指出一個變數之改變方向或比率的統計學術語。	direction or rate of change of a variable(s)

8. 參考文獻 （References）

ICH Q8 Pharmaceutical Development. ISO/IEC Guide 73:2002 - Risk Management - Vocabulary - Guidelines for use in Standards.
ISO/IEC Guide 51:1999 - Safety Aspects - Guideline for their inclusion in standards.
Process Mapping by the American Productivity & Quality Center, 2002, ISBN 1928593739.
IEC 61025 - Fault Tree Analysis (FTA).
IEC 60812 Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA).
Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983.
Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press, ISBN 0849319102.
The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996, ISBN 0527763209.
WHO Technical Report Series No 908, 2003, Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals.
IEC 61882 - Hazard Operability Analysis (HAZOP).
ISO 14971:2000 - Application of Risk Management to Medical Devices.
ISO 7870:1993 - Control Charts.
ISO 7871:1997 - Cumulative Sum Charts.
ISO 7966:1993 - Acceptance Control Charts.
ISO 8258:1991 - Shewhart Control Charts.
What is Total Quality Control?; The Japanese Way, Kaoru Ishikawa (Translated by David J. Liu), 1985, ISBN 0139524339.

附件I：風險管理方法和工具 （Appendix I: Risk Management Methods and Tools）

本附件之目的在於就可能被業界及主管機關使用於品質風險管理之一些主要工具，提供其一般的概觀及參考資料。這些參考資料是為幫助取得關於特定工具之更多知識及細節而納入。這不是一個詳細周全的清單。重點是沒有任何一件或一套工具可適用於品質風險管理程序之每一種情況。	The purpose of this appendix is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 基本風險管理之簡易方法 （Basic Risk Management Facilitation Methods）

一些藉由組織數據及促進決策之制定，以普遍用來建構風險管理之簡單技術是：	Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating

	decision-making are:
• 流程圖；	• Flowcharts
• 檢查單；	• Check Sheets
• 過程圖示；	• Process Mapping
• 原因和效應圖表（亦稱為石川圖或魚骨圖）。	• Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)
I.2 失敗模式效應分析 （Failure Mode Effects Analysis (FMEA)）	
FMEA (參見 IEC 60812) 係就程序及其對結果及/或產品性能之可能的效應，提供潛在失敗模式的評估。失敗模式一旦建立，風險減低便可用以排除、圍堵、減少或控制該潛在失敗。FMEA 倚賴對產品及製程的瞭解。FMEA 在方法上將複雜程序的分析分解成可管理的步驟。對於總結失敗之重要模式、引起這些失敗的因素及這些失敗之可能效應，這是一個強而有力的工具。	FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.
潛在的使用領域 （Potential **Areas of Use(s)**）	
FMEA 可用於安排風險優先順序及監測風險管制活動的效果。	FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.
FMEA 可應用於設備及設施，及可用於分析製造作業及其對產品或製程的影響。這可辨識使系統脆弱之因素/操作。FMEA 之產出/結果可用為設計或進一步分析或指引資源配置的基礎。	FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.
I.3失敗模式，效應及關鍵性分析（Failure Mode Effects and Criticality Analysis，FMECA）	

FMEA 可加以延伸，納入結果之嚴重程度的調查、其個別之發生機率，以及其檢測性，轉變為失敗模式，效應及關鍵性分析（FMECA；參見 IEC 60812）。為執行這樣的分析，應建立產品或製程規格。	FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established.
FMECA 能確認在何處追加預防措施，可能將風險減至最低。	FMECA can identify places where additional preventive actions might be appropriate to minimize risks.
潛在的使用領域（Potential **Areas of Use(s)**）	
FMECA 在製藥產業之應用，應主要用於與製造過程有關之失敗及風險；然而，並不侷限於該應用。FMECA 之結果是每一失敗模式之相對風險"分數"。該分數在相對風險的基礎上，將這些模式分級。	FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.
I.4 缺失之樹狀分析 （Fault Tree Analysis，FTA）	
FTA 工具(參見 IEC 61025)是假定一個產品或製程有功能性失效之方法。這個工具每次只評估造成系統(或子系統)失效的一個原因，但可將失效之數個原因以確認其為原因鏈的方式組合在一起。該結果以缺失模式樹的形式圖示之。在該模式樹中的每一層級，其缺失模式間的關連以邏輯運算符號（"及"、"或"等）描述之。FTA 有賴於專家對製程的瞭解，以確認原因的因素。	The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts’ process understanding to identify causal factors.
潛在的使用領域 （Potential Areas of Use(s)）	

