Evaluation of Statistical Methods for Estimating Shelf Life of Drug Products: A Unified and Risk-Based Approach

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ABSTRACT
Shelf life of a drug product is often determined based on a confidence interval approach recommended in the ICH Q1E. Several alternative methods such as prediction and tolerance intervals have been proposed in literature, aiming at providing greater product quality assurance. Some researchers even suggested that regulatory authorities adopt the new methods. However, because of lack of a common framework, the risk and benefit of the alternative methods has never been carefully studied and quantified. Nor has there been any consensus among researchers and regulators regarding which method is more appropriate to use. The authors propose a unified risk-based approach for evaluations of the existing methodologies in the same statistical context. Our investigation indicates that, although conceptually appealing, neither prediction nor tolerance approach renders a reasonable balance between consumer and producer's risk and is practically unsuitable for shelf-life estimation. Our evaluation also shows that high quality assurance can be achieved through improvement of manufacturing process and analytical assays used for stability testing based on quality-by-design (QbD) principles.

INTRODUCTION
For all marketed pharmaceutical products, the US Food and Drug Administration requires that an expiration dating or “shelf life” be determined and indicated on the immediate container label. The shelf life of a drug product is the time period during which the average characteristics such as identity, potency, and purity of the drug product remain within their respective specifications (1). Because shelf life is often unknown, it is estimated through a well-designed stability study in which the degradation of the drug is evaluated through various analytical methods. In the literature, the average drug characteristic is usually described using a linear regression model (2). When the degradation curve appears to be non-linear, the data might be linearized through a proper transformation. ICH Q1E recommends that the shelf life be estimated as the time point at which the lower limit of the one-sided 95% confidence interval (CI) for the mean predicted value intersects with the approved lower specification (3). As shown by Shao and Chow, such a method leads to an estimated shelf life that is the lower 95% confidence bound of the theoretical mean shelf life (2). It is a conservative estimate, intended to provide consumers with 95% confidence that the estimated (labeled) shelf life is smaller than the theoretical mean shelf life.

Recently, manufacturers of pharmaceutical products are facing increasing regulatory pressure to develop robust and reliable manufacturing processes using risk-based approach, technological advances,
and modern quality management techniques so as to warrant quality of finished products. As shelf life is a quality attribute that may impact drug safety and efficacy, understanding and quantifying the level of quality assurance a shelf life provides to the product is of great importance. The confidence interval method recommend in ICH Q1E only provides quality assurance for the mean of all units in a batch to remain within specification limits (4, 5). It does not address the stability of individual units. Therefore, it might not adequately protect consumer’s risk. As a remedy, the prediction interval (PI) is suggested for shelf-life estimation, in lieu of the confidence interval, to warrant that with 95% confidence at any time before the expiration dating a unit from the batch would meet specifications (4, 5). Although the prediction interval is more conservative than the confidence interval, it might not fully address the issue regarding quality assurance of all units of the batch as a whole. For example, for m units randomly chosen from the batch, the probability for at least one unit to be out of specification at the shelf life determined using one-sided 95% PI is 1-(0.95)m. When m ≥ 5, this probability is greater than 22%, which may represent a risk unacceptable to drug recipients. To overcome the issues of the ICH-recommended approach and prediction interval method, several researchers proposed to determine the shelf life based on tolerance interval (TI) (6, 7). This method guarantees that at the time of expiration with a pre-specified level of confidence, say, 95%, a fixed percent of units from a batch (e.g., 95%) have potency values exceeding the lower specification limit. Because determining shelf life using the new approaches results in much greater protection to consumers, some researchers suggest that regulatory authorities adopt the alternative methods (6).

