

Integrating Biomarkers into Drug Development: The Importance of a Suitable Regulatory Strategy

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Types of Biomarkers

1. Diagnostic/Screening markers
2. Variations in drug metabolism
3. Surrogate endpoints
4. Prognostic or companion diagnostics

All biomarkers can benefit from a clear regulatory strategy.

Types of biomarkers:

Diagnostic/Screening markers

- Usually serum protein(s)
- Classic example: Prostate Specific Antigen (PSA)
 - Utility unclear: “*The existing evidence from randomised controlled trials does not support the routine use of screening for prostate cancer with prostate specific antigen...*” Djulbegovic *et al.*, 2010 British Medical Journal
- Other examples in development include:
 - Urinary biomarkers for kidney cancer diagnosis
 - Protein markers for lung cancer
- Clinical usefulness of most markers yet to be demonstrated

Types of biomarkers: Variations in Drug Metabolism

- Most but not all are genetic variations in Cytochrome P450 genes
 - Affect the metabolism of a number of drugs including some cancer medications such as tamoxifen
- Another example:
 - Lack of dihydropyrimidine dehydrogenase (DPD) is contraindicated for capecitabine/5-fluorouracil
- Such biomarkers illustrated the importance of proper understanding of the drug pharmacology

Types of biomarkers: Surrogate Endpoints

- A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm.
- Example of clinical need for a surrogate endpoint is multiple sclerosis (MS)
 - MRI is used in some clinical trials but has not been validated
 - Pivotal clinical trials for MS require 2 years with clinical endpoints

Types of biomarkers: Prognostic Biomarkers

- So far most prognostic biomarkers are used for oncology therapeutics
- Used to identify which tumours will respond to a particular therapy
- Mutation or misregulated expression of genes, most often classic oncogenes or cell surface receptors
- Critical for modern antibody therapies that target a specific protein target

Examples of Prognostic Biomarkers

Biomarker	Drug	Cancer
Philadelphia chromosome	Imatinib mesylate (Gleevec)	Chronic myeloid leukemia (CML)
C-Kit Expression	Imatinib mesylate (Gleevec)	Gastrointestinal stromal tumors (GIST)
EGFR expression	Erlotinib (Tarceva)	Non-small cell lung cancer (NSCLC)
EGFR expression	Cetuximab (Erbitux)	Colorectal cancer
Her2/neu Over-expression	Trastuzumab (Herceptin)	Breast cancer
KRAS mutations	Panitumumab (Vectibix)	Colorectal cancer (Contraindicated for KRAS mutations)

Biomarkers are becoming critical in the development of medicines

Two case studies:

- Setback:

Delay of NDA of Omapro by Chemgenex because of an inadequate test for the targeted mutation

- Success:

MAA approval of Vectibix by Amgen

Case study: Omapro

- The NDA of Omapro (omacetaxine mepesuccinate) by ChemGenex Pharmaceuticals has been delayed because of an inadequate test for the targeted mutation (Bcr-Abl T315I) in chronic myeloid leukaemia
- Major issues included:
 - *"Assays with different performance characteristics were used at the two central laboratories to detect the T315I mutation"*
 - *"Information for the assays to detect the T315I mutation has not been submitted to FDA's Center for Devices and Radiological Health (CDRH)"*
 - Oncologic Drugs Advisory Committee, QUESTIONS, March 22, 2010

Case study: Omapro

Result:

"ChemGenex Completes pre-NDA Meeting with U.S. FDA and Clarifies Timing for Second New Drug Application for OMAPRO"

- ChemGenex press release 5 Oct 2010

Case study: Omapro

Stage of Biomarker Development	Case Study	Ideal World
Identify and qualify target biomarker	✓	✓
Develop and validate method for detection of biomarker	Unknown	Method of detection for is validated
Analytical validation of diagnostic kit/assay	Developed two diagnostic assays with different performance characteristics	Single diagnostic assay/kit is developed with appropriate characteristics (Accuracy, specificity, etc.)
Clinical validation	✗	Clinical utility of biomarker is validated in clinical trials

