Ensuring an Adequate Stockpile of Antivirals

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Vaccines and Antivirals

- Vaccines provide the best prevention option
- But there are limitations:
  - Time from strain identification to vaccine availability
  - Vaccine would probably not be available for the first pandemic wave
  - Manufacturing capacity will be stretched in a pandemic
  - Efficacy dependent on the vaccine ‘match’
Vaccines and Antivirals

- Roche is committed to promoting vaccination in all its promotional materials

- Antivirals are:
  - effective for treatment and prophylaxis of influenza
  - a very valuable adjunct to vaccines
  - an essential component of pandemic preparedness
Which antiviral?

- M2 protein inhibitor class
  - amantadine, rimantadine
    - lower cost
    - Long shelf life
    - up to 30% resistance & more serious side effects (include CNS effects)

- Neuraminidase Inhibitors –
  - Oseltamivir, Zanamivir
    - safe and effective,
    - low resistance
    - higher cost
    - only two manufacturers
Oseltamivir (Tamiflu™) approved indications

- **Treatment** of influenza types A & B for adults and children ≥ 1 year old (5 days bid -capsules /suspension)

- **Prevention** of influenza types A & B for adults and children ≥ 13 years old and (qd 10 days to 6 weeks) excluding Japan
Meeting the needs of a pandemic

- Surge capacity will not be able to meet demand in the midst of a pandemic
- Tamiflu can be stockpiled for use in a pandemic
- The challenges of building a stockpile are considerable for both government and industry
  - Treatment &/or prophylaxis?
  - Who should be treated?
  - Cost
  - Manufacturing capacity & drug availability
Meeting the needs of a pandemic

- We are all on a steep learning curve
- We can’t afford to get it wrong!
- Trust, mutual understanding and true partnership between government and industry is essential if we want to put up a good fight against a pandemic
- Roche is committed to being a responsible partner, and to working diligently with governments to find optimal solutions
Manufacturing challenges

- Supply is based upon demand
- Current Tamiflu capacity is geared towards seasonal epidemics
# Seasonal use of Tamiflu

<table>
<thead>
<tr>
<th>Flu Season</th>
<th>Number of Treatments</th>
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<tbody>
<tr>
<td>1999/2000</td>
<td>696,636</td>
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<td>2000/2001</td>
<td>740,678</td>
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<td>2001/2002</td>
<td>664,316</td>
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<td>2002/2003</td>
<td>585,695</td>
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<tr>
<td>2003/2004</td>
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Manufacturing challenges

- Supply is based upon demand
- Current Tamiflu capacity is geared towards seasonal epidemics
- To date the number of governments that have placed pandemic orders is limited
- One major government has placed an order to cover approx 20% of its country’s population, which has been accommodated within the existing capacity
- Increasing capacity for drug substance (oseltamivir) or drug product (Tamiflu) requires significant lead time
- In absence of firm orders any increase in capacity is at risk
Manufacturing challenges

- The risk is compounded by the fact that the additional capacity is for a ‘one off purpose’
- The supply chain is complex requiring third party involvement for some intermediate steps
- Granulation process for Tamiflu is not common
- Currently Basel is the only site for manufacture of oseltamivir and Tamiflu
- In order to be equitable and fair orders will be processed on a first come, first serve basis.
- Free Trade may be disrupted in a pandemic
Roche as a Responsible partner

• Roche is offering a two options for pandemic stockpiling
  – API model
  – Capsule model (commercial)

• The two options have different advantages/disadvantages

• Governments are free to choose either option, or a mix of the two, based upon their requirements and specific needs
API Model

- Creative solution. Roche sells oseltamivir API to governments.
- API is supplied in drums which are stored by government.
- In a pandemic the API is made up into a solution for dispensing to patients.
- Flexible
- Lower price option (no galenical manufacture)
- Longevity
- Shorter lead times
- Logistics of distribution are more complex
  - User manual and additional solution stability underway
- Requires a bureaucratic ‘leap of faith’
  - Bioavailability
API Model
Capsule Model

- Commercial material used for seasonal epidemics
- Full regulatory package
- Logistics of distribution easier
- More costly than API model
- Longer lead times than API model
- Capsules not appropriate for small children, thus would need to stockpile suspension for small children
A Good Partnership

- Good dialogue and working relationship with CDC
- Evaluating a number of options and scenarios
  - Different volumes
  - Capsules vs suspension
- Trying to find manufacturing solutions that meet CDC needs
- Already considering alternative manufacturing options based on these discussions.
Frequently asked questions

• Can manufacturing capacity be increased beyond current levels?
  – Yes, but it requires an estimate of demand, and time to scale up facilities and suppliers
  ......................partnership

• Can third party manufacturers scale up quicker than Roche?
  – No. Transfer of technology to a third party normally takes 12-18 months
Frequently asked questions

• Do further pandemic supply options exist?
  – No. Due to the property of the drug substance, e.g. high bulk volume and the flow characteristics:
    • Drug substance in capsules not possible
    • Drug substance in sachets not possible
    • Drug substance in bottles not possible

• Can Roche rotate stock?
  – No. Since the seasonal epidemic volumes are low the rotation of stock is not possible
A few concerns

• During the last flu season inappropriate dosing and use of the drug was observed.

• If this trend is followed during a pandemic it would be a major problem.

• If inappropriate use catalyses the emergence of a resistant strain we will lose a powerful weapon from our armory.

• Very few compounds in development since the area is perceived to be financially unattractive.

• Arguably the best preparation for a pandemic is to have good physician and patient experience of antiviral during seasonal epidemics. The current situation is far short of this.