

'Realising the potential of stratified medicine' case studies

This document presents a collection of eight case studies of stratified medicine which were developed for use in the Academy of Medical Sciences' project that resulted in the report '*Realising the potential of stratified medicine*'.¹ They were developed with a view to setting out the drug and/or diagnostic development pathways used by industry and draw out the lessons learnt. They were used in the discussion papers for, and provided to delegates attending, the symposium held in October 2012.

Stratified medicine refers to the categorisation of patients according to disease risk or likely therapeutic response as determined using diagnostic markers. The case studies presented herein were drawn from examples covering a range of diseases, therapeutic agents, diagnostic test methodologies and product development pathways.

As drugs and companion diagnostics are not necessarily co-developed, a range of possible scenarios for the temporal relationship between drug development, biomarker identification, and diagnostic development is explored. Attention is paid to the assessment of diagnostic test value, the impact of laboratory developed tests, the contribution of patient stratification to clinical trial outcome and clinical use, and the influence of various stakeholders throughout the development and approval process.

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Table 1: Therapeutic and diagnostics used for case study research

Case Study	Combination (drug/diagnostic)	Rationale
1	Herceptin / HercepTest	First case of co-development of therapeutic and stratifying diagnostic.
2	Ziagen / HLA-B*57:01 screening assay	Example of stratification to decrease risk of hypersensitive reactions.
3	Oncotype DX	Example of a prognostic diagnostic panel assay.
4	Vectibix / EGFR pharmDx and therascreen®: KRAS RGQ PCR Kit	Example of a drug with two different stratifying diagnostics indicated over its life cycle.
5	Zelboraf / cobas® 4800 BRAF V600 Mutation Test	Example of therapeutic development driven by knowledge of biomarker.
6	Xalkori / Vysis ALK Break Apart FISH probe kit	Example of rapid approval.
7	Kalydeco / G551D mutation test	Example of a new paradigm of combining genomics, proteomics and therapeutics resulting in rapid approval.
8	BRAF and MEK inhibitor / BRAF™ mutation kit (V600E & K)	Example of two drugs with a shared stratifying marker, and of combination therapy trials driven by molecular understanding of resistance.

¹ <http://www.acmedsci.ac.uk/p47prid104.html>

Case study				US approval		EU approval	
		Drug (Rx)	Companion Diagnostic (CDx)	Rx	CDx	Rx	CDx
1	Breast cancer	Herceptin (trastuzumab) Roche/Genentech	HercepTest Dako	Sep 1998	Sep 1998	Aug 2000	Yes
2	HIV	Ziagen (abacavir) GSK/ViiV Healthcare	HLA-B*57:01 screening assay	Dec 1998	N/A: unbranded test	Jul 1999	N/A: unbranded test
3	Breast cancer	N/A: Dx only	Oncotype DX Genomic Health	N/A: Dx only	Not FDA approved: use supported by literature	N/A: Dx only	2007
4	Colorectal cancer	Vectibix (panitumumab) Amgen	EGFR pharmDx kit Dako therascreen®: KRAS RGQ PCR Kit Qiagen	Sep 2006	Sep 2006 July 2012	Sep 2007	Yes Yes
5	Melanoma	Zelboraf (vemurafenib) Roche/Plexxikon	cobas® 4800 BRAF V600 Mutation Test Roche	Aug 2011	Aug 2011	Feb 2012	Yes
6	Non small cell lung cancer	Xalkori (crizotinib) Pfizer	Vysis ALK Break Apart FISH probe kit Abbott Molecular Diagnostics	Aug 2011	Aug 2011	Jul 2012 (Conditional Marketing Authorization)	Sep 2011
7	Cystic fibrosis	Kalydeco (ivacaftor) Vertex Pharmaceuticals/Cystic Fibrosis Foundation Therapeutics Inc.	G551D mutation test	Jan 2012	N/A: unbranded test	Jul 2012	N/A: unbranded test
8	Melanoma	BRAF/MEK inhibitor (trametinib and dabrafenib) GSK	BRAF™ mutation kit (v600E & K) bioMerieux	In development			

Case study 1: Breast cancer

Therapeutic Herceptin (trastuzumab) **by** Genentech

Diagnostic HercepTest **by** Dako

Background:

After nearly a decade of dedicated research, Genentech created Herceptin (trastuzumab) and filed an IND in 1992. Subsequently, Genentech entered into a partnership with DAKO to develop a commercial test to identify patients who over-express the HER2 protein. In 1998, biologics license application (BLA) for Herceptin and pre market approval (PMA) for HercepTest were filed simultaneously. Herceptin's BLA was approved under Priority Review. The Dako HercepTest was approved on the same day as the drug in September 1998. Herceptin was approved by EMA in August 2000. Additional diagnostics were approved subsequently for use with Herceptin and supplementary BLAs filed to effect changes in Herceptin's label to include references to these tests, e.g. PathVysion FISH assay kit.

- Example of biomarker identification before clinical phase.
- Herceptin was the first therapeutic antibody targeted to a specific cancer-related molecular marker (HER2) to receive FDA approval.
- First case of simultaneous approval of therapeutic and its companion diagnostic.

1. Key features:

Drug

- Herceptin (trastuzumab) is a humanised monoclonal antibody that binds to the HER2 protein and inhibit the proliferation of human tumor cells that overexpress HER2.

Companion diagnostic

- HercepTest is a semi-quantitative immunohistochemical assay for determination of HER2 protein (c-erbB-2 oncoprotein) overexpression in breast cancer tissues.

2. Summary of development and marketing process:

Time taken to get to market

- In the US, 6 years from IND and 4 months from BLA:
 - IND for trastuzumab was filed in 1992.
 - BLA was submitted in May 1998.
 - FDA approval in September 1998.
- In the EU, 1 year and 3 months from MAA:
 - MAA submitted in February 1999.
 - EMA approval in August 2000.

When the companion diagnostic was developed – before, after or simultaneously

- HercepTest was developed during Phase III trial.

Financing of the companion diagnostic

- Genentech.

Impact of any laboratory developed tests

- High risk of misdiagnosis due to lack of: standardisation, appropriate controls and validation in general.
- In the EU, companion diagnostic data and assay validation is not reviewed as thoroughly as in the US. In addition, “me-too” assays can be brought to market with simple CE marking and no review by authorities is required.

