|  |  |  |
| --- | --- | --- |
| */Logotype/* | Research Study Report | Study Number: …… (………) |
| Study Title: Infectious Disease Product Testing to complete Data Gaps identified in Design History File for VIROTROL I (……..) | DHF ID: VIROTROL I (……..) |
| Prepared by: A. Covey/C. Simmer  | Signature: *AileneCovey / /Signature/* | Date: 0*6/20/14* |

POST-STUDY APPROVALS

|  |  |  |  |
| --- | --- | --- | --- |
| **Department** | **Name** | **Signature** | **Date** |
| R&D | Mitch Gonzales | */Signature/* | *29 June 2014* |
| RA/QA | Fay Farmand | */Signature/* | *7-10-14* |
| ME | N/A |  |  |
| Project Management | N/A |  |  |
| Marketing | Joshua Pulido | */Signature/* | *10 JUL 2014* |
| Others | *John Owens* | */Signature/* | *17 July 2014* |

1. **Executive Summary**

This report fulfills Validation / Verification gaps identified in the design history file for VIROTROL I (Cat. ……..) with data originating from the following studies:

* Real Time shelf life stability data (minimum of three lots) to support 36 month dating.
* Open Vial stability data (minimum of one lot) to support 60 day claim.
* Heat Stress and Freeze-Thaw Testing to simulate shipping conditions (minimum of one lot).
* Precision - Inter-runs (within-laboratory) reproducibility was performed with at least three lots of VIROTROL I, while Intra-run (within-run) reproducibility was performed with at least one (1) lot of VIROTROL I (Cat. ……. (one lot for each assay from test kit replacement studies).

The data evaluated in this report supports the following for VIROTROL I (………):

* Shelf life stability: 36 months closed vial shelf stability at recommended 2-8°C storage condition.
* Open vial: 60 days open vial at 2-8°C as claimed.
* Heat Stress: Can withstand a minimum of 28 days at 25°C without compromising or negatively affecting product performance.
* Freeze Thaw: Can withstand up to five (5)-freeze thaw cycles without compromising or negatively affecting product performance.
* Inter-run Precision Testing for VIROTROL I (…….): Inter-assay precision was run with a minimum total of n=15 replicates over a minimum 5 day range with an expected “Reactive/Positive” result for all analytes specifying “Reactive/Positive” in Bottle Release specifications meeting the criteria in section 3.3.4.
* Intra-run Precision Testing for VIROTROL I (………): Intra-assay precision was run with minimum of n=20 replicates within one run with an expected “Reactive/Positive” result for all analytes specifying “Reactive/Positive” in Bottle Release specifications meeting the criteria in section 3.3.4.
1. Deviations Made to the Protocol and Justifications

Inter-run Precision data was derived from the data available in the Performance Database. Three lots could not be identified for VIROTROL I (……...) for n=3 replicates for five days for all applicable assays. Therefore, an analogous experimental design format to EP15-A2 testing was followed for a minimum of n=2 or more replicates over a minimum period of five calendar days with minimum replicates of n=15. The minimum number for days and total number of replicates are consistent with those of EP15-A2 experimental design approach. Therefore, this deviation was deemed acceptable.

1. Results and Observations
	1. Materials

All VIROTROL I lots shown below (refer to Table 1-3) were tested following manufacturer’s instruction(s) for unknown specimens.

