5.0 HET-CAM TEST METHOD DATA AND RESULTS

5.1 Description of the HET-CAM Test Method Protocols Used To Generate Data

As noted in **Section 3.1**, 12 published reports contained sufficient data on which to conduct an analysis of HET-CAM test method accuracy. These reports are: CEC (1991), Gettings et al. (1991, 1994, 1996), Bagley et al. (1992), Vinardell and Macián (1994), Balls et al. (1995), Kojima et al. (1995), Gilleron et al. (1996, 1997), Spielmann et al. (1996), and Hagino et al. (1999).

The HET-CAM protocols used by these investigators are similar to each other, with a few exceptions (see **Appendix B1** for a comparative summary of test method components). Fertilized hen's eggs were incubated using conditions established by the investigator. A portion of the eggshell was removed and the CAM exposed. Then, the test substance was applied to the CAM surface. After a predetermined exposure period, the test substance was rinsed from the CAM. Irritant effects in the CAM blood vessels and albumen were subjectively assessed and either the times to the development of irritant endpoints were determined or the severity of the irritant endpoints was scored at predetermined time intervals.

Examples of some of the test method components that differed among the HET-CAM protocols used to generate data used in the accuracy analysis of **Section 6.0** include:

- Relative humidity during egg incubation ranged from 52.5 to 62.5%.
- Volume or quantity of the test substance applied to the CAM (when reported) was either 0.1 or 0.3 mL for liquids and 0.3 g for solids.
- Number of replicate eggs per test substance ranged from three to six.
- Some studies included concurrent positive control substances, while others did not.

The extent to which the differences among the various protocols impact on HET-CAM study results and the classification of a test substance as an ocular corrosive or severe irritant is unknown.

5.2 Availability of Copies of Original Data Used to Evaluate the Accuracy and Reliability

NICEATM staff made attempts to obtain original HET-CAM data for substances that also had been tested *in vivo* using the standard rabbit eye test. An *FR* notice (Vol. 69. No. 57, pp. 13589-12861; available at http://iccvam.niehs.nih.gov/methods/eyeirrit.htm), requesting original HET-CAM (and comparative *in vivo* rabbit) data was published on March 24, 2004. A second request for original HET-CAM (and comparative *in vivo* rabbit) was published on February 28, 2005 (Vol. 69, No. 38, pp. 9661-9662). In addition, NICEATM staff contacted authors of selected published HET-CAM studies to request the original HET-CAM data. In response to these efforts, the following *in vitro* data were obtained:

- Summaries of HET-CAM results (e.g., Q-Scores) were obtained for the 60 substances evaluated by Balls et al. (1995) from European Centre for the

Validation of Alternative Methods (ECVAM). The summary data included the substance name and the average HET-CAM score for the substance.

- *In vitro* data for the substances evaluated in Spielmann et al. (1996) were obtained from Drs. H. Spielmann and M. Liebsch. The data provided included the overall HET-CAM scores obtained by each laboratory for each substance evaluated. *In vitro* data for two control substances also were provided.
- Drs. Philippe Vanparys and Freddy Van Goethem provided individual endpoint scores for each egg evaluated for substances described in Gilleron et al. (1996, 1997). *In vitro* data for four control substances also were provided.

5.3 Description of the Statistical Approaches Used to Evaluate the Resulting Data

As described in **Section 2.0**, the approach used to analyze HET-CAM study data varied and depended on the method used to collect the data. For test method protocols that evaluated the time to development of endpoints (i.e., hemorrhage, lysis, coagulation) which are correlated with ocular corrosivity or irritation (**Section 2.2.9.1**), an IS, Q-Score, or mtc value was calculated. For test method protocols that evaluated the severity of the toxic response (**Section 2.2.9.3**), an S-Score was calculated. For test method protocols that evaluated the lowest test substance concentration needed to produce a minimal response on the CAM (**Section 2.2.9.2**), the ITC was determined. The ITC was typically combined with the IS for the test substance to evaluate ocular irritation or corrosivity potential of a substance.