Regulatory issues

- A laboratory developed test was used to measure expression of HER2 protein during the trials and the results were used in defining eligibility.
- FDA indicated that a HER2 test would be required at the time of product approval and suggested approaches that Genentech consider to meet this need.

Evidence on cost effectiveness

- No comment.

Pricing and reimbursement issues

- No comment.

R&D Issues

- No comment.

3. Lessons**What worked well?**

- Fast track submission to FDA and approval under its Priority Review – which concluded one month earlier than planned.
- Patient advocacy that generated political interest and will to work quickly to bring product advancement to market, which cut through the bureaucracy and standard operating procedures. This is a poster child for ‘Breakthrough Therapies’.
- Inclusion only of patients whose tumors over-expressed HER2 allowed efficient activity-seeking phase I and phase II studies and enabled a moderately sized phase III program to be completed relatively quickly.

What didn't work well?

- Sluggish patient recruitment during Phase III posed very significant challenges and required changes to testing procedures, eligibility requirements and options for concurrent chemotherapy.
- Unexpected cardiac toxicity emerged during Phase III.
- Absence of long term risk assessment in trials and adverse drug reactions like cardiomyopathy and lung related problems gave rise to scepticism towards the drug's claims.
- Genentech did not include HercepTest in any Phase III testing, causing a "regulatory conundrum".

What were the critical success factors?

- The swift development of Dako test kit that averted submission delays – although partnership should have started earlier.
- Continuous engagement with FDA and close collaboration between Centre for Drug Evaluation and Research and Centre for Devices and Radiological Health.

Other points for consideration

- Targeted treatment will likely lead to restricted patient populations that must be reliably identified in trials and in the market.
- Introduction of diagnostic tests that will be used in the market into clinical trials is highly desirable, ideally with a sound diagnostic hypothesis so that you can transition smoothly to filing. The case of MetMab shows that even if you have a test, you will be delayed if your diagnostic hypothesis turns out to need tweaking on the basis of Phase III outcomes.
- New ways of thinking are required: sensitivity and specificity are not the issue – predictive value is. This, however, is hard to test explicitly in the context of drug development. In the case of Herceptin, non-HER2 over expressing patients were not included in the clinical trials. While rational, this limits the information that can be learned about the predictive value of the diagnostic (e.g. what is the positive and negative predictive value of a given test for Herceptin efficacy?).

Acknowledgement: Prepared with the assistance of Mr Kent Kost, Head of Global Quality and Regulatory Affairs, Roche Diagnostics.

Case study 2: HIV

Therapeutic Ziagen (abacavir) **by** GSK and ViiV Healthcare

Diagnostic *HLA-B*57:01* test

Background:

The nucleoside reverse transcriptase inhibitor, Ziagen (abacavir), was developed for use in combination therapy of HIV-1 infection. It was approved in the US in 1998 and in the EU in 1999. Abacavir hypersensitivity (ABC HSR) is a treatment-limiting and potentially life-threatening adverse event that occurs in 2-9% of patients receiving ABC. In addition to instituting an education and clinical management program, work to identify prognostic markers for ABC HSR for prospective use - as an adjunct to clinical vigilance - was initiated by GSK. Following over eight years of retrospective and prospective studies to identify, validate and confirm the clinical utility of the biomarker, HLA-B (type 57:01) (*HLA-B*57:01*) allele, the product labeling was amended to include: "prior to treatment with abacavir, screening for the HLA-B*5701 allele is recommended". At the time of the labeling change, testing for this allele was available through several commercial labs.

- Example of biomarker identification after the drug marketing authorization (10 years).
- One of earliest examples demonstrating that genetic markers which predict drug-associated adverse events with clinical utility can be identified.
- The clinical utility of prospective *HLA-B*57:01* screening was demonstrated in a blinded randomized clinical trial and in open-label cohorts.

1. Key features:

Drug

- Ziagen (abacavir) is a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV-1. In combination with other antiretroviral agents, it is indicated for the treatment of HIV-1 infection.

2. Summary of development and marketing process:

Time taken to get to market

- In the US, 4 years from IND and 6 months from NDA:
 - IND was filed in June-July 1994.
 - NDA was submitted in June 1998.
 - FDA approval (under accelerated approval regulations) in December 1998.
- In the EU, 1 year and 1 month from MAA:
 - MAA submitted in June 1998.
 - EMA approval in July 1999.

- Recommendation for *HLA-B*57:01* screening was included in product labeling in 2008.
- Performing studies in multiple populations to confirm the presence of racial differences of ABC HSR increased the time to determine the clinical relevance *HLA-B*57:01* in non-European populations.

When the companion diagnostic was developed – before, after or simultaneously

- Screening assays for *HLA-B*57:01* were developed by a number of clinical laboratories, which were already proficient in HLA genotyping to support transplantation, before formal evaluation of clinical utility of prospective screening (see section below).

Financing of the companion diagnostic

- N/A

Impact of any laboratory developed tests

- Some early publications from HIV clinicians who initiated *HLA-B*57:01* screening in their own practices highlighted the importance of robust DNA methods for *HLA-B*57:01* determination.
- In response to request from HIV health-care providers, a number of *HLA-B*57:01* screening assays were developed by clinical laboratories:
 - LabCorp (US) in 2004.
 - Delphic (UK) in 2005.
- GSK worked with laboratories in the US and Europe to ensure the quality of screening assays being offered.

Regulatory issues

- To support the marketing approval of Ziagen in US and Europe, GSK agreed to conduct post-approval research to further understanding of ABC HSR.
- EMEA requested GSK to develop 'diagnostic tests for ABC HSR'.
- Robust evidence of clinical utility was needed for inclusion of *HLA-B*57:01* screening information into product labeling. Data was required to: demonstrate that prospective *HLA-B*57:01* screening decreased the incidence of ABC HSR without inadvertently increasing the severity of ABC HSR outcomes in *HLA-B*57:01*-negative patients due to decreased clinical vigilance; and identify which patient groups would benefit from prospective screening.
- EU product labeling occurred in two phases: first, product labeling was updated to note a genetic association between carriage of *HLA-B*57:01* and risk of ABC HSR and later to recommend prospective screening. The FDA waited for the PREDICT study data before label change.

Evidence on cost effectiveness

- Several studies that investigated the cost-effectiveness of prospective *HLA-B*57:01* screening prior to abacavir use support reimbursement for testing.

Pricing and reimbursement issues

- No specific issues – particularly in relation to reimbursement of companion diagnostic as this is not applicable.

