# The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)

**Pharmaceutical Medicine**

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**PHARMACEUTICAL EVALUATION MANAGEMENT**

**PRE-REG UNIT EVALUATION REPORT FORMAT**

**BIOEQUIVALENCE EVALUATION REPORT**

| | |
|---|---|
| Application number | |
| Product (proprietary) name | |
| Approved name (INN) (INNM) | pKa: BCS Classification: |
| Applicant | |
| Date of application | |
| Manufacturer | |
| Manufacturer applied for | |
| API Manufacturer | |
| API manufacturer applied for | |
| Dosage form | |
| Dosage & relation to food intake | |
| Foreign registration | |
| Review pathway | |

**biostudy in-vivo, invitro as applicable*

**TECHNICAL SCREENING:** The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
*Red*: Initial screener conclusions
*Blue:* Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow

| **Protocol (in-vivo, in-vitro, waiver)** | |
|---|---|
| API pk | |
| Linearity | |
| Food effect | |

| | | |
|---|---|---|
| Absorption | | |
| T max | | |
| Elim half-life | | |
| Sample size calculation | | |
| Ethics | | |
| **Study title (BE, dissolution, biowaiver)** | | |
| CRO (BE) | | |
| Principal investigator<br>Sponsor (BE) | | |
| Study Protocol Number(s) (BE) | | |
| Report number(s) | | |
| *Study design – washout 5 x t½ dose within SA approved range?* | | |
| Test batch name and strength<br>Test Batch size, batch number | | |
| Date of manufacture | | |
| Reference product / HCR<br>Batch Number & Exp date | | |
| RSA Innovator Product/Applicant<br>Batch Number & Exp date | | |
| *Study period (dates)* | Clinical: Period I | |
| | Period II | |
| | | |
| | Completion | |
| | Analytical method validation | |
| | Analysis | |
| | Bioanalytical | |
| | Final report | |
| Dates of report and submission i.e. Biostudy age at the time of submission; if more than 5 years, | Confirm that the Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| then include standard sentence *(stated in next column – delete if not relevant)* | participant files are available for verification by the Inspectorate and indicate the facility(ies) where they may be inspected | | | | | | | | | |
| Subjects | | | | | | | | | | |
| Sample collection and storage | | | | | | | | | | |
| Peak concentration normally | | | | | | | | | | |
| Samples in absorption phase | | | | | | | | | | |
| Samples in elimination phase | | | | | | | | | | |
| Protocol BE parameters | | | | | | | | | | |
| Primary parameters<br>*Note: Change values if not same as minimum* | $AUC_{0-t}$, $C_{max}$ …… for: *state analyte*<br>Minimum 90 % CI of the relative mean of test & reference between 80,00 % and 125,00 % for log transformed data. | | | | | | | | | |
| Secondary parameters (indicate with x) | $AUC_{0-inf}$ | | $T_{max}$ | | $T_{1/2}$ | | $K_{el}$ | | | |
| Statistical procedure | | | | | | | | | | |
| Study reporting –<br>GCP, GLP, cGMP | | | | | | | | | | |
| **Analytical method validation** | | | | | | | | | | |
| Date *if old check for appendices* | | | | | | | | | | |
| Experimental Parameters | | | | | | | | | | |
| Analyte | | | | | | | | | | |
| Biological matrix & anticoagulant | | | | | | | | | | |
| Selectivity incl haemolysis | | | | | | | | | | |
| Carryover<br>(internal & active analytes) | | | | | | | | | | |
| Analytical range | | | | | | | | | | |
| Calibration curve/linearity | | | | | | | | | | |
| Accuracy | LQC | | MQC | | HQC | | | | | |
| Dilution integrity | | | | | | | | | | |
| Precision (inter and intra) | | | | | | | | | | |
| Freeze-thaw cycles | | | | | | | | | | |

| | |
|---|---|
| Working soln stability for controls and sample | |
| Drug interference<br>(more recently applicable) | |
| **Analytical report (BE)** | |
| Analytical method | |
| LOQ and CC range | |
| Number of samples collected | |
| Number of samples received | |
| Number of samples analysed | |
| Repeat analysis | |
| Reanalysis/incurred analysis | |
| Representative chromatograms | |
| Comprehensive index to identify subject number | |
| Calibration curves and QC samples included in correct sequence | |
| Calibration curves correspond | |
| Injection sequence chronological with no gaps, interspersed with control samples | |
| Dates are logical | |
| Annotations logical, correspond with the chromatograms | |
| Are samples identifiable? | |
| **Pk and statistical report** | |
| Pre-dose concentrations | |
| $AUC_{0-t}$ / $AUC_{0-inf}$ (80 %) /<br>AUC extrapolated < 20 % | |
| ***Results (*or copied below if there is a similar table)** | |