The focus of the accuracy analysis in this BRD is on the ability of the HET-CAM test method to identify ocular corrosives or severe irritants, as defined by the GHS, EPA, and EU classification systems (EPA 1996; EU 2001; UN 2003). However, because of variations between *in vitro* analysis methods and the historical HET-CAM classification systems developed there were some retrospective evaluations that needed to be conducted. For example, no single irritancy classification scheme for distinguishing between nonirritants and various classes of irritants has been applied to *in vitro* HET-CAM data. Depending on the type of *in vitro* data collected and the method used to analyze the data, various irritation classification schemes have been developed. Even when HET-CAM data were evaluated using a common approach (e.g., IS), investigators used different decision criteria for classifying test substances as nonirritants or irritants.

Furthermore, most of the irritancy classification schemes used by the *in vitro* studies were not developed to meet the needs of the ocular irritation classification schemes currently used by the U.S. (EPA 1996), the EU (EU 2001), or the GHS (UN 2003). Therefore, substances classified based on *in vitro* data were usually defined as "severe irritant" or "mild irritant." These substances were not typically classified, based on *in vitro* data, according to the categories of the GHS (UN 2003), EPA (1996), or EU (2001) classification systems (e.g., Category 1 for the GHS classification system, Category I for the EPA classification system, or R41 for the EU classification system). It is noted that there have been attempts by some investigators (Gettings et al. 1991, 1994, and 1996; Spielmann et al. 1996) to correlate HET-CAM scores with the ocular irritation classification scheme described by the FHSA

classification system (CPSC 1988) and by the EU classification system (EU 1992), respectively (see **Section 2.2.13**).

To evaluate the ability of HET-CAM to identify ocular corrosives and severe irritants, as defined by the EPA (1996), GHS (UN 2003), and EU (2001) classification systems, HET-CAM results obtained using each of the four different analysis methods were assigned an ocular irritancy classification based on the *in vitro* classification system most commonly used for that particular data analysis method. Thus, substances were classified in categories, based on the *in vitro* score, ranging from nonirritant to severe irritant. EU classifications were assigned, based on the *in vitro* results, for the substances tested in Spielmann et al. (1996). These investigator assigned classifications then were used in evaluating the ability of HET-CAM to identify ocular corrosives and severe irritants as defined by the EU classification system (EU 1992).

For some of the studies evaluated, the HET-CAM results for different testing laboratories were available (Balls et al. 1995; Spielmann et al. 1996; Hagino et al. 1999). In these cases, an overall "consensus classification call" was made for each multiply tested substance. The result of each testing laboratory (e.g., IS value) was converted to the corresponding irritation classification. The classification obtained by a majority of the testing laboratories was used to develop a "consensus classification call." In those cases where the same number of testing laboratories had different results, the more severe result was used for the overall classification call (e.g., if two testing laboratories classified a substance as a moderate irritant and two testing laboratories classified the same substance as a severe irritant; the overall classification call was severe irritant).

Some investigators (e.g., Gettings et al. 1996) classified the ocular irritancy potential of test substances using two or more different analysis methods. In such cases, these data were reclassified according to the approach used most commonly for each *in vitro* classification scheme and an accuracy assessment was conducted for each analysis method.

5.3.1 IS

5.3.1.1 *IS Analysis Method*

For those test method protocols that assigned a score to each of the endpoints evaluated at preset time intervals, the values assigned to each endpoint were totaled to give an IS value for the test substance (i.e., IS[A] analysis method). The possible IS values range from 0 (for test substances that do not induce development of any of the toxic endpoints of interest over the range of time intervals) to 21 (for test substances that induced development of all three toxic endpoints within 30 seconds of application of the test substance) (Luepke 1985).