Although the prediction and tolerance interval approaches are conceptually appealing, seemingly rendering greater chance to ensure product quality, there has not been any attempt to quantify the risk and benefit of the three methods. This is primarily due to lack of a common framework, as the three methods deal with shelf-life estimation from completely different perspectives. In this paper, the authors demonstrate that the confidence and prediction interval methods are special cases of the tolerance interval approach. With such characterization of the three intervals, quality assurance provided by the three methods within the same statistical context can be quantified and compared. The evaluation is conducted through both theoretical arguments and a simulation study. It is shown that the gain in quality assurance warranted by the prediction and tolerance interval approaches can only be achieved at costly expense of the producer. For example, for an overall process and analytical variability as small as 5%, shelf lives determined from the PI and TI methods are 46% and 74% shorter than that obtained from ICH-recommended approach. For certain drug products, such drastic shortening of shelf life makes commercialization of the products extremely difficult if not completely impossible. Thus the PI and TI methods are unsuitable for practical use, as they do not maintain an acceptable balance between consumer and producer’s risk. Our investigation further suggests that high quality assurance can be achieved through improvement of manufacturing process and analytical assays used for stability testing based on the QbD principles in ICH Q8 (8).

All theoretical results and proofs are given in the Appendix.

### SHELF-LIFE ESTIMATION

This section introduces a basic regression model and discusses the three interval methods for shelf-life estimation and their relationships from a unified perspective.

#### The Model

Throughout the article, we assume the following linear model is used for describing the relationship between the stability characteristic y_i and time x_i, i = 1,...,n:

$$\gamma_i = \alpha + \beta x_i + \epsilon_i$$  \hspace{1cm} \text{(Model 1)}

where \(\alpha\) and \(\beta\) are the intercept and slope parameters, and \(\epsilon_i\) are measurement errors that are assumed to be independently and identically distributed according to a normal distribution N(0, \(\sigma^2\)). Without loss of generality, we suppose \(y_i\) is the potency value determined by an analytical assay at time point \(x_i\).

#### Three Interval Approaches

Under model 1, the average potency at time \(x\) is \(\alpha + \beta x\). Based on stability data \((x_i, y_i)\), the unknown parameters \(\alpha\) and \(\beta\) can be estimated and the one-sided 95% confidence band, shown as blue dotted line in Figure 1, of \(\alpha + \beta x\) constructed. Let \(\delta_{\alpha\beta}\) be the shelf-life estimator based on the ICH-recommended one-sided confidence interval method. Then it is the time at which the 95% confidence band intercepts the lower specification limit assumed to be 90 (see Figure 1). A one-sided 95% prediction band for the individual potency measurement of a randomly selected unit from a batch can also
be constructed and is shown as the solid orange line in Figure 1. At time \( x \), such prediction band warrants with 95% confidence that the individual potency \( y \) is above the band. Using \( \delta_{PI} \) to denote the shelf life defined as the time point at which the 95% prediction band intercepts the lower specification limit, it can be inferred that the potency of any randomly selected unit of a batch would be above the lower specification limit with 95% confidence. Lastly, let \( \delta_{TI} \) be the shelf life estimated to the time at which the one-sided 95% tolerance band (see the dashed orange line in Figure 1) intercepts the lower specification limit. Assuming the tolerance band covers 100\( \zeta \)% of the distribution of potency values of all units, it is guaranteed that at the end of shelf life \( \delta_{TI} \), 100\( \zeta \)% of units of a batch would be above the lower specification with 95% confidence. Formal mathematical constructs of the three intervals and their corresponding shelf-life estimates are given in the Appendix.

Relationship Among Three Interval Approaches
Based on the definitions of confidence and prediction intervals in the previous session, we can demonstrate that a prediction interval of the potency of a unit from a batch at time \( x \) can be expressed as a confidence interval of the mean observations of all units of the batch at the same time point \( x \). The mathematical formulation of the above statement and proof is provided in the Appendix. We can further prove that confidence interval of the mean observations can be expressed as a tolerance interval with either a pre-specified content or confidence level. A proof of this statement is also relegated to the Appendix. As a result, both confidence and prediction intervals are special cases of tolerance interval, guaranteeing that with certain level of confidence a fixed percent of all units are within specification before expiration date. The question of interest is how much quality assurance each of the three methods provides when used to determine product shelf life.