Table 1. **Test Kits used for Validation / Verification Studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Test Kit | Part No. | PTK | Lot# | **Exp. Date** |
| Abbott Auzyme Proc. C | 1980 | PTK-0200 | 01701M100 | 09/16/03 |
| 01982M201 | 08/28/03 |
| 04692M300 | 10/31/03 |
| 06355M300 | 02/28/04 |
| 07509M200 | 04/23/04 |
| 08591M200 | 05/27/04 |
| 11128M100 | 05/27/04 |
| 11505M200 | 07/08/04 |
| 13871M101 | 08/12/04 |
| 15896M100 | 01/01/05 |
| 16728M100 | 10/31/04 |
| 18302M200 | 03/16/05 |
| 18456M100 | 01/06/05 |
| 20556M100 | 04/27/05 |
| 24617M200 | 07/20/05 |
| 25578M200 | 10/07/05 |
| 29655M100 | 12/12/05 |
| 32430M100 | 02/25/06 |
| 90083M101 | 12/22/02 |
| 92902M202 | 02/27/03 |
| 92902M202 | 02/27/03 |
| 93773M301 | 05/07/03 |
| Abbott CMV Total Ab EIA | 6163 | PTK-0207 | 11831M100 | 08/27/04 |
| 16171M100 | 01/03/05 |
| 19539M100 | 04/28/05 |
| 23117M100 | 07/01/05 |
| 29433M200 | 11/03/05 |
| 30592M100 | 03/01/06 |
| 34173M200 | 07/21/06 |
| 38738M100 | 10/06/06 |
| 41197M201 | 1 02/24/07 |
| 46426M100 | 06/29/07 |
| 50008M100 | 11/03/07 |
| 53219M100 | 02/16/08 |
| 59809M100 | 05/24/08 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Test Kit | Part No. | PTK | Lot# | Exp. Date |
| Abbott Corzyme Anti-HBc | 9977 | PTK-0203 | 11300M200 | 04/20/04 |
| 11496M200 | 04/20/04 |
| 15046M200 | 08/09/04 |
| 16792M200 | 11/24/04 |
| I8488M100 | 01/21/05 |
| 19804M100 | 03/09/05 |
| 23326M100 | 05/03/05 |
| 23360M100 | 05/03/05 |
| 24532M201 | 08/30/05 |
| 26459M200 | 10/15/05 |
| 28026M100 | 02/28/06 |
| 31572M100 | 12/29/05 |
| 32238M100 | 05/24/06 |
| 42553M200 | 02/15/07 |
| 43139M100 | 03/09/07 |
| 49301M200 | 09/23/07 |
| bioMerieux VIDAS CMV IgG | 30204 | PTK-0082 | 824055001 | 04/25/09 |
| 827017201 | 08/23/09 |
| 828359001 | 09/27/09 |
| 831105401 | 01/09/10 |
| 833622107 | 05/02/10 |
| 834834501 | 06/19/10 |
| 837494501 | 09/27/10 |
| 839023801 | 11/29/10 |
| 841666601 | 03/07/11 |
| 864687401 | 06/23/11 |
| 1001812120 | 10/18/13 |
| Bio-Rad MONOLISA Anti-HBc | 26186 | PTK-0072 | 011EGG | 11/30/10 |
| 029EGG | 12/22/10 |
| 090FGG | 10/11/11 |
| 129FGG | 04/04/12 |
| 176EGG | 04/17/11 |
| 194DGG | 01/28/10 |
| 207CGG | 05/13/09 |
| 246HGG | 08/09/14 |
| 278DGG | 07/15/10 |
| 281EGG | 08/20/11 |
| 293FGG | 09/14/12 |
| Bio- Rad GS HBsAg EIA3.0 | 32591 | PTK-0071 | 331CCC-05 | 11/29/09 |
| 070DCC-05 | 01/08/10 |
| 077ECC-05 | 02/02/11 |
| 119DCC-05 | 03/17/10 |
| 144ECC-05 | 04/12/11 |
| 163GCC-05 | 05/05/13 |
| 188ECC-05 | 05/27/11 |
| 275DCC-05 | 07/21/10 |
| 3I7DCC | 09/09/10 |
| 317DCC-05 | 09/09/10 |
| 321GCC-05 | 11/30/13 |