For those test method protocols that noted the time that a specific endpoint was first observed, the IS value was calculated (i.e., IS[B] analysis method) using the formula (Kalweit et al. 1987, 1990):

$$\left(\left(\frac{(301 - \textit{Hemorrhage time})}{300}\right) \times 5\right) + \left(\left(\frac{(301 - \textit{Lysis time})}{300}\right) \times 7\right) + \left(\left(\frac{(301 - \textit{Coagulation time})}{300}\right) \times 9\right)$$

where:

Hemorrhage time = time (in seconds) of the first appearance of blood hemorrhages
Lysis time = time (in seconds) of the first appearance of vessel lysis
Coagulation time = time (in seconds) of the first appearance of protein coagulation

The IS value, when calculated using this formula, has a maximal value of 21.

When the development of hyperemia, injection, or another toxic endpoint was evaluated instead of vessel lysis, the time to first appearance for the alternative endpoint replaced the lysis time point.

5.3.1.2 *IS Classification Scheme*
For studies that used the analysis methods developed by Luepke (1985) or Kalweit et al. (1987, 1990), the ocular irritancy classification scheme described in **Table 5-1** was used for the accuracy analysis presented in this BRD (see **Section 6.0**). Therefore, substances with an IS(A) or IS(B) value of nine or greater were classified as severe irritants for the purposes of this analysis. The rationale for the decision criteria used in this classification scheme were not provided and the correlation of these categories to irritancy categories described by the EPA (1996), GHS (UN 2003), and EU (2001) classification systems is unknown.

Table 5-1 IS Classification Scheme Used to Classify Substances For Accuracy Analysis[1]

HET-CAM Score Range	Irritation Category
0 to 0.9	Nonirritant
1 to 4.9	Slight Irritation
5 to 8.9	Moderate Irritation
9 to 21	Severe Irritation

[1]According to Luepke (1985) and Kalweit et al. (1987, 1990).

5.3.2 Q-Score
5.3.2.1 *Q-Score Analysis Method*
To determine the Q-Score, the irritation potential of both the test substance and a reference substance are evaluated. The irritation potential could be determined using any approach, but typically was expressed as an IS value. The IS value of the test substance was then compared to the IS value of the reference standard to calculate a ratio, which was then used to assess the irritation potential of the test substance.

5.3.2.2 *Q-Score Classification Scheme*
The study that used Q-Scores to classify the ocular irritation potential of test substances used the classification scheme of Balls et al. (1995) (see **Table 5-2**). This classification scheme was used in the BRD; substances with a Q-Score of at least 2 were classified as a severe irritant. The rationale for the decision criteria used in this classification scheme were not provided and the correlation of these categories to irritancy categories described by the EPA (1996), GHS (UN 2003), and EU (2001) classification systems is unknown.

Table 5-2 Q-Score Classification Scheme Used to Classify Substances For Accuracy Analysis[1]

Q-Score	Irritation Category
< 1.5	Nonirritant
1.5 ≤ Q < 2	Moderate
≥ 2	Severe

[1]Classification scheme according to Balls et al. (1995)

5.3.3 mtc10

5.3.3.1 *mtc10 Analysis Method*

To determine the mtc10, the mean detection time for the appearance of the coagulation endpoint when using a 10% solution was evaluated. The mean is calculated over the total number of replicate eggs used for each experiment.

5.3.3.2 *mtc10 Classification Scheme*

Two different cut-off values were used to classify a substance as a severe irritant. Linear discriminant analysis was performed, assuming equal *a priori* probabilities. With this linear model, a value of 174 seconds (for 142 chemicals) and 139 seconds (for 189 chemicals) was calculated to separate the severe substances (i.e., R41 chemicals) from the nonsevere substances (**Table 5-3**). For the accuracy analyses described in **Section 6.0** of the BRD, two evaluations are provided. Substances with an mtc value less than 174 seconds and 139 seconds were classified as severe irritants (R41). The classification scheme was developed for the EU classification system (EU 1992).

Table 5-3 mtc10 Classification Scheme Used to Classify Substances For Accuracy Analysis[1]

mtc10 (Range 1)	mtc10 (Range 2)	Irritation Category
< 174 seconds	< 139 seconds	R41
≥ 174 seconds	≥ 139 seconds	Remainder

[1]From Spielmann et al. (1996).

