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Assessment of drugs as suitable Surge Dose[®] candidates

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1 Introduction

Imaginot's Surge Dose[®] technology allows strategic design of optimised swallow tablet formulations which will achieve ultra-fast activated, pH-controlled drug dissolution under a wide range of favourable and unfavourable physiological conditions. Surge Dose[®] minimises the in vivo drug dissolution time so that dissolved drug rapidly reaches the small intestine for fast and consistent absorption independent of gastrointestinal pH and gastric emptying. Surge Dose[®] tablets are designed so that the drug absorption profile is more like an oral solution or an injection than a conventional solid oral dosage form as demonstrated by PK studies on Surge Dose[®] formulations of lornoxicam and diclofenac.

Rapid drug dissolution in co-administered liquid and gastric contents provides a high drug concentration in the small intestine to drive absorption across the mucosa resulting in high peak plasma concentrations (C_{max}) with short T_{max} . In turn, high plasma concentrations drive distribution to effect compartments by passive diffusion resulting in faster onset of action and earlier clinical response compared with conventional tablet formulations.

Surge Dose[®] formulations are optimized for each drug or drug combination using Imaginot's in vitro dissolution test methods that simulate a range of physiological conditions^{1, 2}. Levels and composition of pH modulating agents (pHMA) and water uptake agents (WUA) are selected to maximize pH dependent solubility effects and exceed 50 % drug release in 5 minutes in 900 mL 0.0033 M HCl at 30 rpm and 5 % dissolution in 300 seconds at 0 rpm. Typically conventional tablet formulations demonstrate significantly slower dissolution, less than 20 % in 5 minutes at 30 rpm and less than 5 % at 0 rpm.

Surge Dose[®] paracetamol tablets have demonstrated good in vitro in vivo correlations (IVIVC) with faster absorption than conventional tablets, halving T_{max} from around 45 to 20 minutes. For the non-steroidal anti-inflammatory drugs (NSAIDs) lornoxicam and diclofenac, Surge Dose[®] has again halved T_{max} and also increased C_{max} values as a result of improved in vivo dissolution and absorption of these relatively insoluble acidic drugs.

Thus Imaginot's Surge Dose[®] development strategy allows cost-effective in vitro optimisation to identify the best formulation for PK studies and follow up PD studies to determine the impact of improved absorption on clinical outcomes.

The document provides summary guidelines for assessing a drug's suitability as a Surge Dose[®] candidate and identifying the relevant patents to cover Surge Dose[®] formulations.

¹ IM 00-03-01 Surge Dose[®] formulation development. Imaginot Pty Ltd 19 Dec 2011

² IM 00-04-01 Surge Dose[®] in vitro dissolution test methods. Imaginot Pty Ltd 17 Dec 2011

2 Considerations in assessing suitability as a Surge Dose[®] candidate

Appendix 1 provides a summary check list for assessing the suitability of a drug as a Surge Dose[®] candidate based on the following considerations. The more criteria that are met, the more likely the drug will be a good candidate for the Surge Dose[®] technology with predicted improved absorption and clinical benefits.

2.1 Clinical indications

2.1.1 On demand usage

Drugs where fast onset of action is a clinical requirement such as those taken 'on demand' for pain, migraine, insomnia, drug addiction, allergies, nausea and erectile dysfunction.

- ✓ *Surge Dose[®] will provide fast dissolution resulting in shorter T_{max} and higher C_{max} driving rapid distribution to effect compartments*

2.1.2 Indications associated with gut stasis

Migraine, nausea and vomiting are often associated with reduced gastric motility that will delay drug transfer to the small intestine and hence slow absorption.

- ✓ *Surge Dose[®] will provide fast drug dissolution in the stomach allowing transfer of dissolved drug into the small intestine independent of gastrointestinal motility*

2.1.3 Concurrent use with antacids or proton pump inhibitors

These drugs increase gastric pH and so have the potential to reduce the solubility of drugs which are weak bases relying on acidic gastric conditions for dissolution. This may result in reduced bioavailability and slow absorption which depending on the drug may fail to reach minimum therapeutic plasma levels, or require a higher dosage that may be associated with a higher incidence of side effects.