| 323FCC-05 | 10/03/12 |
| 347CCC-05 | 11/29/09 |
| 362gGCC-05 | 11/30/13 |
| Murex HIV 1.2.0 | C04087 | PTK-0266 | D132010 | 08/31/13 |
| D157610 | 01/31/14 |
| L251210 | 07/31/09 |
| H827510 | 08/01/04 |
| H827910 | 2004/10 |
| H887411 | 04/01/05 |
| H928513 | 05/01/05 |
| H980710 | 11/01/05 |
| H985810 | 12/05/05 |
| J090510 | 06/01/06 |
| J152210 | 2006/12 |
| J221910 | 05/01/07 |
| L288110 | 01/31/10 |
| L325510 | 05/31/10 |
| L325610 | 08/31/10 |
| L325910 | 08/31/10 |
| L364610 | 11/30/10 |
| L366210 | 01/31/11 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Test Kit | Part No. | PTK | Lot# | Exp. Date |
| Murex HIV 1.2.0 (Cont’d) | C04087 | PTK-0266 | L463710 | 06/30/11 |
| Murex HTLV I/II E1A | GE80 | PTK-0265 | H839710 | 11/01/04 |
| H920210 | 02/01/05 |
| H942710 | 06/01/05 |
| 11967010 | 08/01/05 |
| H986810 | 06/01/05 |
| H994710 | 12/01/05 |
| J091210 | 07/01/06 |
| J205110 | 02/01/07 |
| J246810 | 08/01/07 |
| J263710 | 02/01/08 |
| L064310 | 03/01/08 |
| L296810 | 03/01/10 |
| L318310 | 08/31/10 |
| L366210 | 01/31/11 |
| Ortho HCV 3.0 ELISA | 930740 | PTK-0210 | H967010 | 08/01/05 |
| H986810 | 06/01/05 |
| H994710 | 12/01/05 |
| J091210 | 07/01/06 |
| J205110 | 02/01/07 |
| J246810 | 08/01/07 |
| L296810 | 03/01/10 |
| L318310 | 06/30/10 |
| TXE 376 | 08/12/04 |
| TXE378 | 10/09/04 |
| TXE 381 | 12/16/04 |
| TXE 401 | 11/03/05 |
| TXE 412 | 05/08/06 |
| TXE 418 | 09/02/06 |
| TXE378 | 10/09/04 |
| TXE381 | 12/16/04 |
| TXE385 | 02/26/05 |
| TXE389 | 05/18/05 |
| TXE395 | 08/01/05 |
| TXE397 | 09/10/05 |
| TXE4004 | 12/10/05 |
| TXE401 | 11/05/05 |
| TXE406 | 01/06/06 |
| TXE423 | 09/14/06 |
| TXE427 | 12/15/06 |
| TXE436 | 01/05/07 |
| TXE506 | 09/04/09 |
| TXE511 | 12/09/09 |
| TXE519 | 04/20/10 |
| TXE522 | 06/22/10 |
| TXE528 | 10/15/10 |
| TXE531 | 11/19/10 |
| TXE533 | 01/21/11 |
| TXE541 | 02/05/11 |
| TXE549 | 06/11/11 |
| TXE562 | 06/23/12 |
| TXE564 | 07/08/12 |
| TXE573 | 11/30/12 |
| TXE591 | 02/22/14 |
| Siemens Enzygnost Anti-CMV/IgG+IgM EIA | OWGM13 | PTK.-0316 | 38129 | 06/15/09 |
| 38229 | 08/10/09 |
| 38601 | 01/15/10 |
| 38978 | 03/26/10 |
| 39014 | 05/14/10 |
| 39137 | 08/16/10 |
| 39347 | 11/01/10 |
| 39459 | 12/31/10 |
| 39824 | 05/02/11 |
| 39980 | 07/29/11 |
| 40080 | 10/24/11 |
| 40323 | 11/21/11 |
| 40630 | 04/03/12 |
| 40717 | 05/01/12 |
| 41060 | 10/16/12 |
| 41301 | 01/08/13 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Test Kit | Part No. | PTK | Lot# | Exp. Date |
| Siemens Enzygnost Anti-CM V/IgG+IgM EIA *(Cont'd)* | OWGM13 | PTK-0316 | 41650 | 05/24/13 |
| 42336 | 12/09/13 |