5.3.4 IS and ITC

5.3.4.1 *IS and ITC Analysis Method*

This analysis method combines two different parameters to determine the irritancy potential of a test substance. The IS value is determined for each test substance at a 10% concentration and the ITC is defined as the lowest concentration producing a slight or weak response on the CAM after application of the test substance.

5.3.4.2 *IS and ITC Classification Scheme*

For the accuracy analysis, substances with (a) an ITC value less than 1%, or (b) an ITC value between 1% and 2.5% and an IS value of at least 16 were classified as severe irritants (R41) (**Table 5-4**).

Table 5-4 IS and ITC Classification Scheme Used to Classify Substances for Accuracy Analysis[1]

ITC (% Concentration)	IS Value (10% Concentration)	EU Irritation Category[2]
> 10%	< 16	None/slight (Nonirritant)
> 10%	> 16	Moderate (Nonirritant)
< 10%	< 16	Moderate (Nonirritant)
< 10%	> 16	Irritant (R36)
< 2.5%	< 16	Irritant (R36)
1% < ITC ≤ 2.5%	≥ 16	Severe (R41)
≤ 1%		Severe (R41)

[1]According to Spielmann et al. (1996)
[2]EU (1992)

5.3.5 S-Score

5.3.5.1 *S-Score Analysis Method*

This score represents the highest total score for any endpoint evaluated for a test substance. The severity scores assigned for each endpoint (which range from 0 to 3 and are assigned at a single user-defined time point after treatment) are totaled across the replicate eggs evaluated per test substance to produce a total score for each irritation endpoint (i.e., three total scores). The toxic endpoint that yields the highest score is the S-Score for the test substance. Many of the test method protocols that evaluated the irritation potential of test substances using this method of analysis advocated the use of six eggs per test substance. In such situations, the maximal S-Score is 18.

5.3.5.2 *S-Score Classification Scheme*

Substances with an S-Score of at least 15 were classified as a severe irritant for the analysis described in the BRD (see **Table 5-5**). The rationale for the decision criteria used in this classification scheme were not provided and the correlation of these categories to irritancy categories described by the EPA (1996), GHS (UN 2003), and EU (2001) classification systems is unknown.

Table 5-5 S-Score Classification Scheme Used to Classify Substances For Accuracy Analysis[1]

S-Score	Irritation Category
< 6	Nonirritant
6 ≤ S < 15	Moderate
≥ 15	Severe

[1]Classification scheme according to Balls et al. (1995); based on six replicate eggs per test substance.

5.4 Summary of Results

A total of 260 test substances were evaluated in 383 HET-CAM studies. A summary of results used to evaluate test method accuracy is shown in **Appendix C.** This table, sorted by reference, provides the CASRN, the concentration tested, the calculated *in vitro* score, the *in vitro* irritation classification of the test substance (based on the irritation classification schemes in **Section 5.3**), and the literature source. Other supporting information, such as purity of the test substance, was included in the table to the extent that this information was available.

5.4.1 CEC (1991)

In vitro data for 15 substances evaluated in 26 studies were extracted. The substances were evaluated in up to seven laboratories. IS(B) values, calculated using the mathematical model developed by Kalweit et al. (1987), were presented in the report. Each tested substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. EU irritancy classifications, based on *in vivo* studies and results, were available for these substances. Therefore, accuracy of the *in vitro* results could only be compared to the EU classification system.

5.4.2 Gettings et al. (1991)

In the CTFA Evaluation of Alternatives Program – Phase I, ten hydroalcoholic formulations were evaluated in one laboratory. Mean IS(B) values, calculated using the mathematical model developed by Kalweit et al. (1987), were presented in the report for nine of the formulations. Each formulation was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for these formulations were obtained from the FDA and the CTFA, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

The report also described an *in vitro* analysis approach developed by Bartnik et al. (1987). The Bartnik et al. approach was not used in the accuracy analysis conducted in this BRD since the quantitative aspects of this model were not available. However, the study authors' conclusions regarding the accuracy of the HET-CAM test method using the Bartnik et al. (1987) analysis method are addressed in **Section 9.0**.

