Use of immunotherapy for cancer treatment

Pre- and post-licensing considerations

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European Pharmaceutical Law

• Allows a single market in pharmaceuticals
• Allows all citizens an equal chance to benefit
• This depends on individual nations
  – Licensing is not synonymous with marketing
  – Marketing does not guarantee use
EU member states and EEA

EU
28 countries

EEA
Norway
Iceland
Lichtenstein
European Licensing Procedures

• Centralized procedure
  – Single application and evaluation
  – Single authorization in all EU Member States
  – European Commission grants the license

• Mutual Recognition
  – Authorized by one EU member state
    • Application for authorization in further EU states

• Decentralized Procedure
  – Application in several states simultaneously
Centralized Procedure

**Mandatory**
- Biotechnology products
- Orphan drugs
- Cancer
- Neurodegenerative diseases
- HIV
- Diabetes
- Auto-immune disease
- Viral disease

**Voluntary**
- All new actives,
- Practically anything else of ‘proven’ community interest
- Generics of products authorised by the centralised procedure
Centralized Procedure

• Countries bid to be rapporteur or co-rapp*
• Rapporteur and co-rapp appointed by CHMP
• Procedure administered by the EMA
• Voluntary comments from other member states
• License based on quality, safety and efficacy
  – Cost is not an issue
• Biological products including biosimilars
  – Evolving set of licensing guidelines
Growth of biologicals

- 27% pharmaceutical sales in Europe
- 5.5% growth v total market growth 1.9%
- Many patents due to expire before 2020
  - Allows development of biosimilar medicines
- Copy version of an authorized biological
  - Not innovative
  - Extensive knowledge gained with originator
- Potential for ↓ cost and ↑ availability

Source: IMS Institute for Healthcare Information October 2014
Biosimilar medicines for cancer

• Mabthera/Rituxan (rituximab)
  – Patent expiry Feb ‘13 in EU; Sept ‘16 in US
    • Biosimilars: Zytux (Iran, 2015); AcellBia (Russia, 2014)
    • Biosimilars in development in US and EU

• Herceptin (trastuzumab)
  • Patent expiry July ‘14 in EU; June ’19 in US
    • Biosimilar: Herzuma (Korea, 2014)
    • Biosimilars in development in US and EU
Promising Innovative Medicine

• Life threatening or seriously debilitating cond\textsuperscript{n}
• High unmet clinical need
• Major advantage over other methods
• Positive benefit:risk
• PIM designation awarded on phase I/II data
• Expectation to develop clinical program
  – Application under the EAMS*

*Early Access to Medicines Scheme
Early Access to Medicines Scheme

• Supply of product made to GMP standards
• Safety profile not fully established
• Information for patients
  – Informed consent form (ICF)
• ICF and application form sent to company
• Patient registration – unique number (NHSE*)
• Prescriber may request drug for 2 cycles
  – Drug supply and case report form

*National Health Service England
Early Access to Medicines Scheme

• Information for physicians
  – Specific training on AE reporting required
  – Letter of agreement

• Clinical alert card for the patient

• Pharmacovigilance & Risk Management Plan
Early Access to Medicines Scheme

• Recurrent applications with same drug
  – Expanding indications
  – Safety data can be pooled

• May impair recruitment to trials
• Location of patients may be decided by company
Adaptive licensing

- Early and progressive access to new drugs
- Quality and non-clinical data sound
- Early discussions on development
  - EMA
  - Company
  - Health Technology Assessment Bodies
  - Organizations issuing clinical treatment guidelines
  - Patient organizations
Adaptive licensing

• Iterative development
  – Restricted patient population then expanding
  – Gathering evidence through real life use
    • Data on use carefully controlled and monitored
    • Supplement clinical trial data
    • Non-randomized
The role of NICE

• Guidance on the use of treatments in the NHS
• Consideration of clinical and cost effectiveness
• Consideration of all therapies
  – Cancer therapy not prioritized
• 4 types of guidance
  – Technical assessment
  – Clinical guidelines
  – Public Health Guidance
  – Interventional procedures
Health Technology Assessment

Multidisciplinary field of policy analysis

• NICE
  – National Institute for Health and Clinical Excellence

• SMC
  – Scottish Medicines Consortium

• AWMSG
  – All Wales Medicines Strategy Group
NICE technology appraisals program

• Burden of disease ($\text{pop}^n$, morbidity and mortality)
• Resource impact
• Clinical and policy importance
• Presence of inappropriate variations in practice
• Factors affecting timeliness of guidance
  – Urgency and relevance of guideline at time of delivery
• Predicted impact on Public Health and QoL*
• Reduction in health inequalities

*Quality of Life
Health Technology Assessment - NICE

• Independent technology assessment group
  – Template for manufacturer’s submission
  – Prepares technology assessment report

• Technology Appraisal Committee
  – NHS, patient organizations, academia and industry
  – Consultee organizations can submit evidence

• Methodological rigor

• Activities transparent
Health Technology Assessment - NICE

• Multiple Technology Appraisal (MTA)
  – 54 weeks from start to issuance of guidance
  – Broad consultation

• Single Technology Appraisal
  – Single technologies for sole indication
  – Manufacturer’s submission
  – 39 week timeline; mainly cancer drugs
  – May be delayed if appeals against decision
Health Technology Assessment

• Standardization of submission

• Drug must be licensed
  – <£20K ($30K)/QALY*: likely to be recommended
  – >£30K ($45K)/QALY: unlikely to be recommended
  – ≤£50k ($75K)/QALY
    • For end of life with prolongation >3/12

• NHS obliged to follow NICE recommendation
Criticism of NICE

• Lack of independence from government
  – Following latter’s agenda
  – Department of Health sets the budget
• Time taken for assessment
• QALY* as Measurement of Health Benefit
• Uneven implementation across NHS

*Quality-adjusted life-years
Cancer Drugs Fund

• Introduced for England in 2011
• £200M ($300M) per year for cancer drugs
  – May have been rejected by NICE
  – May not have been submitted for assessment
  – Technical assessment may not be complete
  – May not have been chosen for appraisal
• Overspent: >£340M ($510M) in 2015
• Data on drug use and outcome not collected
Cancer Drugs Fund

- Not designed to reduce uncertainties
- Costs sometimes driven up
- Money given to Regional Committees
  - Differing priorities for drugs
  - ‘Post Code Lottery’
- To be discontinued from March 2016
- Transitional fund to be introduced April 2016
  - NHS England holds the budget
  - NICE to make recommendations
New Cancer Drugs Fund

• All cancer drugs and significant new indications
• Clear entry and exit criteria
• NICE assessment pre marketing authorization
  – Recommendation for routine use
  – Not recommended for routine use
  – Conditional recommendation within CDF
    • Limited by time
    • Acceptable commercial access agreement
    • Agreement on data collection required
Bringing immunotherapy to patients

• Biosimilar medicine development
• Pre-licensing
  – Promising Innovative Medicine
  – Early Access to Medicines Scheme
  – Adaptive licensing
• Post-licensing
  – NICE and other HTAs
  – Post marketing safety studies
    • Assiduous collection of data
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