COMPARISONS OF INTERVAL METHODS
This section evaluates the risk and benefit of the methods.

Method of Comparison
In the previous section, the authors provide a unified perspective of shelf-life estimation based on confidence, prediction, and tolerance intervals. Specifically both confidence and prediction approaches can be viewed as special cases of tolerance interval method.

The authors define quality assurance of the product as the percent of units of a batch remaining within specification at the end of the shelf life. Such percent is hereafter referred to as content. It is often of interest to estimate the contents of three intervals at their respective shelf lives. Theoretically, it can be shown that the one-sided 95% confidence interval is a one-sided 95% tolerance interval that has a content of 50% and that the one-sided 95% prediction interval is a one-sided 95% tolerance interval that has a content no less than 50% (see Corollaries 1 and 2 in the Appendix). In the following, we empirically estimate the contents of the three intervals. Data are simulated from Model 1 in Section 2.1, using the stability design suggested in ICH Q1E, namely \( x_1 = 0, 3, 6, 9, 12, 18, \) and 24 months, with three replicates at each \( x \). The model parameter \( \alpha, \beta \) and the lower specification limit \( \eta \) are chosen to be 105, -0.5, and 90, respectively, same as the parameters used in the simulation by Shao and Chow (2). Four values (0.01, 0.5, 2.0 and 5.0) are used for the variability parameter \( \sigma \) to simulate the scenarios that the variability of the production process and assay is extremely low, very low, low, and moderate, respectively.

Results of Comparisons
The simulated data are fit to Model 1 to give rise to estimates of model parameters. Both contents and
shelf lives of the three intervals are estimated. The results are presented in Table I. It is shown that the 95% confidence interval covers a content of 50%. The content covered by the 95% prediction interval is over 81%, increasing as the overall variability increases. The content of the 95% tolerance interval remains 95% regardless of the variability. Overall the PI covers 31% or more content than CI does, and TI covers 45% more content than CI, resulting in marked gains in quality assurance to consumers.

When the variability is extremely low ($\sigma = 0.01$), all three methods give rise to the same shelf life of 30.1 months. However, the shelf lives based on prediction and tolerance interval decrease drastically when variability increases. For example, for the moderate variability, $\sigma = 5$, which corresponds to 5% total CV as the target potency is 100, the estimated shelf lives based on prediction and tolerance interval are 12.7 and 6.1 months, respectively, compared to 23.5 months based on the confidence interval approach. They represent 46% and 74% reduction in shelf life.

### DISCUSSIONS

The risk and benefit assessment conducted in the previous session indicates that the prediction and tolerance interval approaches lean overly towards protecting consumer risk. Even for a very moderate total process and assay variability of 5% CV, the producer would end up with an unreasonably shortened shelf life of either 12.7 or 6.1 months if PI or TI were to be used for shelf-life estimation. A six-month shelf life would make many drug products commercially not viable, giving manufacturers little incentive to commercialize the products. The investigation also shows that difference in shelf life between PI and CI or TI and CI is marginal when the process and analytical variability is extremely or very low. This implies that by carefully controlling manufacturing process to ensure product uniformity and improving precision of assays for stability testing, both desired shelf life and level of protection to the consumer’s risk can be achieved.

Ever since the publication of the current good manufacturing practices (cGMP) guidelines by the US Food and Drug Administration in 2002, pharmaceutical companies have strived to adopt risk-based approaches and modern quality management techniques to design, analyze, and control manufacturing processes and products with the goal of ensuring final product quality. Understanding the targeted and actual drug stability profiles, process, and assay variability early on in the process allows the manufacturer to minimize the risk that the final product would not have the desired shelf life to make it viable. Quality of product should be built in by design as opposed to testing at the end of process or product development or applying more stringent acceptance criteria such as 95% percent of units from a batch having potency values above the lower specification limit at the time of batch expiration.

