Analysis of the Global TB Drug Market and Country-Specific Case Studies of TB Drug Distribution Channels

UK Case Study

Prepared with IMS Consulting  November 2006
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After years of increases, the incidence of TB in the UK has only recently begun to plateau

- Prevalence and incidence of TB has been rising in the UK for more than 15 years
- This has been attributed to increased migration from countries with high TB burden
- The ageing UK population and increase in HIV/AIDS has also contributed

### Prevalence and incidence of TB and HIV/AIDS in the UK

<table>
<thead>
<tr>
<th>YEAR</th>
<th>NUMBER OF TB CASES</th>
<th>RATE OF TB (PER 100 000)</th>
<th>ANNUAL PERCENTAGE CHANGE IN TB</th>
<th>NUMBER OF HIV/AIDS CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NO. OF CASES</td>
<td>RATE</td>
</tr>
<tr>
<td>1999</td>
<td>5761</td>
<td>10.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2000</td>
<td>6323</td>
<td>11.8</td>
<td>+9.8</td>
<td>+9.4</td>
</tr>
<tr>
<td>2001</td>
<td>6652</td>
<td>12.4</td>
<td>+5.2</td>
<td>+4.8</td>
</tr>
<tr>
<td>2002</td>
<td>6861</td>
<td>12.7</td>
<td>+3.1</td>
<td>+2.4</td>
</tr>
<tr>
<td>2003</td>
<td>6837</td>
<td>12.5</td>
<td>-0.3</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

### Distribution of age groups in the UK in 1971 and 2004

<table>
<thead>
<tr>
<th>Age group</th>
<th>1971</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 16</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>16-65</td>
<td>62%</td>
<td>65%</td>
</tr>
<tr>
<td>Over 65</td>
<td>13%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Source: Health Protection Agency; [www.avert.org](http://www.avert.org); Office of National Statistics
TB cases are concentrated in inner city areas -- London has by far the highest number of cases.

- The largest proportion (45%) of TB cases reported in 2003 were located in London.
- A majority of cases in the UK occur in inner cities (there is almost no incidence in rural locations). This is thought to be associated with the large immigrant populations and relatively high levels of poverty.
- 70% of TB patients were born abroad, with the greatest proportion born in India, Pakistan and Bangladesh (36%).

Source: Health Protection Agency
There is no National TB Control Programme in the UK. TB Control falls under the Communicable Diseases Branch of the Department of Health.
The role of the Communicable Diseases Branch is one of policy, not implementation.

The Communicable Diseases Branch is responsible for developing policy for the surveillance, prevention, and control of communicable diseases. The Branch develops policy for the following diseases:

- CJD, Diphtheria, Hepatitis, Flu, Rubella, Polio, TB

It is not responsible for implementation.

Source: Department of Health website, interviews
Within their region, the Primary Care Trusts (PCTs) set budgets for GPs and hospitals for all diseases, including TB.

**Flow of Funding**

1. **Department of Health (DH)**
   - Grants market access (Medicines and Healthcare products Regulatory Agency); approves price/regulating profitability; sets reimbursement status; develops healthcare policy

2. **28 Strategic Health Authorities (SHAs)**
   - Ensure that healthcare policies are implemented by the Primary Care Trusts (PCTs)
   - Oversee 1 of 28 regions

3. **303 Primary Care Trusts (PCTs)**
   - Control 75% of the NHS budget and are responsible for commissioning healthcare in their area
   - Required to ensure all types of healthcare are available, including; GPs, hospitals, dentists, pharmacies etc.
   - Allocate budgets and implement new DH policies
   - When hospitals and GPs receive their budgets they are free to allocate the money as they wish

**Source:** PQ Systems
TB Control in the UK

As of 2005, the BCG vaccination is no longer routine in the UK and only high risk patients receive it.

**Pre-2005**

- All children between the ages of 10 and 14 were vaccinated within schools through the School Vaccination Program.
- Also offered to those who may be exposed at work, immigrants from countries in which TB is endemic and people going to live in countries in which TB is endemic.
- Children at a particularly high risk received the BCG when <10 years old.

**Post-September 2005**

- Offered to those who may be exposed at work, immigrants from countries in which TB is endemic and people going to live in countries in which TB is endemic.
- School Vaccination Program was abolished.
- Strongly recommended for:
  - All infants (0-12 months) living in areas where incidence is 40/100,000 or more.
  - All infants with a parent or grandparent born in a country where incidence of TB is 40/100,000 or more.

Source: Department of Health
National Institute for Health and Clinical Excellence (NICE) is an independent advisory board to the NHS – they published guidelines for the treatment of TB in March 2006.

**National Institute for Health and Clinical Excellence (NICE)**

Independent organisation responsible for reviewing clinical data and developing national guidance on drugs and therapy areas. The DH commissions NICE to develop clinical guidelines and guidance on public health and technology appraisals. NICE is funded primarily by the DH.