R&D issues

- Demonstration of clinical utility of prospective *HLA-B*57:01* screening required multiple studies over several years and a prospective study, through a time of significant technical advancement in genetic science.
- The differences in ABC HSR case criteria/definitions – and accuracy of diagnosis - led to differences in *HLA-B*57:01* sensitivity estimates among studies. The development of ABC skin patch testing by academic clinical investigators proved instrumental in identifying a robust ABC HSR phenotype for ongoing investigation.

Clinical infrastructure issues

- Having the testing infrastructure consistent with good clinical/laboratory practice was essential for incorporation into medical practice. Adoption of prospective screening for *HLA-B*57:01* benefited from an international network of clinical laboratories already proficient in high resolution HLA genotyping and clinical laboratory accreditation standards for transplantation.
- When the patient is diagnosed with HIV, it is not necessary for the treatment to be initiated immediately and there is time to wait for the results of the screening assay. The situation may be different for medicines in an acute setting where the turnaround time to stratify patients may become a limiting factor.

3. Lessons

What worked well?

- Being able to conduct studies with a sufficient sample size. If ABC HSR happened less frequently it may not have been possible to conduct the research.
- HIV disease and medicine development was progressing rapidly at the time.
- Availability of robust *HLA-B*57:01* screening assays by the time of product labeling change.

What didn't work well?

- Accurate phenotyping turned out to be a much bigger issue than expected and it took a while for the research team to realise this, adding to the overall timeline.
- General issues relating to post-authorisation research:
 - the need to take account of a number of confounding issues including: compliance with dosing recommendations; concurrent medical conditions and/or infections; concomitant medications; and unanticipated environmental factors.
 - having much less control on the clinical data that is collected and made available for analysis to define the clinical phenotype of interest.

- availability of DNA samples – it has become more routine for Phase I-IV clinical drug studies to collect samples, but post-approval sampling may be critical for newly marketed medicines, particularly if emerging clinical data suggests potential harm to patients.

What were the critical success factors?

- HIV physicians and patient communities that understand the value of research and are receptive to innovation. Independent studies by academic researchers following launch of the medicine, which complemented the research carried out by the manufacturer.
- The frequency of adverse events and strength of biomarker association. It may have been more difficult to change physician behavior if a much higher volume of patients needed screening to avoid an event.

Acknowledgement: Prepared with the assistance of Dr Arlene R Hughes, Director of Translational Genetics, GSK Genetics and Dr Martin Gartland, Global Medical Lead – Kivexa/Epzicom, ViiV Healthcare.

Reference:

“Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility”, *Pharmacogenomics* (2008) 8(6): 365-74

“Genetic association studies to detect adverse drug reactions: abacavir hypersensitivity as an example”, *Pharmacogenomics* (2009) 10(20): 225-233

“Designing pharmacogenomic studies to be fit for purpose”, *Pharmacogenomics* (2010) 11(12): 1657-1667

Case study 3: Breast Cancer

Diagnostic Oncotype DX by Genomic Health

Background:

Oncotype Dx is a prognostic test for breast cancer that aids oncologists plan prognosis by identifying low risk breast cancer patients unlikely to benefit from chemotherapy. It was developed by conducting retrospective studies on tissue archives. The clinical data demonstrating the test's potential to restrict healthcare costs facilitated full reimbursement from most payers in US. Genomic health opted for a Clinical Laboratory Improvement Amendment (CLIA) regimen for the US which was faster than gaining FDA approval and it was launched in 2004. It was CE marked in 2007 and became available in EU in late 2007.

1. Key features:

Diagnostic

- Predicts likelihood of breast cancer recurrence and benefit of adjuvant chemotherapy in node-negative, ER+, HER2- BC (roughly 60% of BC patients).
- Calculates the Recurrence Score based on an algorithm combining the expression of 21 genes (16 cancer genes and 5 reference genes).
- RT-PCR test performed on paraffin embedded tissue (in vitro diagnostic multivariate index assay [IVDMIA]).
- Included in major breast cancer guidelines (National Comprehensive Cancer Network [NCCN], American Society for Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO] and St Gallen).
- Laboratory-developed test (LDT); no official FDA approval (not needed as regulated under Clinical Laboratory Improvement Act).
- Value based priced diagnostic (approx. €3000).
- Cost-effectiveness analyses from 11 countries.

2. Summary of development and marketing process:

Time taken to get to market

- 4-5 years to develop Oncotype DX and bring it to market (thanks to the possibility of conducting prospective studies on archived tissues).

When the diagnostic was developed

- Developed after the chemotherapy treatment, though chemotherapy regimens change over time.

Financing of development

- Private investors in Genomic Health.
- Trials sponsored by SWOG (RxPONDER) and NCI (TailorX).

Impact of other tests

- Other multigene assays currently on the market (Mammaprint, Mammostrat, PAM50) but not seen as providing the same level of evidence regarding clinical validation and clinical utility (see recommendations from clinical guidelines).

Regulatory issues

- No specific requirement as the test is not performed within EU (so under the US regulation where it is performed) / only kit boxes are CE marked.
- In wake of the 2007 IVD MIA draft guidance, Oncotype Dx may require PMA/PMN approval from the FDA, and Genomic Health's internal CLIA lab may be required to stop offering these tests until additional approval is received. The current guidelines suggest that if the test is high-risk, it may be subject to additional scrutiny and therefore pre-market approval by the FDA. Currently, Oncotype DX is marketed directly to oncologists and patients.

Pricing and reimbursement status

- 99% coverage in the US with special LDT reimbursement status in US Medicare program.
- UK: still under review by NICE / reimbursement by all major private health insurers (including BUPA).
- Ireland/ Israel: full public (NCPE assessment) and private reimbursement.
- Greece/ Spain: public reimbursement by several payers/ provinces.
- Germany: selected sick fund reimbursement.

Pricing and reimbursement issues

- Capacity within HTA bodies (specific expertise to assess molecular diagnostics / acceptance of prospective-retrospective design (Simons et al, JNCI 2009)).
- Lack of specific reimbursement pathways for molecular diagnostics (e.g. Germany).
- Lack of ability to request reimbursement (need to go through a third party) (e.g. France).
- Willingness to pay for diagnostics and acceptance of same CE thresholds than those used for drugs.
- Budget silos and incentive to prescribe chemotherapy (e.g. Germany, UK, France).