- ✓ *Surge Dose[®] will provide fast dissolution independent of gastric pH*

2.1.4 Use by diabetics, elderly patients or those with low gastric acidity

Such patients have relatively high gastric pH which has the potential to reduce the solubility of drugs which are weak bases relying on acidic gastric conditions for dissolution. This may result in reduced bioavailability and slow absorption which depending on the drug may fail to reach minimum therapeutic plasma levels, or require a higher dosage that may be associated with a higher incidence of side effects.

- ✓ *Surge Dose[®] will provide fast dissolution independent of gastric pH*

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2.1.5 Use by elderly patients and those with impaired gastric emptying or reduced gastrointestinal motility

Delayed absorption dependent on Phase III gastric emptying of the MMC (migrating motility complex) cycle occurs in many patients with progressive chronic conditions such as Parkinson's Disease.

- ✓ *Surge Dose[®] will provide fast dissolution and allow gastric emptying of dissolved drug into the small intestine independent of gastric motility*

2.1.6 Drugs which cause gastro-toxicity or irritation and are taken with food

Some drugs, particularly NSAIDs and bisphosphonates, cause local gastric irritancy and therefore are taken with food to reduce irritancy or administered as an enteric coated formulation to reduce local toxicity. Both will result in delayed and variable absorption that is dependent on Phase III MMC gastric emptying.

- ✓ *Surge Dose[®] will provide fast dissolution in the stomach in both fasted and fed conditions and the resultant rapid emptying of dissolved drug reduces the gastric residence time thus reducing the potential for local gastrotoxicity*
- ✓ *Surge Dose[®] maximises solubility such that the drug will be present in solution in the ionised rather than the unionised form in the stomach which minimises local absorption into the gastric mucosal cells*

2.2 Pharmacokinetics (PK)

2.2.1 Multiple peaks

Many drugs administered in conventional tablet formulations show more than one peak in individual subject PK profiles resulting from gastric emptying effects. In some subjects and with some drugs this is more pronounced and is even evident with dispersed tablets where the time for in vivo disintegration has been eliminated. These multiple peaks result from early emptying of liquids independent of the gastric emptying cycle, and then the later bolus emptying of undissolved drug, or dissolved drug retained in gastric mucosa folds, during Phase III MMC.

- *Surge Dose[®] achieves fast maximum dissolution in the stomach so that the bulk of the solution can empty continuously with the coadministered water through the open pyloric sphincter independent of gastric emptying resulting in a single early absorption peak with a high C_{max}*

2.2.2 Faster absorption from solution than conventional solid dosage forms

Many drugs with high solubility classified as BCS1 or BCS3 drugs demonstrate dissolution rate dependent absorption, which is evident where PK data for a soluble formulation show faster absorption than from a conventional solid dosage form.

- *Surge Dose[®] achieves fast maximum dissolution in the stomach so that the PK of a Surge Dose[®] tablet is more like that of a solution than a conventional tablet*

2.2.3 Wide range of individual subject T_{max} values

Individual subject PK data often indicate significant inter- and intra-subject variability with a wide range of T_{max} values from 15 minutes to 2 hours for the same drug formulation. The lowest T_{max} values are usually associated with administration around the time of Phase III MMC and represent the shortest T_{max} that is likely to be possible particularly if the drug is administered as a solution. Such variability often results in a very wide mean PK profile.

- *Surge Dose[®] achieves fast maximum dissolution in the stomach with absorption less dependent on gastric emptying so that the distribution of T_{max} values is shifted towards the lower end of the range*

2.2.4 Non-normal distribution of individual T_{max} values

Mean PK data frequently show a significant difference between mean and median T_{max} values with the mean usually much longer than the median reflecting a tail of subjects with long T_{max} as a result of gastric emptying dependent absorption.