**NICE guidance**

Prepared by independent groups, the guidance is heavily influenced by health economic data. There is a high level of compliance with these guidelines.

**Positive recommendation**

Funding must be made available by PCTs for at least a limited number of patients in all regions.

**Negative recommendation**

Immediately implemented by NHS related organisations, drug will not be used.

Source: PQ Systems
NICE and BTS Guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Initial phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>New patient</td>
<td>Patient not having previously received care</td>
<td>2HRZ* / 2HRZE</td>
<td>4HR</td>
</tr>
<tr>
<td>Single drug resistance</td>
<td>Infected with TB resistant to one of the 1st line drugs (shown by DST)</td>
<td>2HRZE</td>
<td>4HR</td>
</tr>
<tr>
<td>Isoniazid resistance</td>
<td>Infected with TB resistant to isoniazid (shown by DST)</td>
<td>6R</td>
<td></td>
</tr>
<tr>
<td>MDR TB</td>
<td>Infected with TB resistant to two or more 1st line drugs (shown by DST)</td>
<td>5 drugs organism is susceptible to (at least 2 of which, preferably 3, should not have been used before) – until sputum negative</td>
<td>At least 3 drugs the organism is susceptible to for a further 9 months (up to 24 months)</td>
</tr>
<tr>
<td>Latent TB</td>
<td>Positive Mantoux test or interferon-gamma immunological test but without symptoms</td>
<td>6H / 3HR</td>
<td>-</td>
</tr>
</tbody>
</table>

BTS guidelines state that ethambutol can be omitted in previously untreated white patients who are known to be HIV negative and have not had contact with a case of known drug resistance. Drug sensitivity tests (DST) are performed by PHLS Mycobacterium Reference Units on all samples taken by specialists. Specialists suspecting a case of drug resistant TB administer 4/5 drugs the patient has not received before and then change to a tailored regimen when the DST results are available.

Source: National Institute for Health and Clinical Excellence, British Thoracic Society
The British Thoracic Society (BTS) also specifies daily doses for 1st and 2nd line drugs

<table>
<thead>
<tr>
<th>1st line drug</th>
<th>Daily dosage</th>
<th>Thrice weekly dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300mg</td>
<td>15mg/kg</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;50kg – 450mg</td>
<td>&lt;50kg – 2g</td>
</tr>
<tr>
<td></td>
<td>&gt;50kg – 600mg</td>
<td>&gt;50kg – 2.5g</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&lt;50kg – 1.5g</td>
<td>&lt;50kg – 3g</td>
</tr>
<tr>
<td></td>
<td>&gt;50kg – 2g</td>
<td>&gt;50kg – 3.5g</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15mg/kg</td>
<td>30mg/kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd line drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>15mg/kg</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15mg/kg</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15mg/kg</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15mg/kg</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>&lt;50kg – 375mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&gt;50kg – 500mg twice daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250-500mg twice daily</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400mg twice daily</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg twice daily</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300-450mg twice daily</td>
</tr>
<tr>
<td>Thiacectazone</td>
<td>150mg</td>
</tr>
<tr>
<td>Clofazamine</td>
<td>300mg</td>
</tr>
<tr>
<td>PAS</td>
<td>5g twice daily</td>
</tr>
</tbody>
</table>

Source: British Thoracic Society
TB patients can be treated in the public or private sector, although most remain in a public setting.

**Public sector**
- Public Hospital (Specialist)
- Ambulatory Clinic (GP)

**Private sector**
- Private Hospital (Specialist)

All patients must first be diagnosed by a GP in the public setting. Most patients remain in the public outpatient setting for treatment.

However, patients can seek referral for a specialist in the private sector from a GP in the public setting once they have been diagnosed with TB.

Source: PQ Systems
TB Control in the UK

Patients may first visit their GP, a hospital Accident and Emergency department or be subjected to screening at their port of entry

**Patient flow through the public sector**

- **Patient presents with TB symptoms**
  - General practitioner
  - Hospital/Accidents and Emergencies
  - Port of entry

Most patients present to their GP in the public sector. Physicians who suspect patients of TB write a hospital referral for chest x-ray - GPs play no further role in treatment. Severe cases present at the emergency room.

Immigrants from countries in which TB is endemic and staying in the country for >6 months have their chest x-rayed in the airport.

Patient who is suspected of having TB after initial chest x-ray are referred to a hospital specialist for further diagnosis and treatment.

Patients may request a referral to a public or private hospital specialist.

Initial diagnosis for TB through chest x-ray

If confirmed patient referred to specialist for further diagnosis and treatment

Source: BTS Guidelines, Interviews
Once diagnosed, patients are referred to a specialist in the public or private setting for further diagnosis and treatment.

**Patient flow through the public or private sector**

- **Specialist diagnosis through sputum**
  - Latent TB
  - Active TB
  - Drug resistant TB

- **Hospital outpatient**
- **Hospital inpatient**
- **Outpatient pharmacy**
- **Retail pharmacy**

Specialists use sputum samples to confirm diagnosis. Samples are sent to a Public Health Laboratory Mycobacterium Reference Units for DST.

