Delivering on the Promise of Personalised Healthcare

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Presentation Outline

- Introduction
- Drug-Diagnostic Co-development Key steps
- Challenges and Opportunities
- An illustrative example
- Bioanalytical Perspective
- Summary



Introduction



All Drugs Don't Work in All Patients

"The vast majority of drugs - more than 90 per cent – only work in 30 or 50 per cent of the people" *Allen Roses (GSK)*

> **Hypertension Drugs 10-30%** ACE Inhibitors **Heart Failure Drugs** 15-25% Beta Blockers **Anti Depressants** 20-50% **Cholesterol Drugs 30-70%** Statins **Asthma Drugs** 40-70% Beta-2-agonists





What is Personalised Healthcare ?

Delivering the right treatment to the right patient at the right dose



Who could argue with this as a worthwhile objective?



Why Personalised Healthcare ?



Because Personalised Health Care is the right thing to do



Companion Diagnostics – Key Drivers



Patients/Physicians



But..... it can look complex (and costly)

Historic pharma industry success based on blockbusters

- Simple to recognise the patients
- Medicines which are easy to prescribe

Personalised Medicines can look difficult and costly to develop

- Complexity of simultaneous development and regulatory approval of drug and diagnostic
- Clinical trials seen as more complex

Personalised Medicines can look complicated to sell

- Increased cost for payer due to testing
- Testing adds a barrier to prescription
- Testing reduces the number of accessible patients



Where Are We Today..

Drug/indication

Table 2 A growing personalized medicine cabinet

Drug developer

- Growing portfolio of drugs with companion diagnostics
 - "Required" testing
 - "Recommended" testing
 - "Informational" testing

- Trastuzumab HER2 testing
 Maraviroc Trofile
- Irinotecan UGT1A1
- Warfarin CYP2C9, VKORC1 etc

Abacavir – HLA-B 5701b
 Imatinib – Ph+ CML

Erbituxciolon cancer Imclone ECFR pharmDVDAKO Cytomation IHC to determine ECFR presence or absonce. Test also and neck cancer Selzentry/HIV AIDS Pfteer Trofile (CCR5 tropian)/ Monogram Bioxcinces Amplification of pairtikes and infection asay Vectibit%tobin cancer Amgen ECFR expression KRAS/DvS The test is required in Europe, KRAS/Indiations may be reflected in Europe, KRAS/Indiatone reflected in Europe, KRAS/Indiatone reflected in	Testing required by FDA			
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PRequired by the European Medicines Agency. Source: US FDA and company materials Nature Biotechnology, Volume 26 (5) May 2008	VFEND (voriconazole)/fungal infections	Pfizer	CYP2C19/Gentris, Roche	A variety of other drugs, including, Prilosec (omeprazole), Protonix (pantoprazole), Nexium (esomeprazole) and Valium (diazepam) are also affected by variation in same gene
Source: US FDA and company materials Nature Biotechnology, Volume 26 (5) May 2008	*Required by the European Medicines Agency.			
	Source: US FDA and company materials		Nature Bi	otechnology, Volume 26 (5) May 2008

Test/selected product developers

Comments

Companion Diagnostic

 A test or method designed to determine if a patient will respond to treatment with a particular drug or not



Is this drug effective and safe for this patient (personalised healthcare)?



Vemurafenib and BRAF/Melanoma

- Zelboraf[™] (vemurafenib) is an orally available serine-threonine kinase inhibitor of the mutated form of BRAF
- The drug is indicated for the treatment of BRAF mutation positive melanoma. Zelboraf[™] is not recommended for use in patients with wild-type BRAF melanoma
- Roche Molecular Systems have developed a companion diagnostic
 Cobas® 4800 BRAF V600 Mutation Test. Test is designed to detect BRAFV600E mutations in DNA isolated from formalin fixed, paraffin-embedded human melanoma tissue
- Simultaneous approval of the drug and the companion diagnostic in the US (ahead of the scheduled PDUFA and MDUFMA dates)







Crizotinib and ALK Positive/NSCLC

- Xalkori (crizotinib) is an orally available kinase inhibitor of ALK, HGFR, c-Met
- Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive
- Abbott Molecular have developed a companion diagnostic Vysis ALK Break-Apart FISH Probe Kit
- Test uses DNA probes with attached fluorescent dyes to detect the presence of chromosomal rearrangements of the ALK gene, located on chromosome 2, in non-small cell lung cancer (NSCLC) tissue
- Simultaneous approval of the drug and the companion diagnostic in the US (ahead of the scheduled PDUFA and MDUFMA dates)







Drug–Diagnostic Co-Development Key Steps



Overview of Drug/Diagnostic Co-Development





Putting the Pieces Together



Putting it into Practice



Patient & Physician Value



Assay Availability Assay Reimbursement



Clinical Guidelines & Practice



Scientific Understanding

- Choosing the right biomarker requires indepth understanding of:
 - the mode of action of your drug
 - the biology of the disease you are trying to treat
- To be successful start early!