R&D Issues

- Two big prospective trials are ongoing:
 - TailorX to look into the intermediary Recurrence Score (sponsored by NCI)
 - RxPONDER in the node positive patients (0-3 nodes) (sponsored by SWOG)
- IP protection: 2 patents for up to 14 genes for breast cancer test in US

3. Lessons

What worked well?

- Test validation:
 - Prospective study on archived tissues – well timed availability of tissue archives, through research consortia funded by NCI, made development short and cost effective.
 - Analytical and clinical validation – claims supported by many studies published in various journals.
- Endorsement by clinical community:
 - Collaboration with study groups (SWOG, NCI, ECO, etc).
 - Inclusion in all major breast cancer guidelines.
- Value based pricing supported by strong pharmaco-economic case:
 - Local pharmaco-economic evidence.
- Clinical utility:
 - Shown to influence chemotherapy decisions (in the US (Hassett et al, JCO 2012) and local decision impact studies (Spain, UK, Germany, France)).

What didn't work well?

- Reimbursement hurdles (see issues raised above) – out of pocket payment for most patients outside the US led to lower penetration in those markets.
- Paradigm change.

What were the critical success factors?

- Strong evidence supporting the analytical and clinical validation / “scientific profile” of Genomic health.
- First test to demonstrate clinical utility and impact on treatment decisions.
- Identified an area of potential cost savings incurred on unnecessary chemotherapy and converted it into a business model that saved more resources than those spent on its development.
- Actual healthcare cost savings.

Acknowledgement: Prepared with the assistance of Juliette Plun-Favreaux, Director Reimbursement and Market Access, Genomic Health International, Geneva.

Case study 4: Colorectal cancer

Therapeutic Vectibix (panitumumab) **by** Amgen

Diagnostic EGFR pharmDx **by** Dako

Diagnostic theascreen®: KRAS RGQ PCR Kit **by** Qiagen

Background:

Vectibix (panitumumab) was approved for the first time in September 2006 in the US via accelerated approval for treatment of epidermal growth factor receptor (EGFR)-expressing colorectal cancers. Soon after approval, prospective-retrospective analysis from the Phase III study showed an association between KRAS codon 12 and 13 mutation status and treatment efficacy. Discovery of this predictive biomarker led to narrowing of its indication in the EU to treatment of EGFR expressing metastatic colorectal cancer without KRAS mutation in codon 12 or 13, when it was approved by The European Commission in December 2007. Most recent data indicate that EGFR expression, as determined by immunohistochemistry, does not correlate with response and EGFR has been removed from the EU label.

- Vectibix is an example of a drug developed against a known biomarker (EGFR), and later had its use restricted with the knowledge of another biomarker (KRAS) that identified non-responders. In addition, recent data indicate that the original biomarker is not useful in stratifying patients.
- It became the first monoclonal antibody to demonstrate the use of KRAS as a negative predictive biomarker.
- KRAS was originally seen as a biomarker to predict lack of efficacy in patients with mutant KRAS status in monotherapy and in combination with chemotherapy (FOLFOX and FOLFIRI). As well as being a negative predictive biomarker it is now also seen as a biomarker for safety when used in combination with oxaliplatin chemotherapy (the combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated in the EU for patients with mutant KRAS mCRC or for whom KRAS mCRC status is unknown).

1. Key features:

Drug

- Vectibix is an epidermal growth factor receptor antagonist indicated as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens. Additionally, in the EU, it is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC):
 - in first-line in combination with FOLFOX
 - in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)

- Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had KRAS mutations in codon 12 or 13.

Diagnostic

- EGFR pharmDx assay is a qualitative immunohistochemical (IHC) kit system to identify EGFR expression in normal and neoplastic tissues routinely fixed for histological evaluation. The assay specifically detects the EGFR (HER1) protein in EGFR-expressing cells. Following incubation with the primary monoclonal antibody to human EGFR protein, this kit employs a ready-to-use visualization reagent based on dextran technology. The assay is FDA-approved as an aid in identifying colorectal cancer patients eligible for treatment with Erbitux (cetuximab) or Vectibix (panitumumab) and carries a valid CE mark.
- therascreen®: K-RAS RGQ PCR Kit (K-RAS Kit) is an *in vitro* diagnostic test intended for the qualitative detection of seven somatic mutations in codons 12 and 13 of the K-RAS oncogene, using DNA samples extracted from formalin-fixed paraffin-embedded colorectal tissue. Depending on the total amount of DNA present, the kit can detect 0.8% - 6.4% of mutant in a background of wild-type genomic DNA, dependent upon the specific allele being measured. The Kit is intended to aid doctors to identify colorectal cancer patients who may not benefit from anti-EGFR therapies such as cetuximab.

2. Summary of development and marketing process:

Time taken to get to market

- In the US, 7 years and 4 months from IND and final BLA module:
 - IND for panitumumab was filed in May 1999.
 - BLA submitted as a rolling submission: Nonclinical module submitted December 2006, CMC module submitted February 2006 and Clinical module submitted March 2006
 - FDA approval in September 2006.
- In the EU, 1 year 8 months from MAA:
 - MAA submitted in April 2006.
 - CHMP positive opinion for conditional marketing authorization in September 2007.
 - European Commission decision received in December 2007.

When the companion diagnostic was developed – before, after or simultaneously

- Use of the Dako EGFR pharmDx kit, developed before marketing authorisation, was specified on the original US label.
- The KRAS biomarker was revealed post marketing and the *therascreen KRAS* kit PMA review is ongoing in the US. In the EU, the label does not specify the use of a particular branded test. However, the therascreen KRAS test (Qiagen) was CE

marked in November 2007 before panitumumab was commercially available (and just after the regulatory approval).

Financing of the companion diagnostic

- In the US, Amgen partnered with Dako to file a supplemental PMA.
- The KRAS testing kit was developed by DxS, which was acquired by Qiagen in 2009. Amgen partnered with DxS (and then Qiagen) to ensure that a KRAS test kit carrying a valid CE Mark was available in the EU at the end of 2007 and to file a PMA in the US.

Impact of any laboratory developed tests

- Availability of laboratory developed tests for KRAS that do not require FDA approval is likely to reduce the market share for Qiagen.
- In the EU, the European Society of Pathologists, and in the US, the College of American Pathologists (CAP), have established External Quality Assurance programs which include Proficiency Tests to raise the standard for KRAS testing across all labs, including those that employ laboratory developed tests. Proficiency Tests are considered critical to ensure ongoing patient safety through accurate testing and to raise laboratory standards.