Under exceptional circumstances e.g. homeless or acutely ill patient will be isolated in the hospital.

Patients can collect their drugs from hospital outpatient or retail pharmacies on a monthly basis.

Source: BTS guidelines, interviews
A further set of follow up tests are implemented to monitor TB patients during treatment

<table>
<thead>
<tr>
<th></th>
<th>Treatment initiation (Week 0)</th>
<th>Week 2</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Check for S/Es</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monitor change over in drug regimen</td>
</tr>
<tr>
<td><strong>Chest x-ray</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>To ensure treatment is working</td>
</tr>
<tr>
<td><strong>Liver function tests</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Liver problems are most common S/Es – testing can be more frequent in high risk patients e.g. alcoholics</td>
</tr>
<tr>
<td><strong>Visual tests</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>S/E of ethambutol is vision damage – patient monitored whilst taking ethambutol</td>
</tr>
</tbody>
</table>

*Source: Interviews*
Physicians are required to report all detected TB cases to the Health Protection Agency.

**Flow of reporting**

Physician sends all sputum smears to Public Health Laboratory Mycobacterium Reference Units for DST.

**Physicians and reference units report cases of TB as and when they are diagnosed, via the Statutory Notification of Infectious Diseases (NOIDS), to their local Consultant in Communicable Disease Control.**

Consultant in regional area of the CDC aggregates for the region and passes data to the HPA.

**Source:** Health Protection Agency Website, Interviews
TB treatment is free in the public sector but not the private sector; the cost of drugs in both sectors depends on treatment location.

**Charges for TB drugs in each healthcare setting**

**Public Hospital**

- **Inpatient**
  - Drugs dispensed by hospital inpatient pharmacy
  - No charge for treatment or drugs

- **Outpatient**
  - Drugs dispensed by hospital outpatient or retail pharmacy
  - No charge for treatment
  - Standard prescription charge of £6.65*

**Private Hospital**

- **Inpatient**
  - Drugs dispensed by hospital inpatient pharmacy
  - Cost of drugs and treatment paid by insurer or out of pocket by patient

- **Outpatient**
  - Drugs dispensed by retail pharmacy
  - Cost of treatment paid by insurer or out of pocket by patient
  - Standard prescription charge of £6.65*

*Exceptions to these charges include pregnant women, children, war and service pensioners, children under 16, students aged 16, 17 or 18 in full-time education, men and women aged 60 and over, etc.

Source: PQ Systems
Immigrants, irrespective of legal status, are entitled to free treatment for TB within the public sector

**Immigrant entitlement to healthcare within the public sector**

<table>
<thead>
<tr>
<th>Status</th>
<th>GPs</th>
<th>Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asylum seekers</td>
<td>Access without charge</td>
<td></td>
</tr>
<tr>
<td>Refugees</td>
<td>Pay standard charge for Rx (unless exempt under normal rules)</td>
<td></td>
</tr>
<tr>
<td>Discretionary leave to stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humanitarian protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed asylum seekers</td>
<td>Emergencies or treatment which is immediately necessary is free</td>
<td>Any course of treatment already underway remains free of charge</td>
</tr>
<tr>
<td></td>
<td>Must pay for other treatment</td>
<td>Any new course is chargeable</td>
</tr>
</tbody>
</table>

- TB is included in a list of ‘exempt diseases for which no charge is made’, including malaria, plague, leprosy and cholera, etc.
- All patients receive TB treatment for free irrespective of their immigration status
  - They must still pay the standard prescription charge, unless exempt under the normal rules
- There is no risk that an illegal immigrant will be reported to the authorities

Source: Entitlement to NHS Treatment, Department of Health (2006)
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- Procurement and Distribution of TB Drugs
- Value and Volume of the UK TB Market
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In the UK, 1st and 2nd line TB drug procurement mechanisms vary according to the setting in which drugs are administered.

### Pricing

<table>
<thead>
<tr>
<th>Public Hospitals</th>
<th>NHS Purchasing And Supply Agency Contract</th>
<th>Direct Negotiations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Hospitals</td>
<td>PCT Pharmacy Purchasing Group</td>
<td>Direct Negotiations</td>
</tr>
<tr>
<td>Retail Pharmacies</td>
<td>Pharmacy Purchasing Group</td>
<td>Direct Negotiations</td>
</tr>
</tbody>
</table>

### Distribution

<table>
<thead>
<tr>
<th>Public Hospitals</th>
<th>Direct to Facility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Hospitals</td>
<td>Via Wholesaler</td>
</tr>
<tr>
<td>Retail Pharmacies</td>
<td>Via Wholesaler and/or Company Warehouse</td>
</tr>
</tbody>
</table>

Source: PQ Systems, interviews
In the public hospital sector, the NHS Purchasing and Supply Agency (PASA) prices many 1st and 2nd line TB drugs via a bid and tender system.