5.4.3 Gettings et al. (1994)

In the CTFA Evaluation of Alternatives Program – Phase II, 18 oil/water formulations were evaluated in one laboratory. Mean IS(A) and IS(B) values, calculated using the mathematical models developed by Leupke (1985) and Kalweit et al. (1987), respectively, were presented. Each formulation was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for these formulations were obtained from the CTFA, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

5.4.4 Gettings et al. (1996)

In the CTFA Evaluation of Alternatives Program – Phase III, 25 surfactant-based personal care cleansing formulations were evaluated in one laboratory. Mean IS(A) and IS(B) values,

calculated using the mathematical models developed by Leupke (1985) and Kalweit et al. (1987), respectively, were presented. Each formulation was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for these formulations were obtained from the CTFA, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

The report also described an *in vitro* analysis approach where the IS value was divided by the ITC to yield a ratio that was used to describe the irritation potential of the test substance. This approach was not used in the accuracy analysis conducted in this BRD since the quantitative aspects of this *in vitro* model were not available. However, the study authors' conclusions regarding the accuracy of the HET-CAM test method using this analysis approach are addressed in **Section 9.0**.

5.4.5 Bagley et al. (1992)

In vitro data for two substances were extracted from this report. The mean IS(A) values, calculated using the mathematical model described by Luepke (1985), were provided in the study report. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for this evaluation were obtained from published literature, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

Although HET-CAM data also were reported for seven additional chemicals and 20 consumer product formulations in this publication, detailed *in vivo* reference data were not available for these substances. Therefore, the HET-CAM data for these substances are not included in this analysis. The study authors' conclusions regarding the accuracy of the HET-CAM test method for these substances are addressed in **Section 9.0**.

5.4.6 Vinardell and Macián (1994)

In vitro data for two test chemicals were extracted from this report. The mean IS(A) values, calculated using the mathematical model described by Luepke (1985), were provided in the study report. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for this evaluation were obtained from published literature, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

Although HET-CAM data also were reported in this publication for two additional chemicals and six consumer product formulations, detailed *in vivo* reference data were not available for these substances. Therefore, the HET-CAM data for these substances are not included in this analysis. The study authors' conclusions regarding the accuracy of the HET-CAM test method for these substances are addressed in **Section 9.0**.

5.4.7 Balls et al. (1995)

In this evaluation of the HET-CAM test method, 52 test substances were evaluated in two to four laboratories. Four of these substances were tested at two different concentrations and two were tested at three concentrations, for a total of 60 different tests. The Q-Score and the S-Score were obtained for each substance in each laboratory. Tested substances were

classified based on the *in vitro* classification system described in **Section 5.3.2** and **Section 5.3.3**. Detailed *in vivo* data for the 60 studies were obtained from ECETOC (1998), allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

5.4.8 Kojima et al. (1995)

In vitro data were extracted for five test substances. The mean IS(A) values, calculated using the mathematical model described by Luepke (1985), were provided in the study report. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. Comparative *in vivo* data for this evaluation were obtained from published literature, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

Although HET-CAM data also were reported for 18 other substances, detailed *in vivo* reference data were not available for these substances, precluding their use in an analysis of accuracy. However, the study authors' conclusions regarding the accuracy of the HET-CAM test method for these substances are addressed in **Section 9.0**.

5.4.9 Gilleron et al. (1996)

In this evaluation of the HET-CAM test method, 46 substances were evaluated in a single laboratory. Average HET-CAM IS(B) values, calculated using the mathematical model described by Kalweit et al. (1987), were provided in the report and individual endpoint scores for each egg evaluated for a substance were obtained. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. EU irritancy classifications, based on *in vivo* studies and results, were available for these substances. Therefore, accuracy of the *in vitro* results could only be compared to the EU classification system.

5.4.10 Spielmann et al. (1996)

In the publication, two different analysis methods were presented. As mentioned in **Section 3.3.1**, the IS and ITC and the mtc10 evaluation were evaluated. Each substance was classified based on the appropriate *in vitro* classification system provided in Spielmann et al. (1996). EU irritancy classification, based on *in vivo* studies and results, were provided in the paper. The results of the accuracy analyses for these analysis methods are presented in **Section 6.0**.

