A TALE OF TWO AUDIENCES:

OPTIMISING YIELD FROM EARLY ADVICE CONSULTATION WITH HTA AND REGULATORY ORGANISATIONS

WORKSHOP: ISPOR EUROPE 2014
Amsterdam, Netherlands
NOVEMBER 12, 2014

CONFIDENTIAL

NEW YORK CITY
SAN FRANCISCO
LONDON
SHANGHAI

Our panel will include:

CYRUS A.CHOWDHURY, MS
CEO & MANAGING DIRECTOR
CBPARTNERS

RACHEL BECKERMAN, PHD
PRINCIPAL, VALUE DEMONSTRATION
CBPARTNERS

MARIJE VAN WEELDEN, MBA, MD, MSC
DIRECTOR, MARKET ACCESS AND PRICING EUROPE
FERRING

MATTHIEU R. CUCHE, PharmD, MBA
DIRECTOR HCE & REIMBURSEMENT
COVIDIEN AG

Agenda

13:45 – 13:55	13:55 – 14:07	14:07 – 14:19	14:19 – 14:31	14:31 – 14:45
Introductions & Objectives	**Models for Early Advice**	**Case Studies**	**The MFG Perspective**	**Wrap-Up and Q&A**
1. Introduction 2. Meeting Objectives 3. Overview of the Issues	1. The Four Early Advice Models 2. Similarities and Differences	1. Publically Available Examples Overview 2. Key Findings	1. Opportunities 2. Challenges 3. Recommendations for Engagement	1. Summary 2. Learnings / Questions

The objective of this workshop is to provide an overview of early models and how they fit into today's market access planning efforts.

OVERALL WORKSHOP GOAL

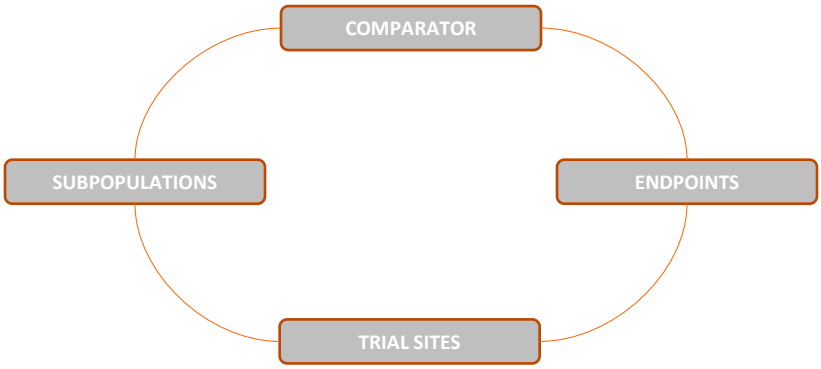
To provide an overview of early models and how they fit into today's market access planning efforts

WORKSHOP OBJECTIVES

- ✓ Explain **models** for early advice
- ✓ Explore **case studies** of recent products that have sought, achieved, and incorporated early advice
- ✓ Understand the associated **opportunities and challenges** of pursuing an early-advice approach

The past few years have clearly demonstrated that key elements of clinical trial design have major and unique effects on both regulatory and reimbursement decisions.

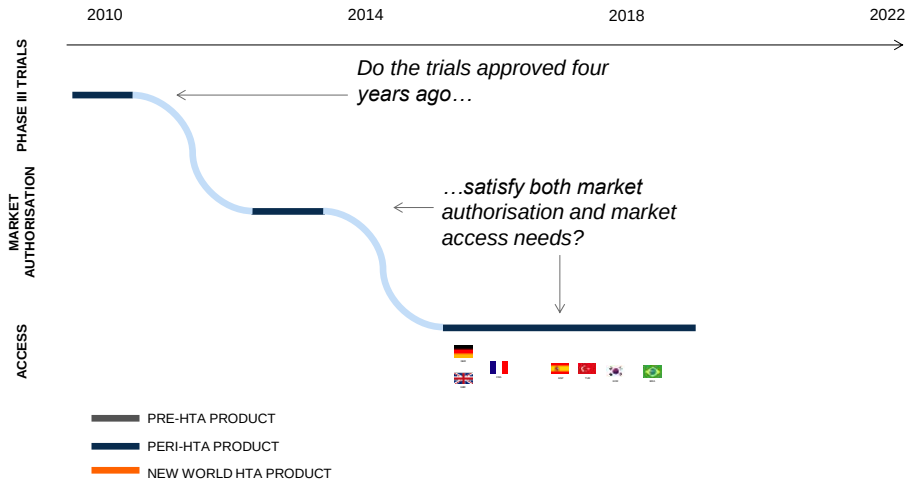
PRICING / REIMBURSEMENT TRIAL DESIGN
DIMENSIONS



SOURCE: CBPartners Experience

Trial designs determined in 2010 and earlier are now achieving market authorisation globally, with access in the EM to follow in the coming years.