**What PASA is**
- NHS Purchasing and Supply Agency (PASA)
- Executive agency within the Department of Health that negotiates contracts with suppliers

**How it works**
- Uses a bid and tender system to select suppliers and determine prices of drugs
- Contracts apply to all NHS facilities
- Selects a supplier on a number of criteria:
  - Price
  - Quality
  - Record of supply

**What it applies to**
- A majority of TB drugs with the exception of pyrazinamide (imported)

*Source: PASA Website, interviews*
Non-PASA drugs are procured by one of 14 Pharmacy Purchasing Groups that work on behalf of the Primary Care Trusts (PCTs)

- Each PCT is represented by one of 14 pharmacy purchasing groups

- Pharmacy purchasing groups consist of Chief Pharmacists from each of the hospitals covered by the group

- Pharmacy purchasing groups aggregate demand and operate a bid and tender system for all purchases >£100,000 (mandatory under EU law)

- Once a price is agreed with a supplier all hospitals within the group are able to purchase at that price

Source: PQ Systems, interviews
Additionally, public hospitals are also able to procure drugs not covered by PASA or Pharmacy Purchasing Group tenders direct from suppliers

- Chief pharmacists may negotiate individually with manufacturers and wholesalers in order to procure drugs not covered by a PASA contract or Pharmacy Purchasing Group

- Public hospitals must operate a bid and tender system for all purchases >£100,000 (mandatory under EU law)

Source: PQ Systems, interviews
Private hospitals and retail pharmacies are not entitled to prices negotiated by PASA or PCT Pharmacy Purchasing Groups and negotiate with suppliers individually

<table>
<thead>
<tr>
<th><strong>Private hospitals</strong></th>
<th><strong>Retail Pharmacies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Negotiate purchases directly with suppliers</td>
<td>• Negotiate purchases directly with suppliers</td>
</tr>
<tr>
<td></td>
<td>• Suppliers may only offer authorised margins and discounts to pharmacists, in turn, pharmacists are only permitted to use specified mark-ups, thus profitability is limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pharmacy Purchasing Group</strong></th>
<th><strong>Direct negotiations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• May form chains to aggregate demand (e.g. the BUPA hospital group) in which one pharmacist is responsible for purchasing for the entire group</td>
<td>• Negotiate purchases directly with suppliers</td>
</tr>
<tr>
<td></td>
<td>• May form chains to aggregate demand e.g. Boots</td>
</tr>
</tbody>
</table>

Source: PQ Systems, interviews
Public and private hospital distribution are similar to one another—the key difference lies in the mark-ups applied as the drugs flow to patients.

### Drug Flow: Public/Private Hospitals

<table>
<thead>
<tr>
<th></th>
<th>Public Hospitals</th>
<th>Private Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st point of sale</strong></td>
<td>Manufacturers holding the contract supply 1st and 2nd line TB drugs at the agreed price direct to hospitals or, if they lack a distribution network, via a wholesaler</td>
<td>Wholesalers holding a PASA contract supply 1st and 2nd line TB drugs at the agreed price direct to hospitals. Free to set margins for generic products (covers most TB drugs) and limited to roughly 2.8% of ex-manufacturers price on branded products</td>
</tr>
<tr>
<td><strong>Wholesaler sale</strong></td>
<td>Wholesalers supply 1st and 2nd line TB drugs at the agreed price direct to hospitals within the group. Free to set margins at any level when dealing with the private sector</td>
<td>Hospitals then distribute 1st and 2nd line TB drugs to the patient either free of charge (inpatients) or for a standard prescription charge (outpatients)</td>
</tr>
<tr>
<td><strong>Hospital sale</strong></td>
<td>Hospitals then sell 1st and 2nd line TB drugs to the patient at a marked up price</td>
<td>Hospitals then sell 1st and 2nd line TB drugs to the patient at a marked up price</td>
</tr>
</tbody>
</table>

Source: PQ Systems, interviews
Once suppliers have been selected, the actual ordering process is automated through a computer system.

**Order Flow: Hospital Pharmacy Sector**

- Manufacturer
- Wholesaler
- Hospital purchasing department
- Hospital pharmacy

*Purchasing department orders directly from approved wholesaler or manufacturer in the system*

*Drugs dispensed are entered into system. Message automatically sent to purchasing department when stock reaches minimum level*

Source: Interviews
In the retail pharmacy sector, 1st and 2nd line TB drugs may flow through a centralized warehouse if procured through a group purchasing process.

**Drug Flow: Retail Pharmacy Sector**

1. **1st point of sale:** Manufacturers supply 1st and 2nd line TB drugs to wholesalers or to pharmacies.

2. **2nd point of sale:** Wholesalers sell 1st and 2nd line TB drugs to pharmacies. Free to set margins for generic products (covers most TB drugs), limited to roughly 2.8% of ex-manufacturers price on branded products.

**Warehousing:** Centralised warehouses may be used to store 1st and 2nd line TB drugs procured on behalf of members of pharmacy chains.