Case study: Vectibix

- Thanks to Scott Paterson, Amgen, for presenting this example
- Vectibix (panitumumab) is an anti-EGFR monoclonal for the treatment of metastatic carcinoma of the colon

Single Use Vial
NDC 55513-954-01

AMGEN®

Vectibix®
(panitumumab)

100 mg

Each 5 mL single-use vial of Vectibix® contains 100 mg panitumumab in a sterile, preservative-free solution (pH 5.8) containing 29 mg sodium chloride and 34 mg sodium acetate in Water for Injection, USP.

**Store at 2° to 8°C.
Do not freeze or shake.
Protect from direct sunlight.**

Rx Only

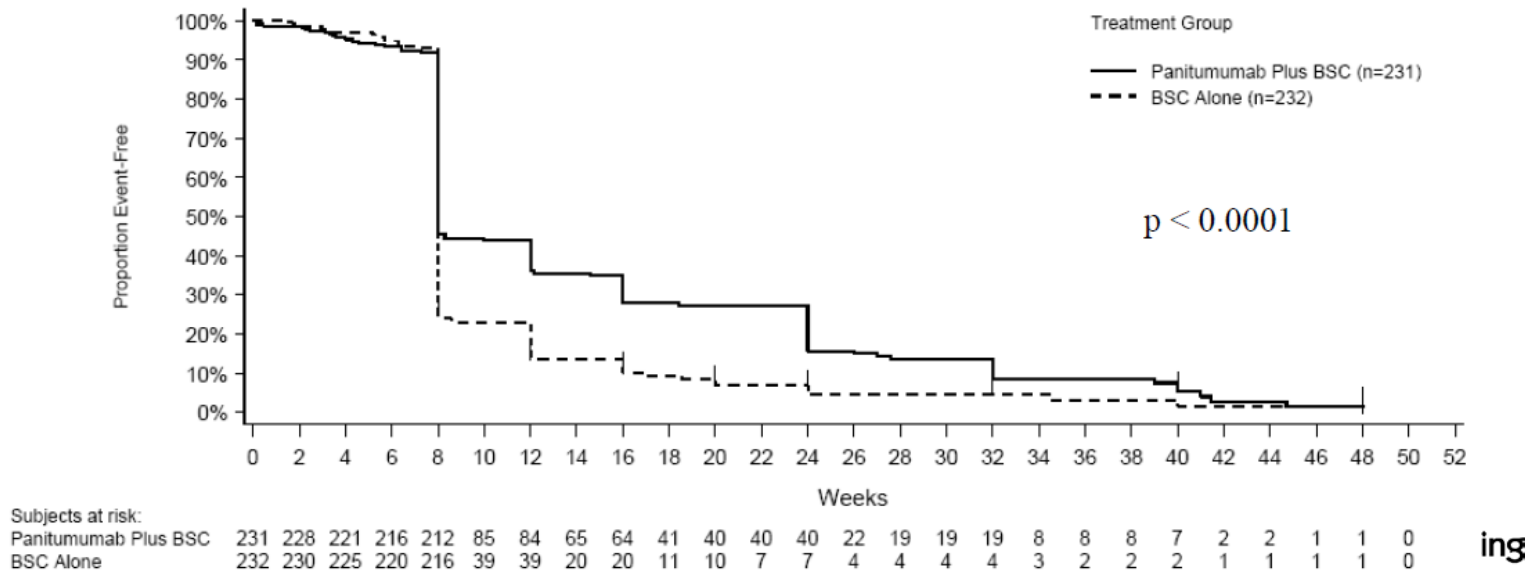
Case study: Vectibix

- In the US: BLA approved 27 September 2006
- In the EU:
 - Application received 28 April 2006
 - The CHMP issued a negative opinion for granting a Marketing Authorisation to Vectibix on 24 May 2007
 - Re-examination requested on 06 June 2007
 - CHMP issues a positive opinion for conditional marketing authorisation on 20 September 2007