- *Surge Dose[®] achieves fast maximum dissolution in the stomach with absorption less dependent on gastric emptying without the tail of slow absorption events resulting in a normal distribution of T_{max} values with similar mean and median values*

2.3 Pharmacodynamics (PD)

2.3.1 PK-PD correlation

Although Surge Dose[®] provides fast absorption to drive distribution to effect compartments, drugs which demonstrate close correlation between plasma concentrations and response are likely to provide the greatest clinical benefit with a Surge Dose[®] formulation. However centrally acting drugs, which cross the blood brain barrier and are eliminated slower from the CNS than from plasma, are also likely to benefit from Surge Dose formulations.

- *Surge Dose[®] quickly achieves high plasma concentrations to drive distribution to effect compartments resulting in faster onset of action even if there is an associated lag*

2.3.2 Low efficacy

High variability in C_{max} can result in some patients not reaching minimum effective plasma concentrations such that no clinical response is achieved. This depends on the drug and its minimum effective plasma concentration relative to the dose but has been demonstrated for paracetamol, where for a conventional tablet more than 10 % of fasted subjects did not achieve the minimum effective plasma concentration of 10 mg/L.

- *Surge Dose[®] provides an increase in the frequency of fast absorption occasions with high C_{max} which is likely to improve efficacy for those drugs where there are non-responders who do not achieve minimum effective plasma concentrations*

2.3.3 Chronic usage drugs associated with variable response

Throughout the day patients experience a wide range of gastrointestinal conditions which can have a significant effect on the absorption of drugs which are taken regularly several times a day. For example variable absorption of Parkinson's Disease drugs can result in delays in onset of action with some doses, particularly those taken after meals, causing great distress to patients.

- *For short-acting drugs taken for chronic conditions several times a day, Surge Dose[®] provides more consistent fast absorption less dependent on gastric emptying which will result in a more consistent clinical response*

2.3.4 Narrow therapeutic window

Inter- and intra-subject variability often results in overlap of plasma concentrations in dose ranging studies, with higher doses than necessary used to achieve minimum effective concentrations even with slow absorption occasions.

- *Surge Dose[®] provides more consistent fast absorption with more high C_{max} values so there will be less overlap of PK results in dose ranging studies such that a lower minimum effective dose can be selected*

2.3.5 Dose related side effects

Some drugs have dose related side effects which may be dose and efficacy limiting.

- *Surge Dose[®] provides more consistent absorption which may allow a reduction in dose without compromising efficacy*

2.4 *In vitro* dissolution

Where conventional solid dosage forms demonstrate slow in vitro dissolution under Imaginot test conditions in 900 mL 0.0033 M HCl at 30 and 0 rpm, Surge Dose[®] formulations would be expected to reach the maximum extent of dissolution as determined by the absolute drug solubility faster. Where drug solubility is pH dependent, then Surge Dose[®] formulations will increase the extent as well as the rate of dissolution compared with conventional solid dosage forms.

3 Determination of relevant Imaginot patents

Appendix 2 provides a tabulation which allows the appropriate patent coverage to be identified based on an assessment of the physico-chemical characteristics of the drug under consideration.

The Surge Dose[®] technology is covered by three patent families filed in US, Canada, Europe, India, Japan and Australia:

- i. PCT/AU 2006/001798 <acids & unionised> originally published as WO/2007/059591 covering acidic and unionised drugs claiming priority from the Australian provisional filed on 28 Nov 2004. This was accepted in Australia in 2011 (AU 2006317530) and US examination is progressing under the PPH.
- ii. PCT/AU 2005/00759 <bases & amphoterics> originally published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. Additional examples and claims were subsequently filed as detailed in US 2008/0287456. This has been granted in Australia (AU 2005247048) and Canada (CA 2,566,384) and is under examination in India, Japan and US. A clean European ISR report was issued.
- iii. PCT/AU 2005/00758 <paracetamol> originally published as WO/2005/115344 covering paracetamol and paracetamol combinations has been assigned to a third party in Australia, Europe, India and Japan. The patent has been granted in Australia (AU 2005247047) and Canada (CA 2,566,331) and in the US (US11/604,972).