**Table 2.** Result Interpretation per manufacturer’s test kit package insert

|  |  |  |  |
| --- | --- | --- | --- |
| **Test Kit Manufacturer** | **Test Kit Name** | **Results** | **Interpretation** |
| Abbott | Auszyme Proc. C (PTK-0200) | Abs. < Cutoff | Nonreactive |
| Abs. ≥ Cutoff | Reactive |
| Abbott | CMV Total Ab EIA (PTK-0207) | Abs. < Cutoff | Nonreactive |
| Abs. ≥ Cutoff | Reactive |
| Abbott | Corzyme Anti-HBc (PTK-0203) | Abs. > Cutoff | Negative |
| Abs. ≤ Cutoff | Reactive |
| Abbott/DiaSorin | Murex HTLV-I/II EIA (PTK-0265) | Abs. < Cutoff | Non-reactive |
| Abs. ≥ Cutoff | Reactive |
| bioMerieux | VIDAS CMV IgG (PTK-0082) | Conc. < 4 AU/mL | Negative |
| 4 AU/mL ≤ Conc. < 6 AU/mL | Equivocal |
| Conc, ≥ 6 AU/mL | Positive |
| Bio-Rad | Genetic System (GS) HBsAg EIA 3.0 (PTK-0071) | Abs. < Cutoff | Non-reactive |
| Abs. ≥ Cutoff | Reactive |
| Bio-Rad | MONOLISA Anti-HBc (PTK-0072) | Abs. < 0.9 x Cutoff | Nonreactive |
| > 1.1 x Cutoff | Reactive |
| 0.9 x Cutoff ≤ Abs. ≤ 1.1 x Cutoff | Borderline |
| Murex | HIV-1.2.0 (PTK-0266) | Abs. < Cutoff | Nonreactive |
| Abs. ≥ Cutoff | Reactive |
| Ortho | HCV3.0 ELISA (PTK-0210) | -0.080 ≤ Abs. < Cutoff | Nonreactive |
| Abs. ≥ Cutoff | Reactive |
| Siemens | Enzygnost Anti- CMV/IgG +lgM EIA (PTK-0316) | Abs. < Cutoff x 0.8 | Negative |
| Abs. > Cutoff x 1.2 | Positive |
| Cutoff x 0.8 ≤ Abs. < Cutoff x 1.2 | Equivocal |

**Table 3. VIROTROL I Lot Numbers**

|  |  |  |
| --- | --- | --- |
| **Test Sample** | **Lot#** | **Exp.** |
| VIROTROL I | B04B0061 | 09/31/05 |
| B04K0321 | 05/31/06 |
| B05C0591 | 09/30/06 |
| C04C1011 | 09/30/05 |
| C05H2051 | 02/28/07 |
| C05K0771 | 05/31/07 |
| C08L0771 | 06/30/10 |
| C09C1681 | 09/30/10 |
| C09K0011 | 05/31/11 |
| C10L115 | 12/31/13 |
| E04D0141 | 10/31/05 |
| E04H0711 | 02/28/06 |
| E05A0861 | 07/31/06 |
| E05F1281 | 12/31/06 |
| E05K0091 | 05/31/07 |
| E09A0401 | 07/31/10 |
| E09E0701 | 11/30/10 |
| E09J0771 | 04/xx/11 |
| E10D0591 | 10/31/11 |
| E10F2051 | 12/31/11 |
| E10I0101 | 03/31/10 |
| E116020 | 01/31/15 |
| F02H0191 | 02/28/02 |
| F04A0021 | 07/31/05 |
| F04B0541 | 08/31/05 |
| F08J0261 | 04/30/10 |
| F09E0421 | 04/30/10 |
| G117000 | 08/31/15 |

***1Note: Reflects the product’s original expiration date of 18 months prior to the extension to 36 months for subsequent lots performed.***

* 1. **Methods**

VIROTROL I (4 mL) is available in different optimized levels referred to as classes. Each class varies in analyte specification and designated by an alphanumeric catalog number. The data summarized in this report is derived from VIROTROL I (Cat. 00101E) which have shared analyte specifications and bracketing applicable analyte by lowest and highest specification and by test kit. It is reasonable to expect by challenging the lowest and highest analyte specification that it would represent highest risk scenario for performance variability and potential failure (Refer to Table 4).