Case study: Vectibix

- Grounds for refusal:
 - *"...The clinical efficacy observed is too small to constitute a clinical benefit and does not outweigh the risks associated to treatment with panitumumab."* Vectibix EPAR

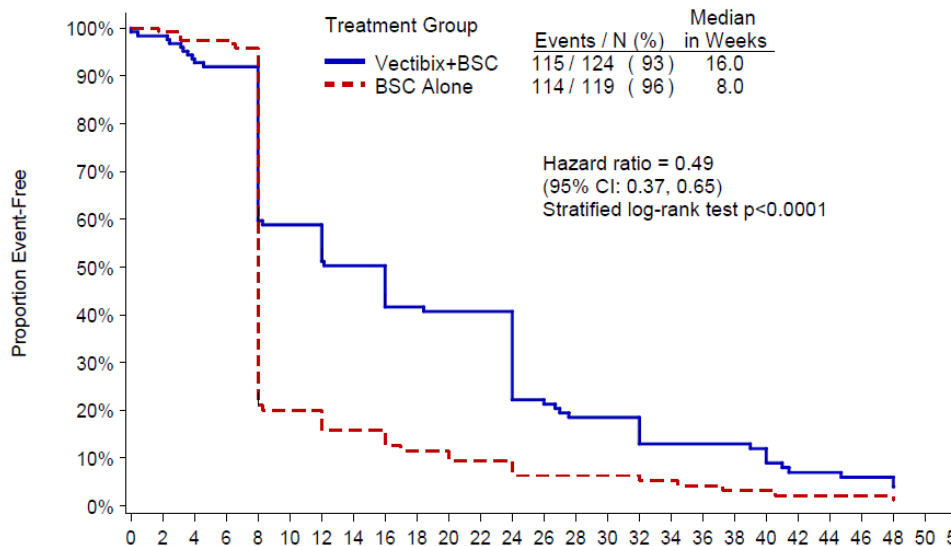
Figure 9. Study 20020408: Kaplan–Meier plot of PFS moving the radiographic times to the closest scheduled visit (ITT, IRC assessment)



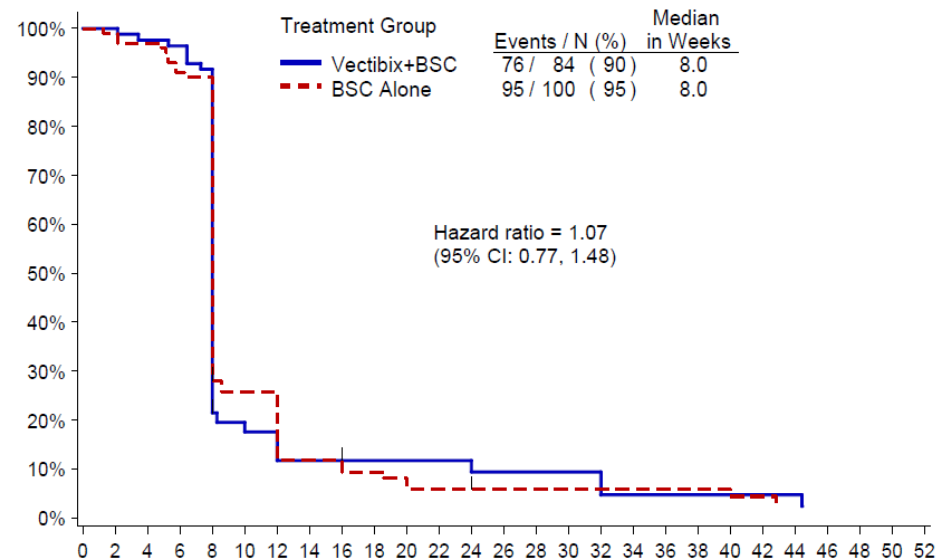
Case study: Vectibix

- Grounds for appeal: Included post-trial genotyping of tumours for KRAS mutations