In addition to the above two analysis methods, an additional analysis was conducted using the data available from this report and obtained from the study authors. For this additional analysis, IS(B) values for 112 substances that were evaluated in two to three laboratories were classified based on the *in vitro* classification system described in **Section 5.3.1**. The IS(B) values were calculated using the mathematical model described by Kalweit et al. (1987). Detailed *in vivo* data for the test substances were provided, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

5.4.11 Gilleron et al. (1997)

In this evaluation of the HET-CAM test method, 52 substances were evaluated and compared to 60 different *in vivo* studies. Average HET-CAM IS(B) values, calculated using the mathematical model described by Kalweit et al. (1987), were provided in the report and individual endpoint scores for each egg evaluated for a substance were obtained. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. Detailed *in vivo* data for the substances were obtained from ECETOC (1998), allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

5.4.12 Hagino et al. (1999)

In this evaluation of the HET-CAM test method, 14 substances were evaluated in five laboratories. Three of these substances were tested at two different concentrations, for a total of 17 different tests. Average HET-CAM IS(A) values, calculated using the mathematical model described in Luepke (1985), from each testing laboratory and the overall average HET-CAM IS(A) from all the testing laboratories were provided in the report. Each substance was classified based on the *in vitro* classification system described in **Section 5.3.1**. Detailed *in vivo* data for the test substances (including the different concentrations tested) were provided, allowing for an accuracy assessment compared to the EPA (1996), GHS (UN 2003), and EU (2001) classification systems.

5.5 Use of Coded Chemicals and Compliance with GLP Guidelines

Ideally, coded chemicals should be used in all validation studies and all data supporting the validity of a test method should be obtained and reported in accordance with GLP guidelines (OECD 1998; EPA 2003a, 2003b; FDA 2003). Data quality was evaluated by a review of the methods section in literature references and the submitted reports. Thus, data quality can be evaluated only to the extent this information was provided in the published reports. Based on the available information, the reports that were identified as following GLP guidelines or used data obtained according to GLP guidelines were Gettings et al. (1991, 1994, 1996), Balls et al. (1995), Spielmann et al. (1996), and Hagino et al. (1999). Furthermore, based on the available information, the reports that identified using coded chemicals were Gettings et al. (1991, 1994, 1996), Balls et al. (1995), Spielmann et al. (1996), and Hagino et al. (1999). Detailed information on coding procedures used in different studies is provided in **Section 3.4**.

5.6 Lot-to-lot Consistency of Test Substances

Ideally, a single lot of each substance would be used during the validation of a test method. In situations where multiple lots of the same chemical must be used, then lot-to-lot consistency of test substances needs to be evaluated to ensure that the same substance is being evaluated over the duration of the study. The procedures used in evaluating lot-to-lot consistency were evaluated by what was described in the published reports. No attempt was made to review original records to assess the procedures used to evaluate different batches of tested substances.

Gettings et al. (1991, 1994, 1996) noted that all substances were dispensed from a single source to ensure test substance consistency. The substances were placed in a secondary container, labeled with appropriate chemical code information, and then provided to the participating testing laboratories. No information was provided in the report about the time frame in which the studies were conducted, or whether more than one lot of a substance was tested.

Balls et al. (1995) noted that substances with the same source and specification as those tested *in vivo* were obtained, whenever possible, to test *in vitro*. When this was not possible, samples of substances with specifications as close as possible to what was evaluated *in vivo* were obtained. Aliquots of each test substance were prepared at one time and provided to the participating testing laboratories. No information was provided in the report about the time frame in which the studies were conducted or whether additional aliquots of the samples were provided to specific testing laboratories.

No information was provided in any of the remaining reports about maintaining lot-to-lot consistency.

5.7 Availability of Data for External Audit

Availability of original study data, for the reports considered in the accuracy and reliability analysis, for an external audit has not been determined.

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