### CONCLUSIONS

There are primarily three interval approaches to shelf-life estimation. A unified framework is developed to allow for quantification of risk and benefit of the methods. Results of the evaluation suggest that neither PI nor TI is suitable for being adopted as the standard method for shelf-life estimation. The ICH-recommended confidence interval approach results in a shelf life that maintains a necessary balance between consumer and producer risk. Key to assurance of product quality is the understanding of manufacturing process, analytical methods for stability testing, and controlling various sources of variations. This can be achieved through adaptation of the new risk-based approaches for the development of process, product, and analytical method as advocated in the cGMP and ICH Q8–Q11 guidelines (8-11).

### Table I: Contents covered by confidence and prediction intervals with 95% confidence.

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>$\sigma$</th>
<th>95% CI</th>
<th>95% PI</th>
<th>95% TI</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>Shelf life</td>
<td>Content</td>
<td>Shelf life</td>
</tr>
<tr>
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<td>0.01</td>
<td>30.1</td>
<td>50.0%</td>
<td>30.1</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td>29.0</td>
<td>50.0%</td>
<td>29.6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>26.7</td>
<td>50.0%</td>
<td>22.8</td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td>23.5</td>
<td>50.0%</td>
<td>12.7</td>
</tr>
</tbody>
</table>
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APPENDIX
THEORETICAL RESULTS AND PROOFS

A1. Definitions of Confidence, Prediction, and Tolerance Interval Approaches

Shelf life based on confidence interval. Let \( (\hat{x}, \hat{\beta}, \hat{\gamma}) \) be the least square estimators of \( (x, \beta, \gamma) \) based on Model 1. The one-sided 95% lower confidence limit for the mean potency value of \( y \) at time \( x \), \( \hat{x} + \hat{\beta} x \), is given by

\[
\hat{x} + \hat{\beta} x - \hat{\gamma} t_{n-2} (0.05) \sqrt{\frac{1}{n} + \frac{(x - \bar{x})^2}{S_{xx}}}
\]

[Equation A1]

where \( t_{n-2} \) is the 95th percentile of the t-distribution with \( n-2 \) degrees of freedom,

\[
\bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i \quad \text{and} \quad S_{xx} = \sum_{i=1}^{n} (x_i - \bar{x})^2.
\]

[Equation A2]

Let \( \hat{\theta}_Q \) be the shelf-life estimator based on the ICH-recommended one-sided confidence interval method. Then it is a root of the following Equation A3 with respect to \( x \),

\[
\hat{\theta}_Q = \hat{x} + \hat{\beta} x - \hat{\gamma} t_{n-2} (0.05) \sqrt{\frac{1}{n} + \frac{(x - \bar{x})^2}{S_{xx}}}
\]

[Equation A3]

Shelf life based on prediction interval. Defined as the time point at which the lower limit of one-sided 95% prediction confidence interval of the potency of a unit intersects with the lower specification, the shelf-life estimator \( \hat{\theta}_P \) is a solution to the Equation A4:

\[
\eta = \hat{x} + \hat{\beta} x - \hat{\gamma} t_{n-2} (0.05) \sqrt{1 + \frac{1}{n} + \frac{(x - \bar{x})^2}{S_{xx}}}
\]

[Equation A4]

Shelf life based on tolerance interval. Let \( \gamma \) be the percent of units meeting quality standards and confidence level or probability for the aforesaid to be true. Let \( \gamma^* = \alpha + \beta + x + \epsilon \) be the potency of a unit randomly selected from the batch at time \( x \) described
through Model 1. The lower tolerance limit for \( y^* \), denoted by \( g(x, \delta) \) with \( \delta = (\hat{c}, \hat{\beta}, \hat{\sigma}) \), is defined as

\[
P_e[\{y^* > g(x, \delta) | \delta \} \approx \zeta] = 1 - \gamma
\]

[Equation A5]

We define shelf life estimate \( \hat{c}_{TL} \) based on TI approach as the time point at which the lower tolerance limit \( g(x, \delta) \) intersects with the lower specification limit \( n \). That is, \( \hat{c}_{TL} \) is the solution to Equation A6,

\[
g(x, \delta) = n
\]

[Equation A6]

Therefore, the estimated shelf life \( \hat{c}_{TL} \) with probability \( (1-\gamma)100\% \), 100\% of all units exceeds the lower potency limit. The quality assurance that the estimated shelf life provides to all units in the batch is characterized by two quantities \( \zeta \) and \( 1-\gamma \).