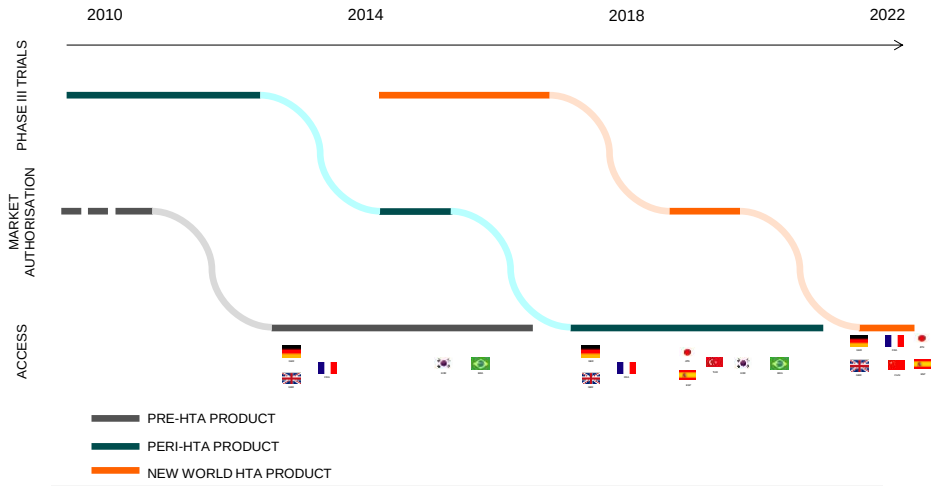
TIMELINE OF TRIALS TO ACCESS
HTA MARKETS – CURRENT / FUTURE



SOURCE: CBPartners Experience

Pivotal trial design decisions must be made far in advance of traditional access engagement with HTA authorities, commonly leading to evidence misalignment.

TIMELINE OF TRIALS TO ACCESS
HTA MARKETS – CURRENT / FUTURE

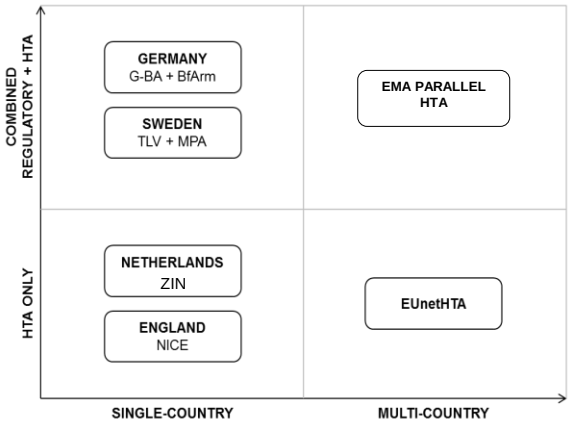


SOURCE: CBPartners Experience

Agenda

13:45 – 13:55	13:55 – 14:07	14:07 – 14:19	14:19 – 14:31	14:31 – 14:45
Introductions & Objectives	**Models for Early Advice**	**Case Studies**	**The MFG Perspective**	**Wrap-Up and Q&A**
1. Introduction 2. Meeting Objectives 3. Overview of the Issues	1. The Four Early Advice Models 2. Similarities and Differences	1. Publically Available Examples Overview 2. Key Findings	1. Opportunities 2. Challenges 3. Recommendations for Engagement	1. Summary 2. Learnings / Questions