The claims in these patents define the target minimum in vitro dissolution performance required for Surge Dose[®] formulation optimisation measured in 900 mL 0.0033 M HCl at 37 °C:

- For acidic and unionized drugs:

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- At least 20 % dissolution in 180 seconds at 30 rpm OR
- At least 40 % dissolution in 240 seconds at 30 rpm OR
- At least 50 % dissolution in 300 seconds at 30 rpm OR
- At least 5 % dissolution in 30 minutes at 0 rpm OR
- At least 5 % dissolution in 300 seconds at 0 rpm
- For basic and amphoteric drugs:
 - At least 70 % dissolution in 180 seconds at 30 rpm OR
 - At least 5 % dissolution in 300 seconds at 0 rpm
- For paracetamol:
 - At least 70 % dissolution in 180 seconds at 30 rpm OR
 - At least 5 % dissolution in 300 seconds at 0 rpm

In general:

- Acidic drugs and amphoteric drugs that behave as an acid will require a relatively high level of alkaline pHMA such that there will be an increase in the pH of 900 mL 0.0033 M HCl above pH 5
- Basic drugs and amphoteric drugs that behave as a base will require a relatively low level of alkaline pHMA such that the pH of 900 mL 0.0033 M HCl will not change
- Weak acids that are predominantly unionised over the physiological pH range will require sufficient pHMA to maximise the extent and rate of dissolution in 900 mL 0.0033 M HCl.

Based on the in vitro dissolution results with more than 30 different drugs:

- Those that require more than 400 mg bicarbonate to maximise the dissolution are generally acidic drugs and amphoteric drugs that behave an acid
- Those that require less than 400 mg bicarbonate to maximise the dissolution are generally basic drugs and amphoteric drugs that behave a base, with higher levels of bicarbonate often showing a reduction in dissolution rate
- Those where the effect of added bicarbonate indicates that solubility is not pH dependent are generally unionised drugs

Appendix 1

Checklist for assessment of a drug as a Surge Dose[®] candidate

	Surge Dose [®] Criteria	Yes ✓ No ✗
Clinical	On demand usage with fast onset of action required	
	Indications associated with gut stasis	
	Concurrent use of PPI or antacids	
	Elderly or diabetic patients with reduced gastric acidity	
	Elderly patients or those with impaired gastrointestinal motility	
	Gastro-toxic drugs	
Pharmacokinetics	Multiple peaks	
	T_{max} solution < T_{max} conventional solid dosage forms	
	Wide range of individual T_{max} values	
	High degree of intra-subject variability in T_{max} and C_{max}	
	Median T_{max} < mean T_{max}	
Pharmacodynamics	Good PK-PD correlation without time lag	
	Low efficacy	
	Variable intra-subject response	
	Narrow therapeutic window	
	Dose related side-effects	
In vitro dissolution	< 20 % dissolution in 180 seconds in 900 mL 0.0033 M HCl at 30 rpm with conventional tablet formulations	
	< 5 % dissolution in 300 seconds in 900 mL 0.0033 M HCl at 0 rpm with conventional tablet formulations	
	pH dependent solubility & dissolution over physiological pH 1 – 8	

The greater the number of ✓, the more likely that a Surge Dose[®] formulation of the drug will demonstrate improved PK and PD outcomes.

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Appendix 2

Patent coverage for drugs formulated to Surge Dose[®] specifications

Drug / optimised formulation characteristics	Acids & unionised based on WO/2007/059591	Bases & amphoterics based on WO/2005/115345	Paracetamol based on WO/2005/115344
Paracetamol	✓		✓
Solubility increases with increasing pH	✓		
Solubility decreases with increasing pH		✓	
pH independent solubility over physiological pH range of 1 - 8	✓		
Weak acid with single pKa >2<7	✓		
Weak acid with single pKa > 7	✓		
Weak base with single pKa >7<10		✓	
Multiple pKa with highest >7		✓	
Multiple pKa with highest < 7	✓		
> 400 mg bicarbonate per tablet for max dissolution	✓		
< 400 mg bicarbonate per tablet for max dissolution		✓	
Paracetamol + weak base drug	✓	✓	✓
Paracetamol + weak acid drug	✓		✓