Developing the Assay

- What is the "intended use" of the assay?
- Ensure assay meets design requirements
 - Analytical validation
 - Clinical validation
 - Manufacturing
- Diagnostic partner engagement



Drug Discovery Today (2010) 15,816-825



Cummings et al., British Journal of Cancer (2010) 103, 1313–1317

Developing the Assay







Proving Biomarker/Diagnostic Utility

 Data from pivotal trial must support drug and diagnostic submission





Regulatory Approval

- Companion diagnostics considered high risk and therefore likely to need to meet the highest regulatory hurdles in the US [Class III, Pre Market Approval (PMA) required]
- Regulatory approvals across multiple territories required







FDA Premarket Approval - PMA

- Contents Specified in 21 CFR 814.20
- General Information Section
- Assay Development / Analytical Validation Section
- Manufacturing and Quality System Section
- Clinical Investigations Section
- Labeling Section
- Process is 180 days....but routinely takes much longer
- Modular PMA

A compilation of sections or "modules" submitted at different times that together become a complete PMA application



Some potential pitfalls en route to PMA

- Poor communication between Rx and Dx companies and Regulators
- Not establishing assay with real clinical samples from intended use population
- Analytical performance not validated & standardized prior to use in clinical trials
- Not addressing 'all-comers' or developing biological rationale for a targeted program
- Bias introduced by only testing a subset of intended use population and/or pre-screening
- Multiple tests (with different performance?) and/or local labs used in clinical trials
- Bridging studies from CTA to companion Dx are risky; they need high sample ascertainment (> 90%recommended)

The pivotal validation study should investigate Dx use in the claimed clinical population using the final Dx configuration



The Commercial World

Key considerations

- Diagnostic must be available at time of drug launch
- Strategies to drive test adoption
- Strategies to remove barriers to testing
- Reimbursement for diagnostic testing





Challenges & Opportunities



Some Challenges

- Scientific understanding advanced but much more to learn.....
- Don't always understand why drug works differently in some patients
- Identifying and developing a biomarker can be difficult
- Tools and technologies don't yet exist (or not good enough)
- A test is never 100% predictive
- Challenging to develop biomarker in time for co-launch with drug (Co-ordination of test development with drug development)
- Clinical trials more complicated Inclusion of test +ve and -ve patients (utility)
- Slower recruitment due to testing
- The regulatory path
- Smaller market



Some Opportunities

- Clear benefits to patients, clinical community and payers
- Better benefit/risk price
- Faster development if clear rationale & evidence
- Potential opportunities to move straight into first line therapy
- Potential for product rescue
- Faster uptake once launched
- If we don't do it someone else will!



Gefitinib – An Example



Gefitinib Early Development

- Gefitinib is an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor
- Phase I: encouraging antitumour activity seen in NSCLC
- Phase II (IDEAL 1 and 2): promising activity observed and welltolerated
 - EGFR expression levels did not correlate with response



Gefitinib mechanism of action



IPASS: PFS by Mutation Status





Iressa[™] (Gefitinib)

IRESSA (Gefitinib) Receives Marketing Authorisation for the Treatment of Non-Small Cell Lung Cancer in Europe

AstraZeneca announced today that the European Commission has granted marketing authorisation for the oral anti-cancer drug, IRESSA for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) *with activating mutations of EGFR-TK* (epidermal growth factor receptor-tyrosine kinase) across all lines of therapy. The authorisation is based on a submission package including two pivotal Phase III studies comparing IRESSA with chemotherapy, IPASS and INTEREST

Working with different partners is key....



Respiratory physician/ surgeon



Oncologist



Pathologist



Diagnostic company



Lab service provider/Molecular Biologist



Diagnostic platform provider



What success looks like



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Bioanalytical Perspective



Regulated Bioanalysis

Guidance for Industry

Bioanalytical Method Validation

DRAFT GUIDANCE

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Contains Nonbinding Recommendations

Draft - Not for Implementation

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Regulated Bioanalysis

- Focus on validation
 - Accuracy, precision, selectivity, sensitivity, reproducibility, stability
- Biomarker data used to support a regulatory action (pivotal determination of drug safety/effectiveness, labeled dosing) – full validation required
- For CDx development (treatment decision) CDRH guidance
- New technologies any data submitted should be supported by data from current gold standard







Summary

- Companion diagnostics are a reality
- Companion diagnostics are a necessity
- The path to drug-test co-development is challenging
- Personalised healthcare offers much promise - potential to benefit everyone in the healthcare system



Thank You!