Four identified main models for HTA advice



CB PARTNERS

8

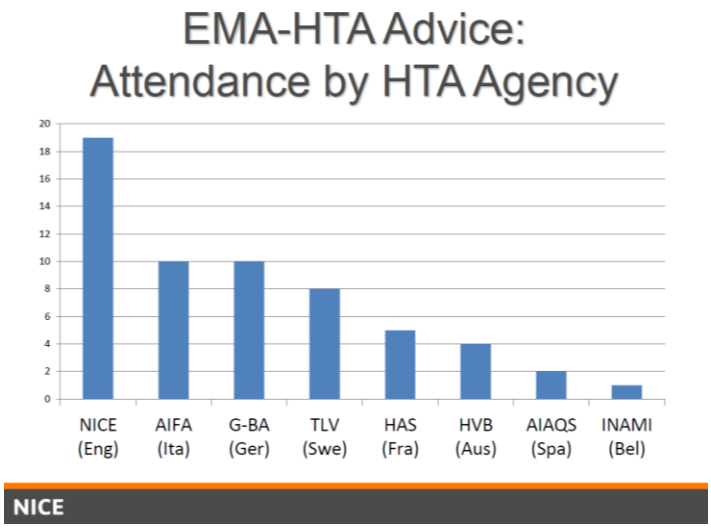
The key characteristics of HTA advice

	GER	SWE	UK	NLD	Pan-EU	Regulatory / EU HTA
	G-BA / IQWiG	TLV	NICE	ZIN	EUnetHTA	EMA / HTAs
CONJOINT REGULATORY ADVICE	Mandatory	Mandatory	Possible	Not Possible	Not Possible	Possible
CONSULTATION TIMELINES (MONTHS)	2	2	4	2	4.5	4.5
FEES (EUROS)	10,000 – 20,000	5,000	20,000 – 60,000	0	0	20,000 – 60,000
OUTPUT	Meeting minutes	Meeting minutes	Report	Report	Meeting minutes	Variable based on HTA body
ABILITY TO ASSESS HEALTH ECONOMICS	N / A	Yes	Yes	Yes	Yes	Variable
LANGUAGE OF MEETING	German	English	English	English	English	English
LENGTH OF MEETING	1 to 2 hours	1.5 hours	~3 hours	Unknown	3 hours	~4 hours
NUMBER OF 'COMPANY ATTENDEES' ALLOWED	4 to 6	No limit	Variable	1 to 2	<10	Variable
INVOLVEMENT OF EXTERNAL EXPERTS POSSIBLE	No	No	Yes	No	No	No

CB PARTNERS

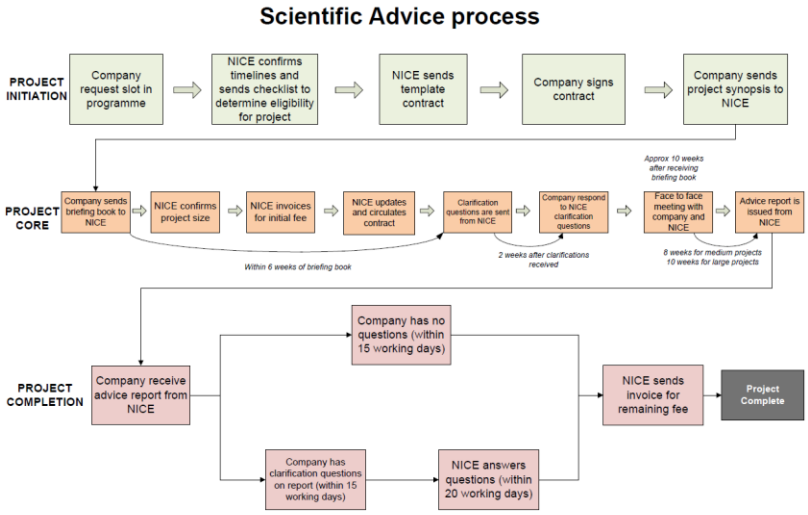
9

EMA – HTA Advice: attendance by HTA Agency



Source Leeza Osipenko – 9 October, representing NICE at PharmAccess Leaders Forum , Berlin

As an example: Flowchart Scientific advice process with NICE (https://www.nice.org.uk)



Agenda

13:45 – 13:55	13:55 – 14:07	14:07 – 14:19	14:19 – 14:31	14:31 – 14:45
Introductions & Objectives	**Models for Early Advice**	**Case Studies**	**The MFG Perspective**	**Wrap-Up and Q&A**
1. Introduction 2. Meeting Objectives 3. Overview of the Issues	1. The Four Early Advice Models 2. Similarities and Differences	1. Publically Available Examples Overview 2. Key Findings	1. Opportunities 2. Challenges 3. Recommendations for Engagement	1. Summary 2. Learnings / Questions

We can rely on three different types of data sources to understand how the early HTA advice process has played out to date.