A2. Relationship Among Confidence Limit, Prediction Limit, and Tolerance Limit

The statement that the confidence and prediction intervals can both be expressed as tolerance interval is mathematically formulated in Theorems 1 and 2. Theorem 1 states that PI can be expressed as a CI, which, in turn, can be expressed as a TI as described in Theorem 2.

First, for a given time point \( x \), we define

\[
PL(\tau) = \hat{\alpha} + \hat{\beta} x - \hat{\sigma} t_{n/2} (\tau) \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2} \sqrt{\left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]}
\]

[Equation A7]

and

\[
CL(\tau) = \hat{\alpha} + \hat{\beta} x - \hat{\sigma} t_{n/2} (\tau) \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2}
\]

[Equation A8]

That is, \( PL(\tau) \) is the lower limit of one-sided \((1-\tau)100\% \) prediction interval of \( y^* = \alpha + \beta x + \varepsilon \) \( CL(\tau) \) and is the lower limit of one-sided \((1-\tau)100\% \) confidence interval of the mean potency \( \alpha + \beta x \).

Theorem 1 (Relationship between CI and PI): There exists a \( \tau_0 < \tau \) such that \( PL(\tau) = CL(\tau_0) \), where \( \tau_0 \) is the unique solution of Equation A9.

\[
\int_{-\infty}^{t_{n/2} (\tau)} \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right] \leq \zeta \Rightarrow 1 - \gamma
\]

[Equation A9]

In other words, \( PL(\tau) \) is the lower one-sided \((1-\tau_0)100\% \) confidence limit of \( \alpha + \beta x \).

Proof: The \( PL(\tau) \) can be re-expressed as:

\[
PL(\tau) = \hat{\alpha} + \hat{\beta} x - \hat{\sigma} t_{n/2} (\tau) \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2}
\]

\[
= \hat{\alpha} + \hat{\beta} x - \hat{\sigma} \Omega \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2}
\]

where \( \Omega = t_{n/2} (\tau) \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2} \).

[Equation A10]

Because \( t_{n/2} (\gamma) \) is a monotonically continuous function varying in \((-\infty, \infty)\), there exists a unique \( \tau_0 \) such that \( t_{n/2} (\tau_0) = \Omega \). Thus

\[
PL(\tau) = \hat{\alpha} + \hat{\beta} x - \hat{\sigma} t_{n/2} (\tau_0) \left[ 1 + \frac{1}{n} \frac{(x - \bar{x})^2}{S_x} \right]^{1/2} = CL(\tau_0)
\]

[Equation A11]

Theorem 2 (Relationship between CI and TI): For a given \( \tau \) and \( y \) satisfying \( 0 < \tau, y < 1 \) there exists \( \zeta_0 \) such that \( CL(\tau) \) is a \((\zeta_0, 1-\gamma) \) lower tolerance limit of \( y^* = \alpha + \beta x + \varepsilon \) with \( \varepsilon \in \mathbb{N} (0, \sigma^2) \), where \( \zeta_0 \) is the unique solution of the equation for a given \( y \).

\[
P \left[ \left( Z_{\zeta_0} - \frac{t_{n/2} (\tau) \Delta y}{\sqrt{n-2}} \right) \leq \zeta \right] = 1 - \gamma
\]

[Equation A12]
where \( \Delta_c = \sqrt{1 + \left[ \frac{1}{\eta} + \left( \frac{\lambda}{\Delta_c} \right) \right]} \), \( U \sim \chi^2_{n-2} \), \( Z \sim \mathcal{N}(0,1) \) and \( z_\% \) is the upper 100 \( \% \) percentile of a standard normal distribution. For a given \( \tau \) and \( \% \) satisfying \( 0 < \tau, \% < 1 \) there exists \( \gamma \) such that \( CL(\tau) \) is a \( (\%, 1 - \gamma) \) lower tolerance limit of \( y^* = \alpha + \beta x + \varepsilon \) with \( \gamma \) being the unique solution of Equation A12.