Regulatory issues

- The EGFR test kit for use with Vectibix was approved through a PMA supplement.
- The therascreen KRAS testing kit was CE marked in November 2007.

Evidence on cost effectiveness

- A number of studies on cost effectiveness have been carried out, e.g. Vijayaraghavan A, et al. (2012). *Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany*. International Journal of Cancer **131**(2), 438-45.

Pricing and reimbursement issues

- Testing is fully reimbursed by NHS.

R&D Issues

- No comments.

3. Lessons

What worked well?

- Vectibix was given an accelerated approval by FDA based on assessment of all-comers (ITT population), and a conditional approval by European Commission based on assessment of KRAS wild-type subset, as its benefits outweighed associated risks and it satisfied the criteria of "meeting unmet medical need".

What didn't work well?

- Pricing had been established prior to the KRAS hypothesis having been tested and proven, with a narrower patient population now being addressed.
- Pricing of test is cost-based and not value-based, which means the diagnostic manufacturer does not capture value for money saved from stratifying patients

What were the critical success factors?

- The drug meets “unmet medical need”
- Availability of KRAS data enabled a negative opinion to become a positive opinion for Vectibix in the EU.

Acknowledgement: Prepared with the assistance of Alan Morrison, VP International Regulatory Affairs & Safety, Amgen.

Case study 5: Melanoma

Therapeutic Zelboraf (vemurafenib) **by** Roche

Diagnostic cobas® 4800 BRAF V600 Mutation Test **by** Roche

Background:

Plexxikon's investigational drug PLX4032 (BRAF kinase inhibitor) showed anti-tumour effects in cellular and animal models of melanomas with BRAF V600E mutations. Plexxikon partnered with Roche Molecular Systems in 2005 to co-develop Zelboraf (vemurafenib) with the BRAF V600 Mutation Test. An IND was filed in 2006 and the clinical phase started in partnership with Roche Pharma. The prototype diagnostic was ready for exploratory use in 2007 and was included in the trials. Zelboraf was approved by FDA under priority review in August 2011 for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation as detected by an FDA-approved test. A companion diagnostic, the cobas 4800 BRAF V600 Mutation Test, was approved by FDA at the same time. The diagnostic was CE marked before EMA approval of the drug for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma in February 2012.

- The drug was selected for development based on knowledge of the biomarker.
- This was one of the fastest FDA approvals in history (only 4 months post-submission), and also represents simultaneous approval of a drug and companion diagnostic.

1. Key features:

Drug

- Zelboraf (vemurafenib) is a potent small molecule inhibitor of oncogenic, V600-mutated BRAF kinase, blocking cell proliferation and promoting cell death.
- The efficacy of Zelboraf in metastatic melanoma has been demonstrated in clinical trials (BRIM-2 and BRIM-3), in which patients whose tumors carried V600 mutations were selected using the cobas® 4800 BRAF V600 Mutation Test.

Companion diagnostic

- The cobas® 4800 BRAF V600 Mutation Test is a real-time PCR test developed as the companion diagnostic for Zelboraf.
- Its clinical utility has been proven in the selection of patients whose tumors carried BRAF V600 mutations for enrolment in the pivotal Phase 3 Zelboraf clinical trial (BRIM-3).
- In clinical trials, the cobas® BRAF Test was more sensitive and had a lower failure rate than Sanger sequencing.
- In addition to detecting the predominant V600E mutation, the cobas® BRAF Test can detect up to 70% of V600K mutations.

2. Summary of development and marketing process:

Time taken to get to market

- From the Zelboraf IND (Investigational New Drug Application) to simultaneous FDA approval of Zelboraf and the cobas® BRAF Test, took less than 5 years.
- This was one of the fastest FDA approvals in history (only 4 months post-submission), and also represents simultaneous approval of a drug and companion diagnostic.
- In the US, 4 years and 7 months from IND and 4 months from NDA:
 - IND for vemurafenib was filed in September 2006.
 - NDA was submitted in April 2011.
 - FDA approval in August 2011.
- In the EU, 9 months from MAA:
 - MAA submitted in May 2011.
 - EMA approval in February 2012.

When the companion diagnostic was developed – before, after or simultaneously

- The development program and regulatory filing of drug and test were done simultaneously and in parallel.

Financing of the companion diagnostic

- For FDA approval, Roche Pharma/Genentech needed a test to select patients who may benefit from therapy. As a result they financed the companion diagnostic.
- Roche Diagnostics bore the costs of manufacturing process validation and diagnostic regulatory filing.

Impact of any laboratory developed tests

- Due to the lack of regulatory oversight, lab developed tests continued to make unsubstantiated and off-labels claims about being clinically validated with Zelboraf. This created an un-level playing field and confused for clinicians who were looking to test patients with the FDA approved test.
- Due to the testing infrastructure that was set-up prior to launch and joint promotion of drug and test by the Pharmaceutical and Diagnostics divisions of Roche/Genentech, both drug and companion test were able to overcome the challenges posed by LDTs and achieve rapid market penetration.

Regulatory issues

- Though the filing and approval process were seamless, some of the Regulatory challenges encountered were:
 - The inability to include next generation (massively parallel) sequencing data to confirm the superior accuracy of the cobas® BRAF Test vs. Sanger sequencing.

- Aligning the timing of drug and test approvals in the various countries across the world. The drug was approved before the test in just 2 markets (Mexico and South Korea). In all other markets the approvals were simultaneous or the test was approved prior to the drug.
- Creating consistent drug and test labels between the US and EU jurisdictions (in the US the drug and test are labelled for V600E, while in the EU the drug and test are labelled for V600 mutations).

Evidence on cost effectiveness

- A recent cost-consequence comparison with Sanger sequencing revealed that the use of the cobas® BRAF test resulted in a total saving of \$14.2 million, or \$1,479.17 per patient.
- Majority of the savings were a result of avoiding unnecessary or inappropriate drug therapy and diagnostic costs accounted for a small fraction of total expenditures.

Pricing and reimbursement issues

For diagnostics

- Current reimbursement systems (based on stacked codes) are archaic and don't incentivize innovative/high medical value tests which guide important therapeutic decisions.
- In the US, some payers are considering adopting a model which reimburses FDA approved tests at a higher level than LDTs, and these changes may drive test adoption and provide IVD manufacturers with a greater incentive in bringing innovative products to market.