EARLY ADVICE CONSULTATIONS
CURRENT PUBLICALLY AVAILABLE EXPERIENCE

INDUSTRY SURVEYS	efpia	*Survey of MFG participation in and perception of early consultation pathways*
PUBLICATIONS	NOVARTIS AIFA	*One MFG's blinded experience engaging with the early consultation process; similar perspective from AIFA*
PILOTS	SEED eunethta Tapestry Networks	*Facilitator perspectives of the early consultation process from both the MFG and payer / regulatory perspective*

Tapestry Networks has held six pilots for the multi-HTA approach; key findings across these pilots have been synthesised.

Tapestry Networks

STATUS: 6 PILOTS COMPLETED

- ☐ SINGLE COUNTRY HTA
- ☐ MULTI-COUNTRY HTA
- ☐ PARALLEL REGULATORY + SINGLE-COUNTRY HTA
- ☑ PARALLEL REGULATORY + MULTI-COUNTRY HTA

TIMING: October 2010 – February 2012

THERAPEUTIC AREA: T2DM, Breast Cancer, Melanoma, NSCLC, Alzheimer's Disease, Antibiotics

PARTICIPANTS:

REGULATOR	PAYER / HTA
	

KEY FINDINGS

- MFGs:
  - Believed early advice was 'valuable' and 'worthwhile'
  - Appreciated the ability to redesign studies based on feedback given
  - Cited the ability to reduce costs via the elimination of unnecessary studies and the ability to foster greater alignment internally in their organisations
- Regulatory / Payer Advisors:
  - Valued the increased stakeholder interaction and mutual education
  - Appreciated the insight into emerging policy and health threats
- Commonalities cited across the process included:
  - Size of the proof-of-concept study
  - Importance of treatment pathway in choosing appropriate comparators
- The major differentiator in advice was related to patient-reported outcomes

Source: http://www.tapestrynetworks.com/initiatives/healthcare/upload/Pilots-of-multi-stakeholder-consultations-in-drug-development-6-June-2012.pdf

CB PARTNERS

GreenPark Collaborative has run an initial pilot exploring the impact of early advice in the Alzheimer's space.

STATUS: 1 PILOT COMPLETED

- ☐ SINGLE COUNTRY HTA
- ☐ MULTI-COUNTRY HTA
- ☐ PARALLEL REGULATORY + SINGLE-COUNTRY HTA
- ☑ PARALLEL REGULATORY + MULTI-COUNTRY HTA

TIMING: October 2011 - April 2013

THERAPEUTIC AREA: Alzheimer's Disease

PARTICIPANTS:

REGULATOR	PAYER / HTA
	

KEY FINDINGS

- International pilot exploring the feasibility of providing early HTA advice; 11 companies with AD products in various stages of clinical development assisted in the development of the guidelines (EGD) by identifying questions about clinical study design that would be most useful to understand from the HTA / coverage perspective.
- The pilot demonstrated that such a multi-faceted consultation process is feasible
- However, key learnings / areas of improvement from the pilot include:
  - Focus first on changes to trials that do not add significant cost or time
  - Highlight comparisons with related guidance
  - Choose topics that offer prominent opportunities for guidance
  - Increase patient and expert involvement
  - Provide additional opportunities for in-person engagement

Source: GPC Pilot Evaluation Report – April 2013

CB PARTNERS

EUNetHTA's Joint Action 2 WP7 workstream has completed 10 early dialogue pilots.

STATUS: 10 PILOTS COMPLETED

- ☐ SINGLE COUNTRY HTA
- ☑ MULTI-COUNTRY HTA
- ☐ PARALLEL REGULATORY + SINGLE-COUNTRY HTA
- ☐ PARALLEL REGULATORY + MULTI-COUNTRY HTA

TIMING: 2012 - 2015

THERAPEUTIC AREA: T2DM, Breast Cancer, Melanoma, NSCLC, Alzheimer's Disease, Antibiotics

PARTICIPANTS:

REGULATOR	PAYER / HTA
N/A	

KEY FINDINGS

- The process is coordinated and hosted by HAS, France; other HTA participants include AIFA, ASSR, IQWIG, GBA, NICE, HVB, CVZ, KCE/INAMI, GYEMSZI, TLV and HAS
- Over 10 pilots, it was concluded that:
  - Some HTA agencies have different focus (relative effectiveness vs. cost-effectiveness)
  - Strong leadership is needed to amalgamate recommendations and provide actionable results •
  - There is a desire for HTA written answers to send to the company
- In the pilots, the pros / cons of including the regulatory perspective in the process was discussed
  - Perspective was seen to be valuable as a 'one stop shop', but potential for too much time on regulatory issues that can be covered during typical SA

The Shaping Early European Dialogues (SEED) consortium is leading a set of 10 early advice pilots as a follow-on to EUnetHTA's efforts.

STATUS: 10 PILOTS ONGOING

- ☐ SINGLE COUNTRY HTA
- ☑ MULTI-COUNTRY HTA
- ☐ PARALLEL REGULATORY + SINGLE-COUNTRY HTA
- ☑ PARALLEL REGULATORY + MULTI-COUNTRY HTA

TIMING: 2014 – March 2015

THERAPEUTIC AREA: TBD

PARTICIPANTS:

REGULATOR	PAYER / HTA
	

KEY FINDINGS

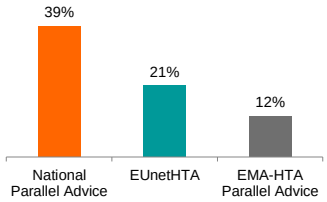
- The SEED Consortium (Shaping European Early Dialogues), led by the French Haute Autorité de Santé (HAS), is a consortium consisting of 14 national and regional HTA bodies; all SEED consortium members are also partners in the EUnetHTA Joint Action 2.
- The objectives of the SEED consortium are to perform 10 multi-HTA early dialogues for new technologies, 7 pharmaceuticals and 3 medical devices
- Several scenarios will be explored in this initiative
  - Sequential vs. independent advice
  - Parallel EMA-HTA and multi-HTA advice
- It is anticipated the pilots will be complete by January 2015; at this point, insights are difficult to gather given that the process is still in-progress
- The goal of the initiative is to have a permanent model for early dialogue at the end of the process

EFPIA has performed a survey to elicit MFG experience with the early advice process.

EFPIA SURVEY
KEY FINDINGS

- In 2013, EFPIA performed a survey of relevant pharma companies to understand how early advice pathways are currently being used
- The overwhelming majority of MFGs believed there was a need for parallel regulatory / HTA advice
- 12 of the surveyed companies reported undertaking early advice, at either the national level (SWE or UK), with EUnetHTA, or the EMA+HTA process

PERCENTAGE SEEKING EARLY ADVICE VIA:



- Those who did not seek advice cited a limited perception of value, uncertainty of process, time constraints, or lack of resources as key barriers
- Key learning about early dialogue from the manufacturer perspective included:
  - Strategically focus on area of issue / uncertainty to company
  - Aim for alignment on realistic achievable requirements
  - Timing: optimally pre-Phase III with an option for pre-Phase II

Source: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155674.pdf

NVS has published their select experiences with early dialogue, as has the Italian Medicines Agency (AIFA).

NVS AND AIFA EARLY DIALOGUE EXPERIENCE
KEY FINDINGS


Early Scientific Advice Obtained Simultaneously from Regulators and Payers: Findings from a Pilot Study in Australia

HEALTH POLICY ANALYSIS
Early Dialogue Between the Developers of New Technologies and Pricing and Reimbursement Agencies: A Pilot Study

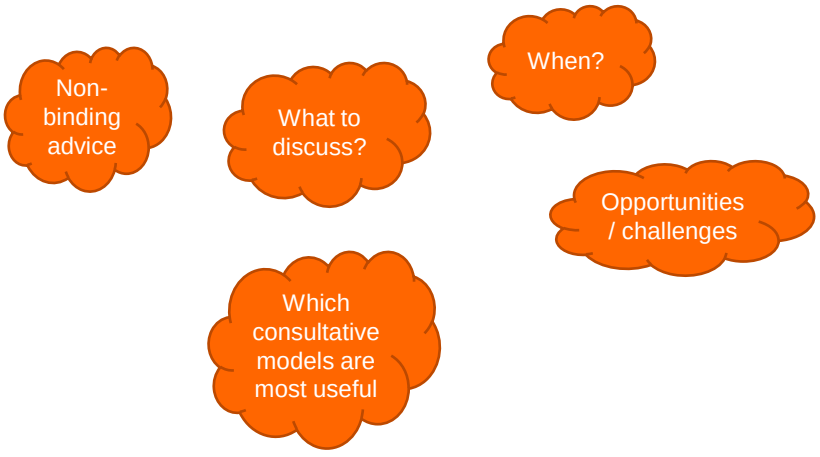
- **NVS EXPERIENCE**
  - ✓ Relatively few differences between demands of regulators and payers
  - ✓ Only one payer agency was able to provide formal written feedback
  - ✓ Company perceived formal and informal advice given to be helpful and worthwhile