Patient population with wild-type KRAS



Patient population with mutant-type KRAS



Case study: Vectibix

- Grounds for appeal: Included post-trial genotyping of tumours for KRAS mutations
 - *“...Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk/benefit balance of Vectibix as monotherapy for ... was favourable and therefore recommended the granting of the conditional marketing authorisation...”* Vectibix EPAR
- New information presented on appeal, breaking EMA rules.
- Lesson: Biomarker regulatory strategy needs to be incorporated into general product development strategy

Overlap between diagnostic and therapeutic development

Diagnostic

Candidate
marker
identification

Marker
verification
and initial
precision
studies

Assay
identification
and validation

Final assay
validation and
performance
testing

Clinical
validation of
biomarker

Regulatory
Approval
and
Launch

Basic
Research/
Discovery

Pre-clinical
development

Phase I

Phase II

Phase III

Therapy

Potential interactions with regulators:

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Stage of Biomarker Development

Interaction (Europe)



Identify and qualify target biomarker

Develop and validate method for detection of biomarker

Analytical validation of diagnostic kit/assay

Clinical validation

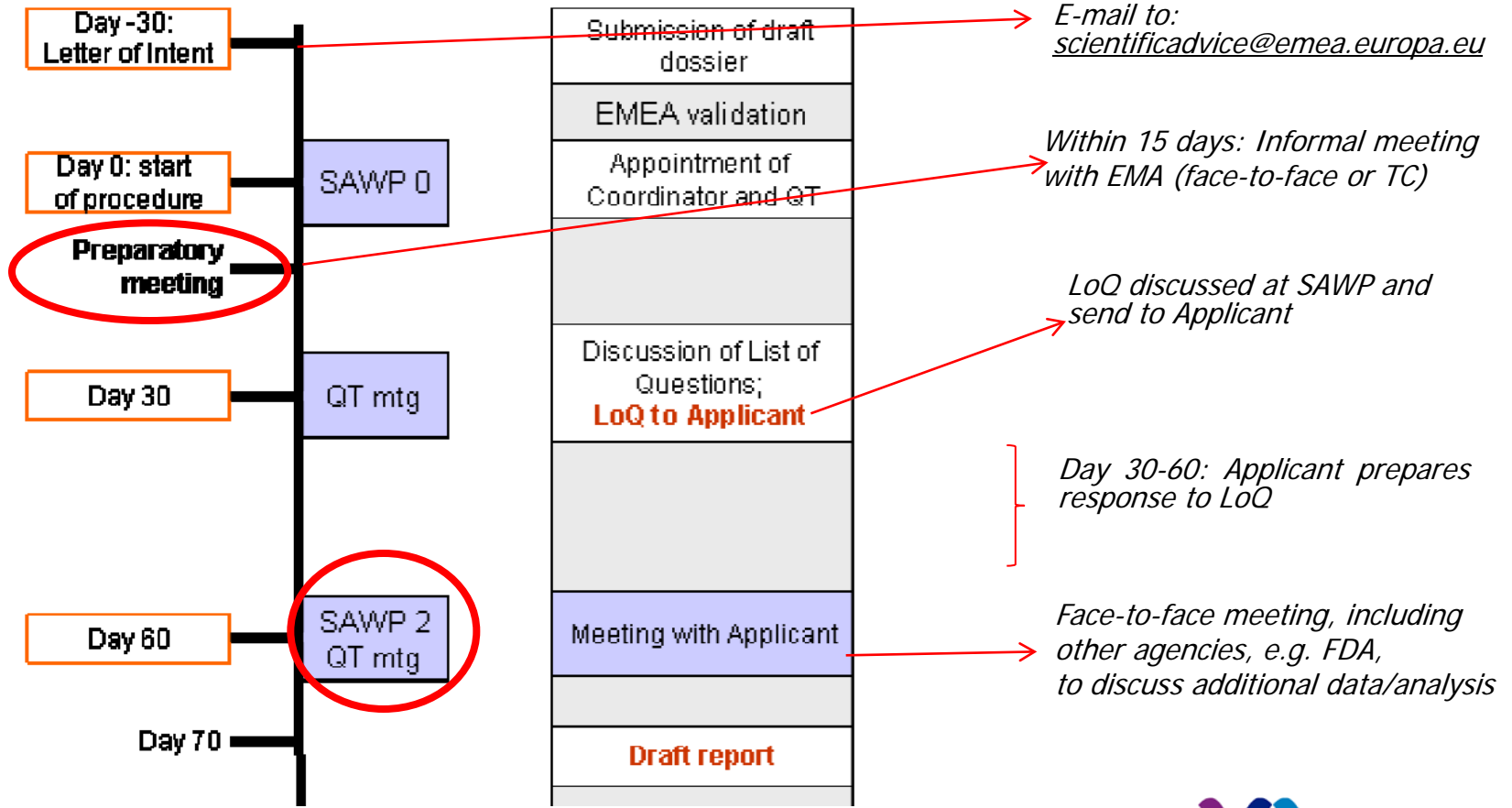
Regulatory Approval

Scientific advice at national agencies if biomarker is a companion to a medicinal product

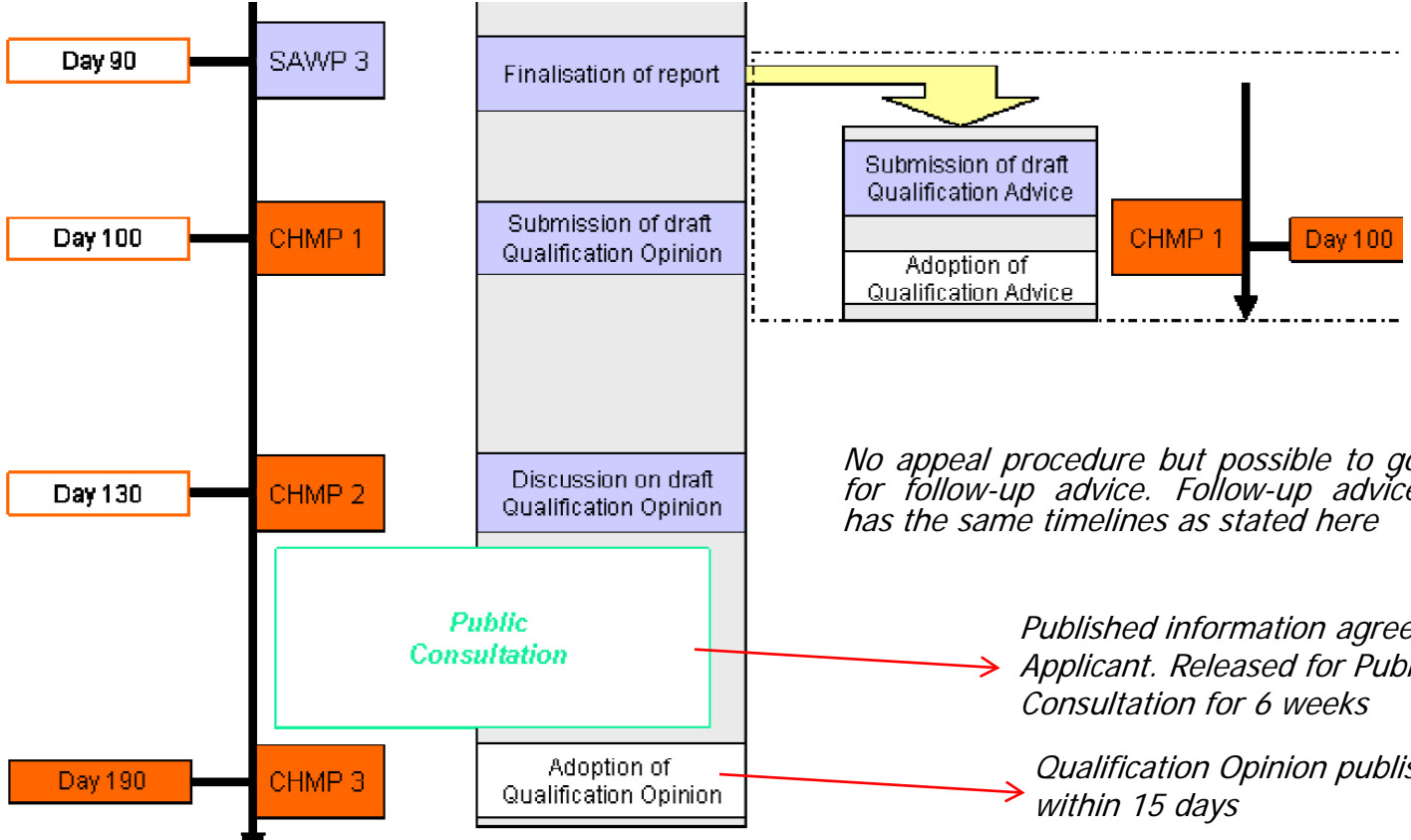
Qualification opinion/advice from European Medicines Agency (EMA)