R&D Issues

For diagnostics

- An instrument platform change during early development (Phase 1 trials) needed additional bridging studies to demonstrate there was no change in patient selection.
- A new sample prep kit had to be developed for FFPE (formalin fixed paraffin embedded) tissues. This kit was optimized for high melanin melanomas to maximize patient clinical trial enrolment.
- Rapid progression of BRIM2/3 trials required accelerated analytical studies and transfer to manufacturing. This had the potential to increase project risk, however the teams were able to deliver on time and meet critical Pharma timelines.

3. Lessons

What worked well?

For the pharma / diagnostic collaboration

- The collaboration between Roche Pharma/Genentech and Roche Diagnostics worked well since both sides were involved in the project from an early stage. The diagnostic was considered a key driver for Zelboraf commercialization and hence it was supported from the beginning.
- Notable shortening of clinical phase due to enrollment of only patients positive by diagnostic in the Phase I extension, Phase II and Phase III trials. Early striking results in Phase I study prompted the launch of Phase II and III trials simultaneously. The NDA/MMA was based on robust treatment effect in a planned interim analysis of Phase III trial.
- When labs were given the opportunity to get personal experience with the test, the key advantages of accuracy, speed/convenience of workflow and reliability/robustness of test led them to switch to the FDA approved cobas® BRAF Test.
- From 3 labs at launch in August 2011, the number of labs (including academic centres) running the cobas® BRAF increased to >15 by August 2012 and this number continues to grow.

What didn't work well?

For the pharma / diagnostic collaboration

- Some KOLs/labs (especially those from academic centers) wanted detailed genotyping information for research purposes vs. clinicians who were looking to make therapy decisions based on the results from a companion test.
- Despite strong evidence confirming the superior performance and safety of the test, the primary objection was cost.
- The close co-ordination required between the drug and diagnostic development, especially given the accelerated clinical development plan. Whilst it was managed, it was difficult, especially for the diagnostic.

What were the critical success factors?

For the pharma / diagnostic collaboration

- Early and integrated collaboration between Pharma and Diagnostics to maintain alignment across rapidly evolving and ever accelerated timelines for clinical trial and regulatory filings.
- Constructive and collaborative dialogue with the FDA (on both the Pharmaceutical and Diagnostic side) laid the foundation for future companion diagnostic approvals.
- Simultaneous approval of Zelboraf and the cobas® BRAF test enabled collaboration at all levels across the commercial organizations during the launch phase.
- Setup of testing infrastructure prior to launch reduced barriers to test adoption by labs.

- Clinician education by the Roche/Genentech sales force on where/how to access the companion test allowed patients to access drug faster.
- Building early awareness and belief that the cobas® test produced more accurate results compared to other methods like Sanger sequencing, allowed clinicians and labs to choose the FDA approved test over other methods.

Acknowledgement: Prepared with the assistance of Mr Kent Kost, Head of Global Quality and Regulatory Affairs, Roche Diagnostics.

Case study 6: Non small cell lung cancer

Therapeutic Xalkori (crizotinib) **by** Pfizer

Diagnostic Vysis ALK Break Apart FISH Probe Kit **by** Abbott Molecular Inc

Background:

In response to a 2007 study linking a subset of NSCLC (non small cell lung cancer) to ALK (anaplastic lymphoma kinase) fusion gene, Pfizer partnered with Abbott Molecular Inc. to develop an assay to detect ALK translocation. The test was used to expand an ongoing phase I trial to include a cohort of patients whose with NSCLC expressing the ALK translocation. Selecting patients according to ALK translocation status led to led to high response rates in the phase I study. Pfizer's Xalkori (crizotinib) was approved by the FDA in August 2011 for the treatment of patients with late-stage NSCLC who express the abnormal ALK gene. At the same time, Abbot Molecular's Vysis ALK Break Apart FISH Probe Kit was given a companion diagnostic status. In Europe, the diagnostic was CE marked in August 2011 and EMA's CHMP adopted a positive opinion recommending conditional marketing authorisation of crizotinib in EU in July 2012 for the treatment of adults with previously treated ALK-positive advanced NSCLC. Since then the VENTANA ALK IHC kit, developed in partnership with Pfizer, has been granted a diagnostic kite mark in Europe.

- Example of biomarker identification before clinical phase.
- Crizotinib provides an example of rapid regulatory passage through accelerated approval by the FDA and conditional marketing authorization by EMA.

1. Key features:

Drug

- Xalkori (crizotinib) is a tyrosine kinase inhibitor indicated in Europe for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Companion diagnostic

- The Vysis ALK Break Apart FISH Probe Kit is intended to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens.

2. Summary of development and marketing process:

Time taken to get to market

- In the US, 5 years and 8 months from IND and 5 months from NDA:
 - IND for crizotinib was filed in December 2005.
 - NDA submitted in March 2011.
 - FDA approval in August 2011.
- In the EU, 11 months from MAA:
 - MAA submitted in August 2011.
 - CHMP positive opinion for conditional marketing authorization in July 2012.

When the companion diagnostic was developed – before, after or simultaneously

- The FISH test was developed simultaneously, and the IHC assay subsequently.

Financing of the companion diagnostic

- Abbot Molecular Inc.

Impact of any laboratory developed tests

- Laboratory developed FISH tests are not prevalent. However, it remains to be seen whether either of the companion diagnostics will be used as the platform test in Europe. Laboratory developed immunohistochemistry (IHC) tests could affect the use of the VENTANA ALK IHC kit.

Regulatory issues

- Regulatory approval was relatively fast, having gone through the ‘fast track’ processes of FDA and EMA.

Evidence on cost effectiveness

- Regulatory approval given following single-arm study. RCT of the drug is ongoing.
- In general, there is a tension between the different data requirements for ‘fast’ regulatory approval (progression free survival rates) and cost effectiveness assessment (overall survival measures).
- Whilst it is possible to statistically extrapolate from progression free survival rates, comparison will only be against historical controls following a single-arm study: if it is a treatment for a newly defined disease sub-type, it is difficult to find retrospective cohorts. There has to be a re-think on traditional model of R&D and evaluation, especially when the drug can address substantial unmet medical need.

Pricing and reimbursement issues

- In the UK there are separate budgets for drugs and diagnostic tests, making any assessment of drug/companion diagnostic pricing as a package artificial.