AIFA
THE ITALIAN MEDICINES AGENCY EXPERIENCE WITH HTA SCIENTIFIC ADVICE ACTIVITIES: A COMPREHENSIVE ANALYSIS OF THREE YEARS OF NATIONAL AND INTERNATIONAL ACTIVITIES.
Siviero PD, Montilla S, Sammarco A, Trotta MP, Tafuri G, Pani L.
Italian Medicines Agency (AIFA)

- **AIFA EXPERIENCE**
  - ✓ Over 3 years, 21 early dialogues were performed across single-HTA, multi-HTA, and parallel regulatory-HTA models
  - ✓ CNS and oncology were main TAs for which advice was sought
  - ✓ Most EDs were performed during Phase II or III of development
  - ✓ A lower concordance between AIFA and the MFGs existed related to target population, subgroup selection, choice of comparators, and resource utilisation data collection

Agenda

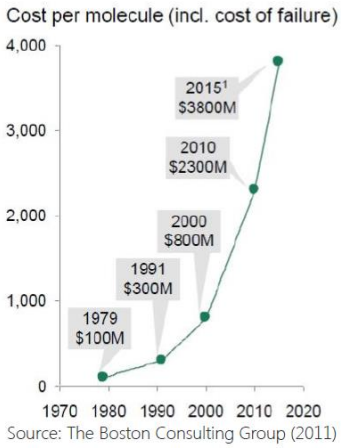
13:45 – 13:55	13:55 – 14:07	14:07 – 14:19	14:19 – 14:31	14:31 – 14:45
Introductions & Objectives	**Models for Early Advice**	**Case Studies**	**The MFG Perspective**	**Wrap-Up and Q&A**
1. Introduction 2. Meeting Objectives 3. Overview of the Issues	1. The Four Early Advice Models 2. Similarities and Differences	1. Publically Available Examples Overview 2. Key Findings	1. Opportunities 2. Challenges 3. Recommendations for Engagement	1. Summary 2. Learnings / Questions



Case study

Regulatory scientific advice not aligned with HTA expectations

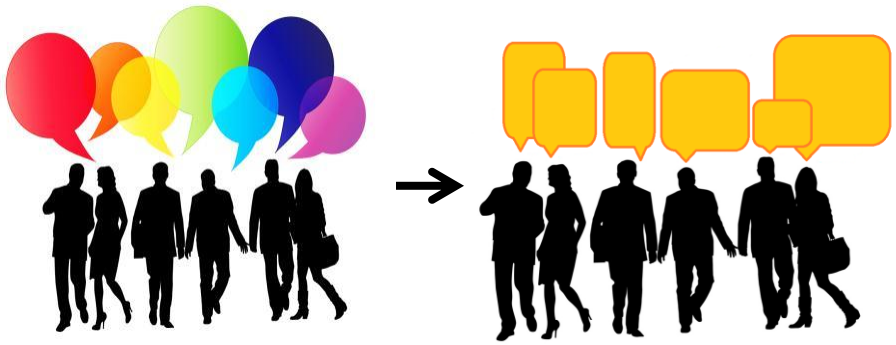
Rationalising R&D Spend



Source: The Boston Consulting Group (2011)

Enhanced internal alignment

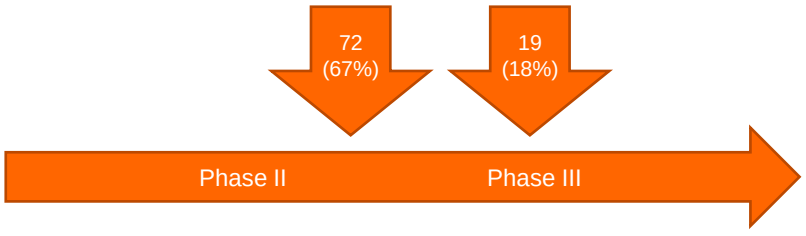
- Historically regulatory approval was only internal focus
- Pricing, reimbursement and market access were an add-on
  - Had to work from regulatory focused trials
- Early HTA scientific advice allows for constructive discussions and aligned expectations



When to conduct Early Scientific Advice?