**Pharmacy sale:** Drugs are always reimbursed at the list price so the larger the discount the pharmacist can obtain the greater the profit.

Source: PQ Systems, interviews
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The overall 1st line drug market value has been increasing over the last five years and is currently 4M USD.

Note: Includes 1st line drugs that may also be used in the 2nd line treatment

Source: IMS MIDAS data
Value and Volume of the UK TB Market

Over that same time period, the volume of 1st line drugs dispensed has fluctuated.

Note: Includes 1st line drugs that may also be used in the 2nd line treatment.

Source: IMS MIDAS data
FDCs currently account for 38% of the UK market by value at 1.5M USD and 57% by volume at 3.3M units.

**Value and Volume of the UK TB Market**

**Total 1st Line TB Market Value by Drug in 2005 (4M USD)**

- **Loose Drugs**: 62%
- **Fixed Dose Combinations**: 38%

**Total 1st Line TB Market Volume by Drug in 2005 (5.8M USD)**

- **Loose drugs**: 43%
- **Fixed Dose Combinations**: 57%

*Note: Includes 1st line drugs that may also be used in the 2nd line treatment*

Source: IMS MIDAS data
Value and Volume of the UK TB Market

Bottom up estimates confirm the top line value data and give a 1st line market estimate of between 4-4.3M USD.

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Resistant</th>
<th>Latent</th>
<th>Retreated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients treated</strong></td>
<td></td>
<td></td>
<td></td>
<td>8,585</td>
</tr>
<tr>
<td><strong>Patients per category</strong></td>
<td>7,172</td>
<td>412</td>
<td>622</td>
<td>379</td>
</tr>
<tr>
<td><strong>Average cost per patient</strong></td>
<td>489.83</td>
<td>1139.10</td>
<td>170.19</td>
<td>468.24</td>
</tr>
<tr>
<td><strong>Total cost per category</strong></td>
<td>3,513,013</td>
<td>469,308</td>
<td>105,859</td>
<td>177,464</td>
</tr>
<tr>
<td><strong>1st line estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td>4,265,644</td>
</tr>
</tbody>
</table>

Note: Includes 1st line drugs that may also be used in the 2nd line treatment

Source: HPA, IMS MIDAS data, IMS analysis, BNF. See appendix for details of calculation
The market value of all 2nd line TB drugs is growing overall - the market is currently valued at 4.5M USD.

Source: IMS MIDAS data

Note: Does not include 1st line drugs that may also be used in the 2nd line treatment.

*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.
The volume of 2nd line TB drugs dispensed has fluctuated widely and currently stands at 3M units.

**Value and Volume of the UK TB Market**

Source: IMS MIDAS data

*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.*
Clarithromycin dominates the 2nd line market with sales of 2.1M USD, whereas clavulanic acid has the greatest volume of sales with 1.4M units in 2005.

**Total 2nd Line TB Market Value by Drug in 2005 (4.5M USD)**

- Clarithromycin: 47%
- Ciprofloxacin: 17%
- Levofloxacin: 14%
- Moxifloxacin: 0%
- Ofloxacin: 2%
- Clavulanic Acid: 20%

**Total 2nd Line TB Market Volume by Drug in 2005 (3M units)**

- Clarithromycin: 28%
- Ciprofloxacin: 20%
- Levofloxacin: 3%
- Moxifloxacin: 0%
- Ofloxacin: 1%
- Clavulanic Acid: 48%

*Source: IMS MIDAS data*

*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.*
Value and Volume of the UK TB Market

Top line value figures and bottom up calculations suggest the 2nd line market value is 0.4M to 4.5M USD

<table>
<thead>
<tr>
<th>Total patients receiving treatment in 2004</th>
<th>Diagnosed in 2003</th>
<th>Diagnosed in 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients per category*</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Average cost of treatment</td>
<td></td>
<td>1,665</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7,242</td>
</tr>
<tr>
<td>2nd line estimate</td>
<td></td>
<td>357,379</td>
</tr>
</tbody>
</table>

Note: Does not include 1st line drugs that may also be used in the 2nd line treatment

Source: *HPA, IMS MIDAS data, IMS analysis, WHO. See appendix for details of calculation
However, it is impossible to perform an accurate bottom up calculation for 2nd line drugs due to large numbers of uncertainties, hence, value is estimated to be 4.5M USD

- A bottom up calculation involves assumptions about which drugs are administered to 2nd line patients, the dose at which they are given and the duration of treatment, all of which vary widely between patients.

- Additionally, in 1st line patients suffering from side effects the 1st line drug responsible for those side effects is often substituted for a 2nd line drug.

- Physicians estimated the incidence of side effects to be between 5-30%, however it is impossible to be certain how many 1st line drugs are substituted in these cases and which 2nd line drugs they are substituted for.

- Hence, there are too many uncertainties for an accurate bottom up calculation and value is estimated to be $4.5M USD (based on IMS MIDAS figures).
If we combine the value and volume of 1st and 2nd line drugs we have a market value of between 8.5M USD and volume of 8.8M units.