Proof: Substitute \( c_L(\tau) \) for \( \alpha \) in A13, we obtain

\[
\Phi(z_\%) = \Phi(z) \leq 1 - \gamma
\]

where \( z_\% \) is the \((100\%)^{th}\) upper percentile of a standard normal distribution, \( Z \) is standard normal variable and \( U \) is a random variables following \( \chi^2 \) distribution with \( df = n-2 \). Given \( \tau \) and \( \% \), one can determine \( \gamma \). The second half of the Theorem can be similarly proved. So the 100(1 – \( \tau \))% confidence interval is equivalent to a \( (\%, 1 - \gamma) \) tolerance interval. In fact, let \( W = Z\Delta_c - \sqrt{U \left( \frac{t_{n-2}(\gamma)}{\Delta_c^2} \right)} \), the cdf of \( W \) can be determined with the following integration

\[
\Phi(W \leq w) = \int_{-\infty}^{w} \Phi\left( \frac{W - \Delta_c}{\Delta_c} \right) g(u) du
\]

where \( \Phi() \) and \( \Phi() \) are the pdf and cdf of standard normal distribution, respectively, and \( g() \) the pdf of a \( \chi^2 \) distribution with \( n - 2 \) degrees of freedom. Let \( Q_\% \) be the 100(1 – \( \gamma \))% percentile of distribution of \( W \). Then \( \gamma = 1 - \Phi(Q_\%) \). Instead of using numerical integration, we can also obtain percentile of \( W \) using a large sample from the distribution of \( W \) by sampling from \( Z \) and \( U \).

A3. A Closed-Form Expression of TI
As a by-product of the proof of Theorem 1, the lower tolerance limit \( g(x\|\beta) \) can be obtained as \( CL(\tau) \) with its confidence level \( 1 - \tau \) being a solution to Equation A12. This closed-form expression simplifies the estimation of shelf life based on TI approach.

A4. Contents of CI and PI

Corollary 1 (Content covered by CI). For a given \( \tau \) such that \( 0 < \tau < 1 \) is a \( (50\%, 1 - \tau) \) lower tolerance limit of \( y^* = \alpha + \beta x + \varepsilon \) with \( \varepsilon \sim \mathcal{N}(0,\sigma^2) \)

Proof: When \( \tau = \% \), the content \( \gamma \) is the solution of

\[
\Phi\left( \frac{Z\Delta_c - \sqrt{U \left( \frac{t_{n-2}(\%)}{\Delta_c^2} \right)}}{\Delta_c} \right) = z_\%
\]

where \( z_\% \) is the upper \((100\%)^{th}\) percentile of \( \mathcal{N}(0,\sigma^2) \), the \((100\%)^{th}\) percentile of \( \mathcal{N}(0,\sigma^2) \) and \( g() \) the density function of a \( \chi^2 \) distribution with \( df = n-2 \).

Because the function on the left hand side of the Equation A15 is strictly decreasing in \( \gamma \), recalling that \( z_\% \) is the upper \((100\%)^{th}\) percentile of \( \mathcal{N}(0,\sigma^2) \), the solution is unique. Note that

\[
\Phi\left( \frac{Z\Delta_c - \sqrt{U \left( \frac{t_{n-2}(\%)}{\Delta_c^2} \right)}}{\Delta_c} \right) = z_\%
\]

where \( \% = 0.5 \) is the unique solution.