Analysis of requests at NICE:

- Before phase III: 72 (67%)
- During phase III (pivotal trials started): 19 (18%)
- Other (prior to) phase II and after phase III: 16 (15%)



Engaging in the early advice process has clear advantages…

- Opportunity for internal engagement and alignment of expectations
- HTA feedback before final data package is available:
  - Obtain payer perspective before clinical trials even start
  - Maximize usefulness of data collected
  - Consider pros and cons of different trial options
  - Obtain ideas on alternative strategies to be developed
  - Integrate CE in early decision making
- **Parallel** advice: members from regulatory and HTA bodies in one meeting
- **NICE** scientific advice: patient's engagement

…although disadvantages and uncertainties exist too

- Preparation can be resource-intensive
- Advice is non-binding and not guaranteed of P&R success
- Output of advice is not always clear or straightforward
- Many models exist; early dialogue does not have a clear 'owner'
- No public examples of facilitated P&R based on the early advice process
- Recommendations regulatory and HTA may differ
  - Different SoC between countries
    - Off-label may be accepted as comparator in some countries, not in others
- Competitive environment might change between consultation and reimbursement submission
- **Parallel** advice: not all parties can be heard

The range of topics discussed can be very broad (slide 1 of 2)

Trial-related topics for early advice

- Study population
  - Including stats: subgroups and stratification
- Position of intervention in treatment pathway
- Comparator(s)
- Design of the trial (duration, dosing)
- Acceptability of endpoints / surrogate endpoints
- PROs – generic and disease specific

The range of topics discussed can be very broad (slide 2 of 2)

Economics-related topics for early advice

- Plans for model to be used
- Sources of data
  - Observational studies
  - Analyses
- Utility value definition
- Resource utilisation collection

Which models are most helpful and why

It depends…

Parallel EMA – HTA Scientific advice has my preference

One meeting where regulatory and HTA bodies come together	Goal to align and find common ground (between HTAs) during the meeting	Essential in era of increasing HTA requirements & cost containment

Which models are most helpful and why

It depends…

In case of a local development strategy: (series of) national advice

In-depth discussion with HTA body	Advice is specifically targeted to later HTA submission in that market	Maybe a chance to "manage expectations" of HTA body

Agenda

13:45 – 13:55	13:55 – 14:07	14:07 – 14:19	14:19 – 14:31	14:31 – 14:45
Introductions & Objectives	**Models for Early Advice**	**Case Studies**	**The MFG Perspective**	**Wrap-Up and Q&A**
1. Introduction 2. Meeting Objectives 3. Overview of the Issues	1. The Four Early Advice Models 2. Similarities and Differences	1. Publically Available Examples Overview 2. Key Findings	1. Opportunities 2. Challenges 3. Recommendations for Engagement	1. Summary 2. Learnings / Questions

Summary

- Manufacturers face many challenges in obtaining reimbursement in the diverse European climate
- 4 models for early dialogues were presented
- Real-world experiences of early dialogues highlighted both the positive experiences as well as where there is room for improvement
- An overview of manufacturer's considerations for engagement in the early dialogue process

Questions?

For a copy of our slides please email us:

CYRUS A.CHOWDHURY, MS
Cyrus.Chowdhury@cbpartners.com
CEO & MANAGING DIRECTOR
CBPARTNERS

RACHEL BECKERMAN, PHD
Rachel.Beckerman@cbpartners.com
PRINCIPAL, VALUE DEMONSTRATION
CBPARTNERS

MARIJE VAN WEELDEN, MBA, MD, MSC
Marije.vanWeelden@ferring.com
DIRECTOR, MARKET ACCESS AND PRICING EUROPE
FERRING

MATTHIEU R. CUCHE, PharmD, MBA
Matthieu.Cuche@covidien.com
DIRECTOR HCE & REIMBURSEMENT
COVIDIEN AG