R&D Issues

- Difficulties finding enough subset of NSCLC patients who express the abnormal ALK gene. Prevalence may be similar to orphan or rare diseases but because of the spread over large geographic area, registration for RCT can be an issue.
- It will be helpful to have the next generation sequencing infrastructure in the UK to enable rapid identification of patients for clinical trials, as well as a number of dedicated molecular development centers.
- Companies are still undertaking trials in isolation from each other. It will be helpful to undertake studies of 2-3 profiled molecular markers jointly which is likely to reduce overall screening failure rates.

3. Lessons

What worked well?

- Favourable timing of EML4-ALK fusion publication during program.
- Well timed partnership with diagnostic company before the beginning of clinical phase which enabled patient stratification.
- Frequent meetings and written correspondences with FDA for advice on the drug development plan, trial design and data requirements.

What didn't work well?

- FISH assay fits less smoothly into the clinical diagnosis process compared to other tests and Pfizer announced the partnership with Ventana to develop the IHC assay soon after approval.
- Only 3-5% of NSCLC patients (expressing ALK translocation) were eligible for enrolment.

What were the critical success factors?

- Defining a subgroup of patients, based on scientific evaluation, who will benefit from the drug and not broadening the criteria.

Acknowledgement: This document was reviewed by Dr David Montgomery, Medical Director – Oncology UK, Pfizer Ltd., for the accuracy of its contents.

Case study 7: Cystic Fibrosis

Therapeutic Kalydeco (ivacaftor) **by** Vertex Pharmaceuticals and Cystic Fibrosis Foundation Therapeutics, Inc

Diagnostic Testing for CFTR G551D mutation

Background:

Based on extensive genomic and proteomic data on the pathogenesis of cystic fibrosis (CF), Vertex developed and FDA approved Kalydeco (ivacaftor) as a targeted therapy for patients with CF who have the G551D gene variant of the CFTR (CF Transmembrane regulator) in January 2012. Kalydeco received a positive opinion from CHMP for approval in the EU on May 25, 2012, after only three months of appraisal. Given the targeted nature of the drug, a linked diagnostic test was vital both to the clinical trials and to the clinical use of the drug.

- Kalydeco is the first available treatment that targets the underlying cause of cystic fibrosis.
- Biomarker was known (“sweat test”) and mutation testing available.
- The drug was granted approval after just three months of review, making it one of the fastest FDA approvals.
- The drug is awarded “orphan status” in the US and EU.

1. Key features:

Drug

- Unique drug targeted specifically at one molecular variant of the CFTR, the abnormal Cl channel responsible for CF. Preclinical work demonstrating improved ion channel function of one variant protein (G551D variant), including improved Cl transport in cells from patients with this variant, lead to *in vivo* demonstration of altered biomarker for CF, the sweat test, and design of a small, targeted clinical trial, enrolling only patients capable of responding to the drug due to their gene variant. Small phase III trials (161 patients over 12 years of age, and an additional 52 patient trial in patients 6-11 years) demonstrated efficacy and large effect size for clinically relevant end—points in the vast majority of patients. Other studies showed lack of efficacy in homozygous F508del mutation (more common variant). It is currently being evaluated as a treatment in other CF populations.
- It is indicated for the treatment of CF in patients aged 6 years and older who have the G551D mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.

Diagnostic

- The vast majority of children with cystic fibrosis have genotyping done at the time of diagnosis, so the program did not include development of a companion

diagnostic. The labeled indication reads: “KALYDECO is indicated for the treatment of cystic fibrosis in patients aged 6 years and older who have the G551D mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.”

2. Summary of development and marketing process:

Time taken to get to market

- The drug development process was relatively fast.
- In the US, 5 years and 9 months from IND and 3 months from NDA:
 - IND was first filed in March 2006.
 - NDA was filed in October 2011.
 - FDA approval in January 2012.
- In the EU, 10 months from MAA:
 - MAA submitted in October 2011.
 - EMA approval in July 2012.

When the companion diagnostic was developed – before, after or simultaneously

- N/A

Financing of the companion diagnostic

- N/A

Impact of any laboratory developed tests

- N/A

Regulatory issues

- Sponsor worked effectively with FDA and made good use of “milestone” meetings (IND, end-of-phase 2, pre-NDA) to work through study designs, etc.
- FDA recommended a study in the more common genotype variant (homozygous F508del mutation), as well as establishing a safety database for the drug.
- FDA has requested an ongoing safety database for the drug.

Evidence on cost effectiveness

- Clear benefit demonstrated for clinically relevant end-points with large effect size and very high response rate across ages and disease severity. The extent of efficacy is striking compared to most therapies currently marketed, was easily determined in small clinical trials, and likely to have substantial impact on treated patients. Current cost of the drug in the US is \$294,000/year. The FDA does not weigh ‘cost effectiveness’ *per se* into the drug approval process.

Pricing and reimbursement issues

- In the US, Vertex Pharmaceuticals is providing a large subsidy for patients without adequate insurance coverage – a very different “market place” than in the UK/EU.
- Provides an opportunity to validate the impact of targeted therapeutics in the US setting.

R&D Issues

- The drug development program was based on sound basic and clinical science. The sponsor understood the genomics of CF, the targeting of their compound to a specific variant, and how to design a small, efficient clinical plan to demonstrate safety and efficacy. All this required a background of outstanding genomic and proteomic research at the NIH and in the academic community, strong support from the CF Foundation, and an outstanding clinical research network that had been in place studying other interventions in CF for many years. The real lesson from this is the need for all aspects – molecular, pharmacologic, patients/patient advocacy, investigative capacity, sponsor, and FDA.

3. Lessons

What worked well?

- Success required broad collaborative efforts from basic science, to drug discovery/development, to clinical trials, to regulatory approval. The ultimate NDA package was well thought through, and together with prior consultation between FDA and sponsor, the review time was only 3 months, half the time of an “expedited review”. FDA was able to coordinate the reviews of many diverse disciplines involved leading to the rapid review process. The elegance of the science, and clear therapeutic need and novelty of the drug acted as real “incentives” to reviewers to undertake a rigorous and extremely efficient review. Given the robust efficacy of the drug, the Center for Drug Evaluation and Research also was able to wave an advisory committee review which further expedited the overall review process.

What didn't work well?

- No comments.

What were the critical success factors?