**Total UK TB drug market value (8.5M USD)**

- 1st line: 4M USD
- 2nd line: 4.5M USD
- Total: 8.5M USD

**Total UK TB drug market volume (8.8M units)**

- 1st line: 5.8M units
- 2nd line: 3M units
- Total: 8.8M units
Country table of contents

- TB Control in the UK
- Procurement and Distribution of TB Drugs
- Value and Volume of the UK TB Market
- Appendix
Total market value and volume figures for all 1st line drugs in 2005

<table>
<thead>
<tr>
<th>1st line drug</th>
<th>Volume (units)</th>
<th>Value (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>929,214</td>
<td>1,267,431</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1,037,371</td>
<td>996,554</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>568,680</td>
<td>248,733</td>
</tr>
<tr>
<td>Pyrazinamide*</td>
<td>1,803,960</td>
<td>213,816</td>
</tr>
<tr>
<td>Rifampicin/isoniazid combination</td>
<td>1,979,166</td>
<td>481,640</td>
</tr>
<tr>
<td>Rifampicin/isoniazid/pyrazinamide</td>
<td>1,329,845</td>
<td>1,055,033</td>
</tr>
</tbody>
</table>

Source: IMS MIDAS

*Figures for 2005 not available so 2002 figures used
Total market value and volume figures for all 2nd line drugs in 2005

<table>
<thead>
<tr>
<th>2nd line drug</th>
<th>Volume (units)</th>
<th>Value (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavulanic acid</td>
<td>1,392,107</td>
<td>913,849</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>604,311</td>
<td>782,092</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>838,599</td>
<td>2,101,591</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>26,393</td>
<td>76,633</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>99,928</td>
<td>644,369</td>
</tr>
<tr>
<td>Moxifloxacin*</td>
<td>19,869</td>
<td>71,798</td>
</tr>
</tbody>
</table>

Source: IMS MIDAS
*Figures for moxifloxacin were not available for 2005, thus data from 2004 were used.
## Manufacturers of 1st line drugs in the UK

<table>
<thead>
<tr>
<th>1st line drug</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>Generics UK; Hillcross; Novartis</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Genus Pharm; Lederle</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>IMS Labs; Novartis; UCB Pharma; Ivax; Martindale; Celltech Pharma</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Merck Sharpe and Dohme</td>
</tr>
<tr>
<td>Isoniazid+Rifampicin</td>
<td>Aventis</td>
</tr>
<tr>
<td>Isoniazid+Rifampicin+Pyrazinamide</td>
<td>Aventis</td>
</tr>
</tbody>
</table>

Source: IMS MIDAS
## Manufacturers of 2nd line drugs in the UK

<table>
<thead>
<tr>
<th>2nd line drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>Aventis</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Aventis; Hillcross; Sandoz; Teva UK; Generics UK</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Hillcross; Sandoz; Teva UK; Generics UK; Ivax</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Teva UK; Hillcross</td>
</tr>
</tbody>
</table>

Source: IMS MIDAS
Method of calculating cost of treating 1st line TB patients

- Patient numbers were sourced from the EuroTB website
- Cost of the regimen (for a 70kg patient) was calculated using prices of the most popular brand and pack size (by units sold) for each of the 1st line drugs
- Patient population was split into active, drug resistant, latent and retreated
- The size of each subpopulation of TB patients was then multiplied by the cost of the regimen they receive
- These figures were then summed to give a top-line value
- The low end estimate was derived by summing the lowest cost regimen to treat each of these subpopulations of patients
- The high end estimate was derived by summing the highest cost regimen to treat each of these subpopulations of patients
Method of calculating cost of treating 1st line TB patients (USD)

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Resistant</th>
<th>Latent</th>
<th>Retreated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients treated</strong></td>
<td>8,585</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients per category</strong></td>
<td>7,172</td>
<td>412</td>
<td>622</td>
<td>379</td>
</tr>
<tr>
<td><strong>Average cost per patient</strong></td>
<td>489.83</td>
<td>1139.10</td>
<td>170.19</td>
<td>468.24</td>
</tr>
<tr>
<td><strong>Total cost per category</strong></td>
<td>3,513,013</td>
<td>469,308</td>
<td>105,859</td>
<td>177,464</td>
</tr>
<tr>
<td><strong>First Line estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>4,265,644</strong></td>
</tr>
</tbody>
</table>

Source: IMS MIDAS, IMS Expertise
# Method of calculating cost of treating 2nd line TB patients

## Hospital

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price per day</th>
<th>Price for one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levo</td>
<td>4.99</td>
<td>1821.04</td>
</tr>
<tr>
<td>Cipro</td>
<td>0.55</td>
<td>201.95</td>
</tr>
<tr>
<td>Clarith</td>
<td>2.01</td>
<td>733.98</td>
</tr>
<tr>
<td>Clav</td>
<td>1.00</td>
<td>364.31</td>
</tr>
<tr>
<td>Ofx</td>
<td>6.94</td>
<td>2534.19</td>
</tr>
</tbody>
</table>