Table 4. Testing Guideline for VIROTROL I (Cat. 00101E).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analytes** | **Part Number Used** **other than 00101B**  | **Classes with Specification Between Lowest and Highest** | **PTK** | **Test Kit** |
| Anti-HBc | 00101B00101C |  | 0203 | Abbott Corzyme Anti-HBc Bio-Rad MONOLISA Anti-HBc EIA |
| 0072 |
| HBsAg | 00101F |  | 0200, Proc. C0071, Proc/ A | Abbott Auszyme Proc C Bio-Rad GS HBsAg 3.0 EIA |
| 00101C | 00101E |
| 00101G |
| Anti HLTV-I | 00101F |  | 0265 | Murex HTLV - I/II EIA |
| Anti-HCV |  |  | 0210 | Ortho HCV Version 3.0 ELISA |
| Anti-HIV-1 |  |  | 0266 | Murex HIV 1.2.0 |
| Anti-CMV | 00101C00101F |  | 0207 | Abbott CMV Total Ab EIA bioMerieux VIDAS CMV IgG (CMVG) Siemens Enzygnost Anti-CMV/IgG+IgM |
| 0082 |
| 0316 |

* 1. **Acceptance Criteria**

**Note: A substitute VIROTROL I class, with an equivalent analyte specification was used when necessary (refer to table 4)**

* + 1. **Acceptance Criteria for Shelf Life Stability**

The ability of VIROTROL I (Cat. 00101E) to yield overall results ≥ 95% in agreement with the expected “Reactive/Positive” result when tested at least 20% beyond claimed expiration dating.

* + 1. **Acceptance Criteria for Open-Vial stability**

The ability of VIROTROL I (Cat. 00101E) to yield overall results 100% in agreement with the expected “Reactive/Positive” result when tested at least 20% beyond 60-day open vial claim (example: T0, T30, T60 (Final) and TFinal+20%= T72).

* + 1. **Acceptance Criteria for Simulated Shipping Conditions**

The acceptance criteria for accelerated stability and simulated shipping conditions will be deemed acceptable if at least one of the following pass/fail criteria is met:

3.3.3.1 The ability of VIROTROL I (Cat. 00101E) to yield overall results ≥ 95% in agreement with the expected “Reactive/Poitive” result.

3.3.3.2 Retrospective analysis of analyte recovery of the tested vials was also examined at +/- 30% of the vials stored at 2-8°C to support simulated shipping conditions.

* + 1. **Acceptance Criteria for Precision Testing**

Inter-run Precision of VIROTROL I, (Cat. 00101E) is run with a minimum of n=15 total replicates over a minimum a 5 day range. Intra-run Precision of VIROTROL I, (Cat. 00101E) is run with a minimum of n=20 repiicates within one run. The minimum criteria for Precision is ≥ 95% in agreement with the expected “Reactive/Positive” result.

* 1. **Results**

**Note: A substitute VIROTROL I class, with an equivalent analyte specification, was used when necessary (refer to table 4).**

* + 1. **Real Time Testing**

Real Time performance monitoring of VIROTROL I, (Cat. 00101E) yields consistently positive/reactive results (100% positive/reactive results for all analytes) when tested at a minimum of 20% beyond the claimed 36 month shelf-life (actual duration ranges from 46 - 69 months) of the product under recommended storage condition at 2-8°C. Performance monitoring yielded results that meet criteria in sections 3.3.1 and were determined acceptable in supporting the 36 month expiration from fill date (Refer to Tables 6-11). In the event of a discontinued test method, data from both the discontinued method and the replacement method is provided for continuity in supporting real-time stability testing through the duration of the study (Refer to Table 5-11).

Table 5. **Summary of test kit used, in Real Time performance monitoring accounting for discontinued and replacement method(s).**

|  |  |
| --- | --- |
| Analyte | Test Kit |
| Anti-HBc | Abbott Corzyme1 |
| Bio-Rad MONOLISA Anti-HBc |
| HBsAg | Abbott AUZYME Proc C1 |
| Bio-Rad GS HBsAg 3.0 EIA |
| Anti-HTLV-1 | Murex Anti-HTLV-I/II |
| Anti-HCV | Ortho HCV 2.0 |
| Anti-HIV-1 | Murex HIV 1.2.0 |
| Anti-CMV | Abbott CMV Total Ab EIA1 |
| bioMerieux CMV IgG |
| Siemens Enzygnost anti-CMV / IgG+IgM EIA |