| | |
|---|---|
| Proposed professional insert | Time to peak ; elimination half-life |
| Safety evaluation | Adverse events |
| Test and Ref Comparable? | |
| In line with API safety profile? | |
| **Test and ref product similarity BE, in-vitro, biowaiver** | |
| Formulations test and reference | Qualitatively the same?<br>Tabulated comparison with formulation of test product could also be under 3.2.R1.1.10; 3.2.R.1.2 and 3.2.P.2.3 |
| Assay | Test and reference CoAs + spec in 32P51<br>*see table below* |
| Dissolution if applicable | Pharmaceutical availability 32R14 –<br>*incl dissoln summary belo*w<br>Test and reference CoAs + spec in 32P51<br>*see separate table below*<br>*For abridged or reliance application pathways: Include the approved dissolution specifications if these are stated in the approval letter, especially US FDA.* |
| Dissolution discriminating ability | |
| Impurity profile | Test and reference CoAs + spec in 32P51<br>*see separate table below* |
| Conclusion re specifications | |
| **More than one strength** | |
| Formulations different strengths | Proportionally similar?<br>Tabulated comparison of strengths? |
| Assay | Test and reference CoAs + spec in 32P51<br>*see table below* |

| | |
|---|---|
| Dissolution if applicable | Pharmaceutical availability 32R14 –<br>*incl dissoln summary belo*w<br>Test and reference CoAs + spec in 32P51<br>*see separate table below* |
| Impurity profile | Test and reference CoAs + spec in 32P51<br>*see separate table below* |
| Conclusion re specifications | |
| **BCS biowaiver additional aspects** | |
| Dose/volume solubility | |
| Relevant solubility values | |
| Other | |
| **Overall study conclusions** | |
| BE of the test & reference prod (in-vivo and in-vitro) | |
| Similarity of Bioref & RSA ref | |
| Proportional similarity | |
| Final product specifications | |
| Recommendations:<br>I recommended<br>II recommended provided that<br>III not approved until<br>IV not recommended | |

**Essential similarity of test & reference products & comparison with specifications 32P51**

| | **Specifications 3.2.P.5.1** | | | **Ref batch** | **Test Batch** |
|---|---|---|---|---|---|
| | Aa mg | Bb mg | Cc mg | Results 3.2.r.1.3 | Results 3.2.r.1.3 |
| Assay % Release<br>Stability | | | | | |
| Dissolution % | | | | | |
| Medium & conditions | | | | | |
| Total impurities R<br>S | | | | | |

### 3.2.R.1.4 Dissolution

**NB Include the actual dissolution results (mean values)**

*Repeat tables as necessary*

| BE Reference(s) name strength country | | | BN | | SA innovator(s) name strength RSA | | BN | |
|---|---|---|---|---|---|---|---|---|
| **Mins** | **0,1 N HCl** | **pH 4,5** | **pH 6,8** | **QC** | **0,1 N HCl** | **pH 4,5** | **pH 6,8** | **QC** |
| **10** | | | | | | | | |
| **15** | | | | | | | | |
| **20** | | | | | | | | |
| **30** | | | | | | | | |
| **45** | | | | | | | | |

| SA Innovators name strength country | | | BN | | Test name strength | | BN | |
|---|---|---|---|---|---|---|---|---|
| **Mins** | **0,1 N HCl** | **pH 4,5** | **pH 6,8** | **QC** | **0,1 N HCl** | **pH 4,5** | **pH 6,8** | **QC** |
| **10** | | | | | | | | |
| **15** | | | | | | | | |
| **20** | | | | | | | | |
| **30** | | | | | | | | |
| **45** | | | | | | | | |

**EVALUATORS**

| **Full name** | **Signature** | **Date** |
|---|---|---|
| 1 Screener: | | |
| 2 Second screener | | |
| 3 Evaluator | | |
| 4 Peer reviewer (Group Meeting) | | |