Conformity assessment (CE marking) by Notified Body

Qualification Opinion and Advice procedure (1)



Qualification Opinion and Advice procedure (2)



Cost Impact

- The Bad News
 - Qualification Opinion: EUR 75,500
 - Qualification Advice: EUR 75,500
 - Follow-up Advice: EUR 37,700
- The Good News
 - Small and Medium sized Enterprises (SME) get a 90% fee reduction

Potential interactions with regulators:

Stage of Biomarker Development

Interaction (USA)



Identify and qualify target biomarker		
Develop and validate method for detection of biomarker	Pre-IDE meeting (Only for Significant Risk Devices)	Voluntary Pharmacogenomic Data Submission (VGDS)
Analytical validation of diagnostic kit/assay	IDE Meeting (Only for Significant Risk Devices)	Or Voluntary Exploratory Data Submission (VXDS)
Clinical validation		
Regulatory Approval	Premarket Approval Application (PMA) or 510(k) application	

Opportunities for Biomarker qualification: VXDS

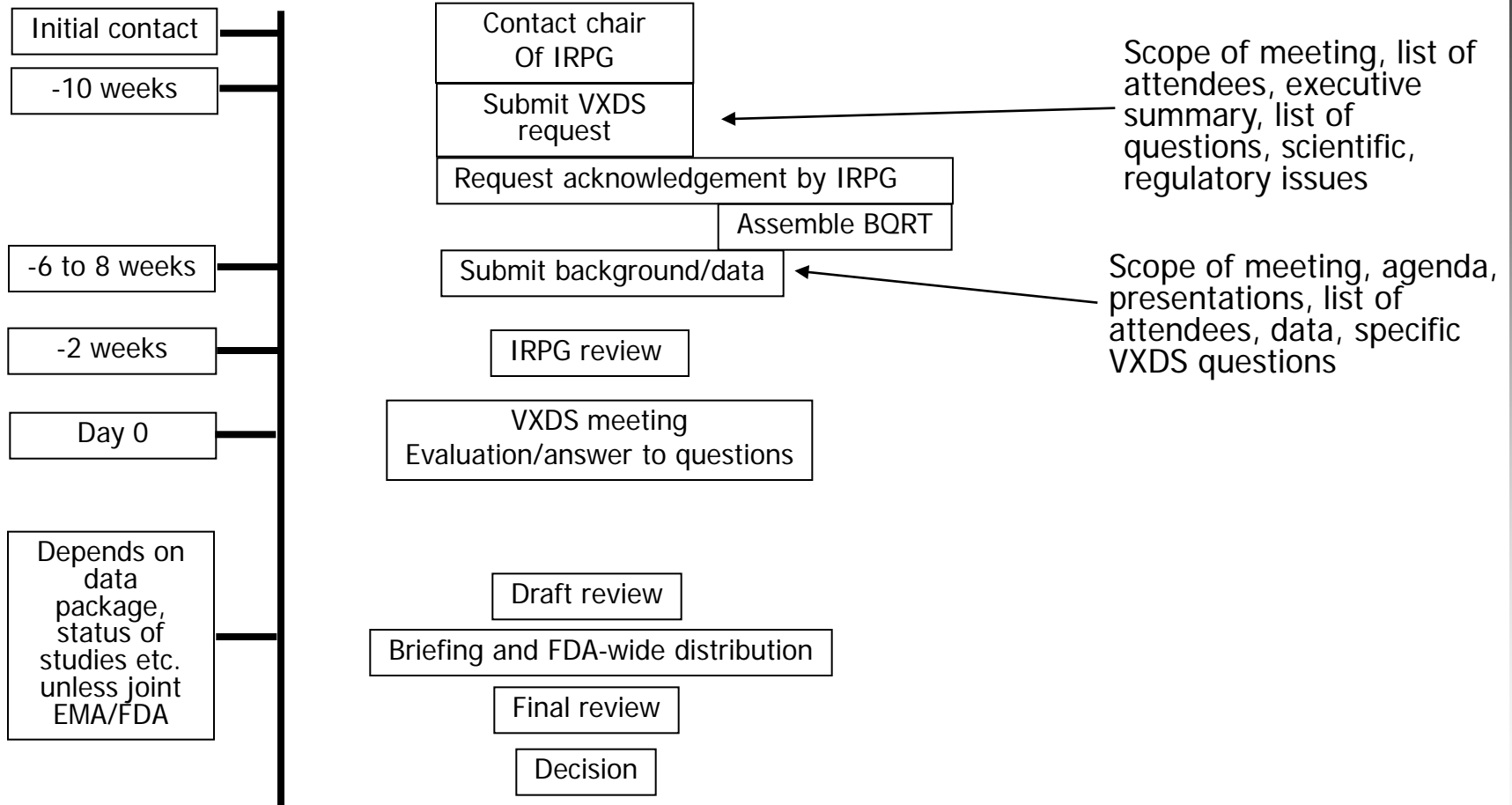
1. Stand alone VXDS

- not submitted within an existing submission
- new pre-IND number is established

2. Associated VXDS

- submission is associated with an already existing IND submission
- VXDS will not obtain an new number and will not change the status of the already existing submission

FDA Biomarker Qualification Pilot Process (VXDS)



Opportunities for Biomarker qualification: VXDS

- Introduced in the final form in 2005
- Up to 2009 there have been over 40 submissions and over 35 face-to-face meetings

Technology platform for VXDS meetings

Platform	2004 - 2006	2006 - 2008	Total
Candidate gene	1	11	12
