreseen that the Final Sustainable Model (FSM) of multi-stakeholder parallel scientific advice would fully respect national competence in delivery of health care and decision making regarding pricing and reimbursement but recognise that evidence generation is global. The aim is to build on synergies between regulators and HTABs, reduce duplication and provide an optimum multi-stakeholder advice output that can facilitate efficient drug development that answers the needs of HTA bodies and regulators. HTAB and regulator participants should be equal partners in parallel advice.

To this end, observations on the elements that could be included for a FSM are made based on the consolidated best practice guide, pilot parallel regulatory HTA advice experience, public consultation and parallel regulatory SEED experience from the regulators' standpoint. This are made as observations to be taken into discussion when the FSM is being designed by all relevant stakeholders. See table 6 below.

[5] http://www.eunethta.eu/news/eunethta-joint-action-3-formal-preparatory-work-starting

The FSM would in principle
• Have a sound legislative basis.
• Provide a networked HTAB coordination integrated or intersecting into the networked model of Medicines' National Competent Authorities giving EU level advice. In essence, a mirror approach to EU regulatory scientific advice, with a single administrative hub would offer the greatest efficiency and seamless interaction. For the HTA element, content coordination and HTA assessment to be provided by the HTA or other relevant national bodies.
• Make clear that HTAB engagement model is at the EU level with representation from each MS.
• The advice output should be a single Final advice letter; with a section for HTABs and a section with the Regulator's view also; divergent views can be documented.
• Be able to cater for demand for advice on promising new medicines..
• Have agreed confidentiality agreement between HTABs and regulators allowing document exchange.
• Have agreed confidentiality policy(/ies) with regard to access to documents.
• Have written HTA advice that is adopted following consideration by A European level group/ committee on Relative Effectiveness Assessment(REA) of the draft advice. The remit and legitimisation of this body would have to be defined.
• The output of advice should have clear relationship and reuse at the appraisal process; any barriers to reuse needs to be understood and addressed where possible.
• Have clear governance, accountability and auditability.
• Have a sustainable funding model.
• Have a common scope and prerequisites for HTAB advice which should be clear. Centrally available collated HTAB information should make clear any National differences in method of HTA (e.g. See Annex 6).
• Provide scientific advice that is not legally binding but scientifically binding (See Box 3).
Regarding experts, the FSM would
• Include senior HTAB experts at meetings empowered to bring forward *draft* advice taking into account face to face discussions and all evidence. Analogous to the SAWP, the draft advice would be considered and adopted at a plenary working party meeting (for HTA bodies) and adopted at a committee level (Composed of HTA body delegates).
• Invite a Health Care Professional as a representative of the relevant EU clinical speciality where possible, and patient representative routinely to such procedures.
• Ensure that all experts at FSM meetings should have submitted and signed a public declaration of interests in line with a conflict of interest policy.
• Be transparent on the selection process of experts and patients representatives.
• Work towards payer involvement.

With regard to process, the FSM would
• Have optional pre-submission teleconferences.
• For pre-submission and pre face to face interactions, virtual/TC meetings are standard.
• Have 1 or more HTAB coordinators.
• Develop the concept of work-sharing across HTABs in preparing advice.
• Produce HTAB preliminary views for day 22.
• Have a HTAB only TC prior to the Closed HTAB Regulators' TC at day 30.
• There should be a collated HTA List of Issues the day 30.
• Preface to face TC to take place in advance of provision of slides.
• Slides to be provided 4 working days before the face to face Meeting.
• Allows for the additional raising of questions at a set point during the procedure.
• A flexible face to face Meeting duration that focuses mainly on issues raised by Regulators and HTAB.
• Have a HTAB only TC following the Discussion Meeting to agree on consolidated HTAB views (joint written answers including agreements where possible and diverging positions where necessary (as with the SEED process).
Administratively, the FSM would
• Have administrative staff as point of Contact with Applicant with the exception of face to face structured meetings.
• Have a single point of contact, administration and document repository.
• Have a secure IT method of sending documents.
• Undergo continuous process improvement.
• Have performance indicators and long term outcome impact assessment.