**Initial Phase**

**Cost of initial phase**

8907 USD

**Cost of initial phase**

7242 USD

**Cost of continuation phase**

1665 USD

**Total cost of treatment**

6956 euros

## Retail

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price per day</th>
<th>Price for one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levo</td>
<td>4.99</td>
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</tr>
<tr>
<td>Cipro</td>
<td>1.98</td>
<td>722.25</td>
</tr>
<tr>
<td>Clarith</td>
<td>4.01</td>
<td>1465.28</td>
</tr>
<tr>
<td>Clav</td>
<td>1.00</td>
<td>364.31</td>
</tr>
<tr>
<td>Ofx</td>
<td>0.58</td>
<td>213.22</td>
</tr>
</tbody>
</table>

**Initial Phase**

**Cost of initial phase**

3268 USD

**Cost of initial phase**

5873 USD

**Cost of continuation phase**

3268 USD

**Total cost of treatment**

7138 euros

**Source:** IMS MIDAS, IMS Expertise
MIDAS data in the UK is collected in public hospitals and retail pharmacies

- MIDAS data in the UK is collected for public hospitals and retail pharmacies – drugs dispensed by private hospitals are not included
  - All prescriptions dispensed by pharmacies in public hospitals and retail pharmacies are captured in the data
  - Public hospital data includes prescriptions dispensed by both hospital inpatient and outpatient pharmacies

- The value data we have used is collected at an ex-manufacturer price and so represents the value of drug sales when sold by the manufacturer (not the value of sales to the end user)

- The volume data we have used collects units sold. The figure given covers the number of individual units sold. In most cases a unit is a single tablet. For injectables, it is a single pre-filled syringe

Source: IMS MIDAS
PharmaQuery Systems is IMS’s unique online database of Pricing and Reimbursement regulations in 22 key world markets

- PQ Systems provides detailed coverage, on a country by country basis, of 22 key pharmaceutical markets
  - Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Denmark, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, South Korea, Spain, Sweden, Switzerland, UK and the USA
- It contains detailed information about pricing and reimbursement regulations in each country
  - This information is divided into 4 areas; facts and figures, healthcare system, pharmaceutical market and useful information
- Information is updated daily by a network of multilingual pricing analysts

Source: www.imshealth.com
In all diseases patient care begins in the ambulatory setting - GPs either treat patients or refer them on to the hospital specialists.

- **Department of Health (DH)**
  - **Strategic Health Authorities (SHAs)**
    - **Primary Care Trusts (PCTs)**
      - **General Practitioners**
      - **Hospitals**

**General Practitioners**
- Primary care is delivered by General Practitioners (GPs) on an outpatient basis
- Services rendered are free of charge
- Referral is needed to gain access to hospital/specialist care

*Source: PQ Systems*
Patients can gain access to specialists in either the private or public hospital setting

**Public Hospital**
- Managed by Hospital Trusts that are contracted by PCTs to provide secondary care in exchange for funding
- Services rendered are free of charge

**Private Hospital**
- Not under the jurisdiction of the NHS
- Patients with private health insurance (13%) or who wish to pay out of pocket may be referred to private hospitals by their GPs
- Patients pay fees for services and treatments rendered at these facilities

Source: PQ Systems
The fee patients must pay for their drugs varies between treatment settings.

**Charges for drugs in each healthcare setting**

- **General Practitioner**
  - Inpatient: Drugs dispensed by retail pharmacy - *Standard prescription charge of £6.65*
  - Outpatient: Drugs dispensed by hospital inpatient pharmacy - No charge for drugs

- **Public Hospital**
  - Inpatient: Drugs dispensed by hospital outpatient or retail pharmacy - *Standard prescription charge of £6.65*
  - Outpatient: Drugs dispensed by hospital inpatient pharmacy - Cost of drugs paid by insurer or out of pocket by patient

- **Private Hospital**
  - Inpatient: Drugs dispensed by hospital outpatient or retail pharmacy - *Standard prescription charge of £6.65*
  - Outpatient: Drugs dispensed by retail pharmacy

*Exceptions to these charges include pregnant women, children, war and service pensioners, children under 16, students aged 16, 17 or 18 in full-time education, men and women aged 60 and over etc*

Source: PQ Systems
In the UK, marketing approval for all drugs occurs through one of three routes:

### Marketing Approval Routes in the UK

<table>
<thead>
<tr>
<th>Route</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centralised Procedure</strong></td>
<td>- The European Medicines Agency (EMEA) reviews applications</td>
</tr>
<tr>
<td></td>
<td>- Grants access throughout the EU</td>
</tr>
<tr>
<td><strong>Mutual Recognition Procedure</strong></td>
<td>- Applies only to all EU member states</td>
</tr>
<tr>
<td></td>
<td>- When a drug is authorised through one country’s national scheme, it is automatically approved in all states who participate in the agreement</td>
</tr>
<tr>
<td><strong>National Procedure</strong></td>
<td>- MHRA (Medicines and Healthcare products Regulatory Agency) reviews application</td>
</tr>
<tr>
<td></td>
<td>- Grants access in the UK only</td>
</tr>
<tr>
<td></td>
<td>- This would result in access being granted in all other EU member states via the mutual recognition procedure</td>
</tr>
</tbody>
</table>