Corollary 2 (Content covered by PI). For a given \( \tau \) such that \( 0 < \tau < 1 \), \( PL(\tau) \) is a \( (\% \% \%, 1 - \tau) \) lower tolerance limit of \( y^* = \alpha + \beta x + \varepsilon \) with \( \varepsilon \sim \mathcal{N}(0,\sigma^2) \), such that \( \% \% \% \) is greater than or equal 50% and a unique solution to

\[
\Phi\left( \frac{Z\Delta_c - \sqrt{U \left( \frac{t_{n-2}(\% \% \%)}{\Delta_c^2} \right)}}{\Delta_c} \right) = z_\%
\]

where \( \Phi() \), \( z_\% \) and \( g() \) being the cdf of the standard normal distribution, the \((100\%)^{th}\) percentile of the standard normal distribution, and the density function of a \( \chi^2 \) distribution with \( df = n-2 \), respectively.
Substituting PL(τ) for \( g(\chi, \delta) \) in
\[
P_\theta[P(Y > g(\chi, \delta) | \theta) \geq \varsigma] = 1 - y, \text{ we obtain}
\]
\[
P_\theta[P(Y > \beta + \beta x - \beta \tau \theta \omega(x)] = 1 - \tau.
\]

[Equation A18]

Following the steps in the proof of Theorem 2, equations A17 and A18 can be re-written as
\[
P\left(Z \leq \frac{\tau \delta \omega(x) + \frac{\theta \omega(x) \Delta_\omega}{\sqrt{n-2}}}{\sqrt{n-2}}\right) = 1 - \tau
\]
\[
\Rightarrow E\left(P\left(Z \leq \frac{\tau \delta \omega(x) + \frac{\theta \omega(x) \Delta_\omega}{\sqrt{n-2}}}{\sqrt{n-2}}\right) \mid \omega\right) = 1 - \tau
\]
\[
\Rightarrow E\left(P\left(Z \leq \frac{\tau \delta \omega(x) + \frac{\theta \omega(x) \Delta_\omega}{\sqrt{n-2}}}{\sqrt{n-2}}\right) \mid \omega\right) = 1 - \tau
\]
\[
\Rightarrow P\left(Z \leq \frac{\tau \delta \omega(x) + \frac{\theta \omega(x) \Delta_\omega}{\sqrt{n-2}}}{\sqrt{n-2}}\right) \mid \omega\right) = 1 - \tau.
\]

[Equation A19]

Therefore \( \varsigma \) is a solution to Equation A16. The uniqueness of the solution is a direct consequence of the fact that the expression on the left hand side of Equation 16 is strictly monotonic as a function of \( c \). Now we prove \( \varsigma \geq 50\% \) by contradiction. Suppose that \( \varsigma < 50\% \). Then \( z_{\varsigma} > z_{0.5} = 0 \). Note that
\[
\left(\xi, U\right): \left[ Z_{\delta \omega(X)} - \sqrt{\frac{t_{0.2}(\tau) \Delta_\omega}{\sqrt{n-2}}} \right] \leq z_{\varsigma} < Z_{0.5}
\]
\[
\left(\xi, U\right): \left[ Z_{\delta \omega(X)} - \sqrt{\frac{t_{0.2}(\tau) \Delta_\omega}{\sqrt{n-2}}} \right] \leq z_{\varsigma} < Z_{0.5}
\]

[Equation A20]

Combining equations A16, A19, and A20, we have
\[
1 - \tau = P\left(Z_{\delta \omega(X)} - \sqrt{\frac{t_{0.2}(\tau) \Delta_\omega}{\sqrt{n-2}}} \right) \leq z_{\varsigma} < Z_{0.5}
\]
\[
\Rightarrow P\left(Z_{\delta \omega(X)} - \sqrt{\frac{t_{0.2}(\tau) \Delta_\omega}{\sqrt{n-2}}} \right) = 1 - \tau
\]

[Equation A21]

which is a contradiction. Therefore the supposition that \( \varsigma < 50\% \) is untrue and \( \varsigma \geq 50\% \).