Table 5: Observations for discussion in design of a final sustainable model for parallel scientific advice

Parallel follow up advice, parallel broad advice, parallel qualification procedures or multi-stakeholder workshops are all possible avenues for further reviewing issues where the divergences are such that a single trial or development program cannot be conducted that meets the needs of the different stakeholders.

6. Conclusions

In the 2013 Workshop, aspects that the pilot on parallel regulatory-Health Technology Assessment scientific advice needed to achieve were drafted. See table 7 below. Using these as a basis for assessing the pilot, it can be concluded that the pilot has been a success in the elements that can be measured to date.

Outcome Measure	Status
Increase early dialogue between different stakeholders	Increased number of procedures markedly with continuing demand across a wide range of therapeutic areas, with advanced therapies, orphans, SMEs also included.
Increase patients' involvement	Increased and now routine.
Respect the roles and responsibilities of all stakeholders	No evidence of increasing regulatory hurdles stemming from HTAB dialogue.
Explain and encourage wider uptake of the scientifically binding approach in the provision of advice	The collated HTAB information shows where scientific advice is not legally binding for participating HTABs.
Maximise efficient resource utilisation to avoid duplication	Timetables and dossier submission have been aligned. The process has been optimised further with HTAB list of issues and written answers. A single development plan for different stakeholders means more efficient use of resources.
Understand the differences between, and perspectives of, different stakeholders	Content analysis shows that a single development plan is achievable in the majority of cases.
Facilitate the development of as many safe, efficient and affordable medicines – with real therapeutic added Value that are available to all patients across the EU	Long term objective- not currently measureable as only 1 of the 2010 cohort is now reaching MAA given lengthy development programs

Table 6: Outcome measures of parallel scientific advice

It is concluded that parallel regulatory-Health Technology Assessment scientific advice under the best practice guide should continue as an operational platform. This is in order to enable applicants to access such parallel advice. Nevertheless, further evolutions of a parallel advice procedure will be needed taking into account possible developments under Joint Action 3, until a final sustainable model is firmly established.

Areas for further development in a final sustainable model could include decision makers' involvement, clear relationship between advice and final appraisal, optimising patient contributions, sustainable funding supporting capacity building/ meeting demand, broader HTAB engagement, bringing in a single point of contact and administration and further process refinements.

Nevertheless, significant progress has been made with multi-stakeholder advice interactions. This has allowed the shaping of evidence plans at an early stage, cross-functional collaboration, reducing duplication and potentially will lead to better evidence generation to support patient access to new and important medicines.

During the EMA's workshop 2013, many of the stakeholders referred to the advice as not being legally binding, but suggested that it should be scientifically binding on the applicant and the regulatory authorities. The EMA views scientific advice to be scientifically binding when the following 2 bullet points are met:

- Regulators give scientific advice based on the current state-of-the-art in medicines development.

- Regulators recognise that in some cases, e.g., as a result of scientific developments, an alternative approach to that advice may be appropriate
- However, where companies choose not to apply the advice, they are requested to justify clearly their position in any subsequent marketing authorisation application. Likewise, regulators will provide argumentation during the evaluation of the marketing authorisation application in the rare case of diverging from its position in scientific advice
- The consequences of failing to adhere to scientific advice are best illustrated by an increased risk of major objections at the time of MAA arising from clinical trial methodology or evidence base for example relating to comparator, or endpoint[6].

Box 3 Scientifically binding advice

6 *Hofer M et al*. *Nature Reviews Drug Discovery* | AOP, published online 17 April 2015; doi:10.1038/nrd4621

7. Annexes

7.1. Consultation on Draft best practice guidance for pilot European Medicines Agency health technology assessment Parallel Scientific Advice procedures

7.2. Report from the European Medicines Agency / health-technology-assessment-body workshop on Parallel Scientific Advice in drug development on 26 November 2013

7.3. Table of specific comments by procedures topic with detailed EMA responses EMA/763805/2014

7.4. Consultation Questions line listing best practice by Question EMA/760382/2014

7.5. The Best Practice Guide(See Parallel Regulatory-HTA Scientific Advice Webpage)

7.6. Collated HTA Body information for participating HTABs