**1 Discontinued test kit method**

3.4.1.1 VIROTROL I, Anti-HBc Real Time Stability (Tables 6.1 - 6.3).

Table 6.1a. VIROTROL I, Lot# B04B006 Real Time Stability Testing, Anti-HBc.

|  |
| --- |
|  |

|  |
| --- |
| Anti-HBc |
|  |  | **Abbott Corzyme** **(PTK-0203)** | **KIT****CONTROLS** |  | **VIROTROL 1 (Lot# B04B006)** |
| **Months** | **Oper** | **Lot No.** | **Exp. Date** | **NC** | **PC** | **Assay****Cutoff** | **Rep1 (Abs)** | **Rep2 (Abs)** | **Rep3 (Abs)** | **Rep4 (Abs)** | **Avg all Reps (Abs)** | **S/CO\*** | **Interpretation** |
| 0 | MC | 11300M200 | 04/20/04 | 1.291 | 0.024 | 0.531 | 0.174 | 0.237 |  |  | 0.206 | 0.39 | **Reactive** |
| 1 | LG | 11496M200 | 04/20/04 | 1.339 | 0.021 | 0.548 | 0.188 | 0.150 |  |  | 0.169 | 0.31 | **Reactive** |
| 5 | LG | 15046M200 | 08/09/04 | 1.163 | 0.025 | 0.480 | 0.176 | 0.184 |  |  | 0.180 | 0.38 | **Reactive** |
| 7 | LG | 16792M200 | 11/24/04 | 1.379 | 0.028 | 0.569 | 0.274 | 0.266 |  |  | 0.270 | 0.47 | **Reactive** |
| 9 | MC | 18488M100 | 01/21/05 | 1.345 | 0.032 | 0.557 | 0.241 | 0.186 |  |  | 0.214 | 0.38 | **Reactive** |
| 11 | MC | 23326M100 | 05/03/05 | 1.381 | 0.036 | 0.574 | 0.207 | 0.203 |  |  | 0.205 | 0.36 | **Reactive** |
| 14 | MC | 23360M100 | 05/03/05 | 1.258 | 0.036 | 0.524 | 0.211 | 0.233 |  |  | 0.222 | 0.42 | **Reactive** |
| 17 | MC | 26459M200 | 10/15/05 | 1.133 | 0.035 | 0.474 | 0.178 | 0.230 |  |  | 0.204 | 0.43 | **Reactive** |
| 20 | LG | 31572M100 | 12/29/05 | 1.372 | 0.050 | 0.578 | 0.276 | 0.239 |  |  | 0.258 | 0.45 | **Reactive** |
| 24 | MC | 32238M100 | 05/24/06 | 1.172 | 0.057 | 0.503 | 0.167 | 0.174 |  |  | 0.171 | 0.34 | **Reactive** |
| 24 | CC | 32238M100 | 05/24/06 | 1.081 | 0.066 | 0.472 | 0.192 | 0.201 |  |  | 0.197 | 0.42 | **Reactive** |

\* S/CO: Average Absorbance / Assay Cutoff

Table 6.1b. **VIROTROL I, Lot# B04B006 Real Time Stability Testing, Anti-HBc.**

|  |
| --- |
| Anti-HBc |
|  |  | **Bio-Rad Monolisa Anti-HBc (PTK-0072)** | **KIT****CONTROLS** |  | **VIROTROL I (Lot# B04B006)** |
| Months | Oper | **Lot No.** | **Exp. Date** | **NC** | **PC** | **Assay****Cutoff** | **Repl****(Abs)** | **Rep2****(Abs)** | **Rep3****(Abs)** | **Rep4****(Abs)** | **Avg all Reps (Abs)** | **S/CO\*** | **Interpretation** |
| 66 | MZ | 194DGG | 01/28/10 | 0.036 | 1.709 | 0.283 | 0.648 | 0.767 |  |  | 0.708 | 2.50 | **Reactive** |
| 69 | NC | 278DGG | 07/15/10 | 0.031 | 1.393 | 0.279 | 0.766 | 0.488 |  |  | 0.627 | 2.25 | **Reactive** |

\* S/CO: Average Absorbance / Assay Cutoff