Source: PQ Systems
Reimbursement — or coverage by the NHS — is normally granted automatically for all drugs

- Pharmacists are reimbursed by the NHS for prescription drugs they dispense:
  - They receive the manufacturer’s list price for branded products
  - The tariff price for generics

- Some products are on the “negative lists”
  - Either not reimbursed or only reimbursed for special populations
  - E.g. lifestyle products such as erectile dysfunction drugs are only reimbursed for a small population identified as having a clinical need

Source: PQ Systems
Profits of all branded drugs sold to the NHS are controlled... but not to generics, OTC drugs or private prescriptions.

The Pharmaceutical Price Regulation Scheme (PPRS) applies to branded drugs....

- Cost control measure negotiated between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI)
- Limits the profit a manufacturer can make across all of its branded products sold to the NHS
  - Manufacturers must submit annual data on sales, costs, assets and profitability
- Those manufacturers exceeding the limit must reduce profitability the following year

...Certain drugs are exempt from profit controls:
- Generics
- Over the counter (OTC) drugs
- Private prescriptions
  - Normally issued for drugs which are not reimbursed e.g. prescriptions of Viagra to those not considered eligible by the state
  - Issued with the understanding the cost of the drug is to be paid in full by patients

Source: PQ Systems
Actual drug utilization for all diseases is restricted by the PCTs, who limit funding and issue formularies

<table>
<thead>
<tr>
<th>General Practitioners</th>
<th>NHS Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Budgetary constraints</strong></td>
<td><strong>Formulary constraints</strong></td>
</tr>
<tr>
<td>• PCTs provide each GP within their area with an annual budget with which they must operate their practice</td>
<td>• A series of formulary committees—all of which include at least one PCT representative—also review drugs on the market and generate formularies</td>
</tr>
<tr>
<td>• PCTs set prescribing budgets for each GP practice</td>
<td>• These formularies indicate when particular drugs can be used and in which patients</td>
</tr>
<tr>
<td>• These budgets limit the number of prescriptions a GP can issue which can then be ‘cashed’ in a pharmacy</td>
<td></td>
</tr>
<tr>
<td><strong>NHS Hospitals</strong></td>
<td></td>
</tr>
<tr>
<td>• NHS hospitals are managed by NHS Hospital Trusts: self-governing, not-for-profit organisations operating within the NHS</td>
<td></td>
</tr>
<tr>
<td>• PCTs form agreement with trusts and provide funding for treatment of a certain number of patients per year</td>
<td></td>
</tr>
</tbody>
</table>

Source: PQ Systems
Pharmaceutical procurement, including that for TB drugs, is negotiated at a local level by pharmacists

**Retail pharmacy procurement**
- Negotiate their purchases directly with manufacturers and wholesalers
- Sometimes form chains to aggregate demand and negotiate volume savings
- Suppliers may only offer authorised margins and discounts to pharmacists, in turn, pharmacists are only permitted to use specified mark-ups, thus profitability is limited

**Hospital pharmacy procurement**
- Entitled to procure drugs at a PASA negotiated price – if a PASA contract exists the hospital must purchase from that supplier at that price
- Additionally, there are 14 pharmacy purchasing groups working on a geographical basis to procure drugs not covered by PASA
  - Negotiate with suppliers to set a price at which all hospitals in the group may procure drugs
  - Each PCT is represented by one of these groups
- In rare cases they may also negotiate their purchases directly with manufacturers and wholesalers

Source: PQ Systems
Specialists use sputum smear tests to confirm the diagnosis and check for drug resistance

**SPECIALIST**

<table>
<thead>
<tr>
<th>Sputum smears are taken (bronchoscopes are used to retrieve pleural fluid if patient is not producing sputum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node biopsies</td>
</tr>
<tr>
<td>Samples are sent to a PHLS Mycobacterium Reference Units for DST</td>
</tr>
<tr>
<td>Results are used to advise the specialist what to prescribe</td>
</tr>
</tbody>
</table>

- Unlike other healthcare providers specialists use sputum samples to diagnose TB, rather than chest x-rays
  - Approx 10% of chest x-ray diagnoses are incorrect, sputum smears are a more reliable method of diagnosis
- Smears are tested for drug resistance using drug sensitivity testing (DST)
- The results of the DST are used to tailor the drug regimen to the patient
  - If the DST is normal then the specialist will follow the NICE/BTS guidelines
  - If the DST is abnormal, i.e. the smear shows drug resistance, then the specialist tailors the regimen to maximise the chance of treatment success

Source: Interviews