- Fundamentally – partnership and collaboration.
- Steadfast CF Foundation advocacy and support.
- Outstanding basic genomic and proteomic science – FDA, and academic communities.
- Outstanding CF clinical trial network – a highly organized and skilled group of clinical/investigators with detailed understanding of the clinical/phenotypic

aspects of the disease and able to efficiently perform the needed clinical studies -
"research ready" when a breakthrough compound came forth

- A focused and sophisticated sponsor.
- FDA expertise to help shape the development program and to efficiently undertake the review process.

Acknowledgement: Prepared with the assistance of Dr. Stephen P. Spielberg, Deputy Commissioner for Medical Products and Tobacco, and Anthony Durmowicz, Medical Officer, US Food and Drug Administration.

Case study 8: Melanoma

Therapeutic Trametinib (MEKi) and dabrafenib (BRAFi) **by** GSK

Diagnostic BRAF™ mutation kit (v600 E & K) **by** bioMérieux

Background:

GSK's BRAF inhibitor dabrafenib and its MEK protein inhibitor trametinib each met the primary endpoint of progression free survival improvement in separate Phase III trials. In addition, a Phase I/II trial that examined the combination of dabrafenib plus trametinib in treatment naïve patients with metastatic melanoma showed promising results. Regulatory submissions related to single-agent use of dabrafenib and trametinib to treat patients with BRAF V600 mutation positive metastatic melanoma has been made in the European Union and US in August 2012. FDA Pre-Market Approval for the companion diagnostic, developed by bioMérieux, has also been filed. GSK entered into a collaboration with bioMérieux in 2010 to develop a molecular theranostic test to detect BRAF V600 (V600E and V600K) gene mutations found in melanoma. The diagnostic is currently being utilised in the Phase III trametinib-dabrafenib combination programme to identify appropriate patients.

1. Key features:

- Chemistry: Targeted therapies that are potent (sub-nanomolar) and selective inhibitors. Trametinib (MEKi) is an allosteric inhibitor and dabrafenib (BRAFi) is an ATP competitive inhibitor with selectivity (>10 µM) against a panel of 260 kinases.
- Biology: Exemplifies precision medicine - Sensitive and specific assay to predict the patient population most likely to benefit.
- Indication: Focused development in high unmet medical need for melanoma – genetically driven cancer where BRAF V600 mutation is present in approximately 50% of population.
- Novel combination of BRAF/MEK (dabrafenib/trametinib) - Understanding the molecular and genetic mechanisms around the development of resistance. Early data suggested that the majority of resistance mechanisms were related to MAP Kinase reactivation and patients may benefit from the combination of BRAF+MEK inhibitor.

2. Summary of development and marketing process:

Time taken to get to market

- Dabrafenib – 3yrs from First Phase I dose to first regulatory submission.
- Trametinib – 4yrs from First Phase I dose to first regulatory submission.
- Dabrafenib/Trametinib Combo – 2yrs from First Phase I dose to Phase III start (occurred in parallel with monotherapy development).
- Companion Diagnostic (cDx) - ~20 months, and the PMA submission coincided with the NDA submissions.

When the companion diagnostic was developed – before, after or simultaneously

- A laboratory developed test was in place at the start of the FTIH studies. This underwent analytical validation to render it an investigational use only (IUO) assay for the start of the pivotal trials. bioMerieux, as GSK's commercial partner, developed the companion diagnostic. Retrospective testing of all samples to demonstrate analytical and clinical concordance was conducted and submitted in the PMA application.

Financing of the companion diagnostic

- Collaborative partnerships between GSK and two diagnostic companies with all parties contributing resources (e.g. financing and people) to support the development of a companion diagnostic.

Impact of any laboratory developed tests

- The laboratory developed test formed the basis on which the companion diagnostic was developed. The assay differentiated between the V600E, K and D mutant forms of BRAF. The companion diagnostic only focused on V600E and K, due to the infrequent nature of the V600D mutation (0.001%), it was determined that this would be too difficult to validate, and so was removed from the final version of the companion diagnostic assay.

Regulatory issues

- There have been no regulatory issues to date. The regulatory agencies have been extremely collaborative and engagement started early and has been frequent, with both formal and informal interactions regarding the drug and diagnostic development plans.

Evidence on cost effectiveness

- Cost effectiveness analyses for dabrafenib, trametinib and the combination of dabrafenib and trametinib is ongoing hence it is a bit premature to speculate on the cost effectiveness of these medicines. The economic models will compare each of these against other treatments being used for the treatment of metastatic melanoma (e.g. DTIC, vemurafenib, ipilimumab).

Pricing and reimbursement issues

- It is too premature to speculate on price or reimbursement since none of these agents have received regulatory approval. However demonstrating the clinical, economic and humanistic (e.g. quality of life) value of these agents to Health Technology Assessment agencies (e.g. NICE, PBAC) and other payers will be important for achieving reimbursement and market access.

R&D Issues

- The biggest R&D challenge was adapting our development plan to the rapidly evolving landscape in melanoma. Prior to 2011, no new drugs were successful or approved for the treatment of metastatic melanoma for over 3 decades. Furthermore, given the rapid development for dabrafenib and trametinib, it was essential to have a companion diagnostic partner who could adapt to the changing environment to keep the diagnostic development on track.

3. Lessons

What worked well?

- Early Patient selection (based on BRAF V600 mutation) in first cohort of Phase I dose escalation.
- POC based on Phase I expansion cohort.
- Full development plans (CMC, Clin Pharm, and pivotal registration studies) for both monotherapy agents (e.g. dabrafenib & trametinib) in metastatic melanoma.
- Initiated novel combination of BRAF+MEK prior to approval for either single agent alone.

What isn't working well?

- No comment.

What are the likely success factors?

- Aligned drug/companion diagnostic development.
- Integrated clinical/regulatory/diagnostic teams formed early during Phase I.
- Met early and often with regulatory agencies; ensuring joint representation of both drug and diagnostic where applicable (e.g. CDER/CDRH).
- Strategic selection of technology and diagnostic testing partners for companion diagnostic development.
- Sample banking processes and systems to support companion diagnostic development.
- Strong relationship with companion diagnostic partner; joint development teams and steering committee for decision making.
- Effective partnering with testing labs and companion diagnostic companies having the necessary global footprint.
- Effective global distribution strategy.

Acknowledgement: Prepared with the assistance of Dr Jeff Legos (Medicine Development Leader) and Dr Anne-Marie Martin (Diagnostic Leader), GlaxoSmithKline Oncology.