Differential gene expression by microarray	11	3	14
Other	5	4	9

Source: Goodsaid *et al.*, (2010) *Nature reviews Drug Discovery*



U.S. Food and Drug Administration



European Commission



European Medicines Agency

Guiding principles
Processing Joint FDA EMEA Voluntary Genomic Data Submissions
(VGDSs)
within the framework of the Confidentiality Arrangement

Source:

<http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf>

What information do you need for agency interactions?

- Submissions are in CTD format
- Important to clearly define your biomarker in context
- Disease setting associated with your biomarker(s)
- Intended use of biomarker, its need and impact, how it will be integrated into drug development and regulatory review
- Relevance and adequacy to extrapolate the preclinical models to clinical setting

What information do you need for agency interactions?

- Details on study design, critical analysis of results, assay validation, statistical plans
- Inclusion of as much supportive data to strengthen the package, such as systematic literature reviews, meta-analysis, study reports
- Gaps (if any) that remain and how these will be addressed in future plans/studies

Summary

- Biomarkers are becoming increasingly important in diagnosis and treatment
- Appropriate engagement with regulators is essential for a successful biomarker development programme
- There are a number of avenues to consult with Regulators and obtain “Buy-in” from them
- **Consider the applicability of the Qualification procedures to your biomarker**

Thank you!

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