FTA 得用於建立導致失敗之根本原因的路徑。FTA 得用來調查申訴或偏離，以完全瞭解其根本原因，並確保其預定的改善將會完全解決該問題，而不會引起其他問題（亦即，解決了一個問題卻又引起另一個不同的問題）。缺失之樹狀分析是評估多重因素對於一個已知問題影響的有效工具。FTA 之產出包含可見的失敗模式描述。這對於風險評價及監測計畫的開發都有助益。	FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.
I.5 危害分析及關鍵管制點 （Hazard Analysis and Critical Control Points，HACCP）	
HACCP 是為確保產品品質、可靠性及安全性之系統性、積極性及預防性的工具(參見 WHO Technical Report Series No 908, 2003 Annex 7)。這是一個結構化的方法。該方法應用技術和科學的原理，分析、評估、預防及管制由產品之設計、開發、生產及使用的危害所產生之風險或不良後果。	HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.
HACCP 包含下列 7 個步驟：	HACCP consists of the following seven steps:
(1) 對製程的每一個步驟執行危害分析，並確認其預防措施；	(1) conduct a hazard analysis and identify preventive measures for each step of the process;
(2) 決定關鍵管制點；	(2) determine the critical control points;
(3) 建立關鍵限量；	(3) establish critical limits;
(4) 建立一個監測關鍵管制點的系統；	(4) establish a system to monitor the critical control points;
(5) 建立當監測出關鍵管制點不在管制狀態時，應採取的矯正措施；	(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
(6) 建立系統，證實 HACCP 系統在有效運作中；	(6) establish system to verify that the HACCP system is working effectively;
(7) 建立一個保存紀錄之系統。	(7) establish a record-keeping system.
潛在的使用領域（**Potential Areas of Use(s)**）	

HACCP 可能用於確認和管理與物理學、化學及生物學上之危害(包括微生物學上的污染) 相關聯的風險。當對產品及製程之瞭解足夠廣泛，以支持關鍵管制點的確認時，則 HACCP 最為有用。HACCP 分析的產出是風險管理資訊。不僅在製造過程上，且亦在其他生命週期的階段中，該資訊皆有助於關鍵管制點的監測。	HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.
I.6 危害操作性分析 （Hazard Operability Analysis，HAZOP）	
HAZOP（參見 IEC 61882）係以假定風險事件是由於偏離設計或作業目的而引起之理論為基礎。這是一個系統性腦力激盪技術。該技術利用所謂"指引字語"來確認危害。"指引字語"（例如，"無"、"更多"、"異於"、"部分"等）應用於相關的參數（例如，污染、溫度）上，以幫助確認離開正常使用或設計目的之潛在偏離。這常常使用一組人員組成之團隊。這些人員具有涵蓋該製程或產品之設計及其應用的專門知識。	HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called “guide-words”. “Guide-words” (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.
潛在的使用領域（Potential Areas of Use(s)）	
HAZOP 可適用於原料及藥品之製造過程，包括委外生產與配方及上游供應商、設備和設施。這亦已使用於製藥工業，主要以評估製程安全性的危害。類似於 HACCP 之情況，HAZOP 分析之產出是一個對風險管理之關鍵作業的清單。這有助於製造過程中之關鍵點的定期監測。	HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.
I.7 事先危害分析 （Preliminary Hazard Analysis，PHA）	

PHA 是一個分析工具，該工具應用先前關於一個危害或失效之經驗或知識為基礎，以確認將來可能引起損害之危害、危害狀況及事件，並預測其在一定的活動、設施、產品或系統之發生機率。其工具包含：	PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of:
1) 確認風險事件發生的可能性，	1) the identification of the possibilities that the risk event happens,
2) 對健康可能造成之傷害或損害程度的定性評估，	2) the qualitative evaluation of the extent of possible injury or damage to health that could result and
3) 利用綜合事件之嚴重性及可能性將危害相對分級，以及	3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and
4) 確認可能之改善措施。	4) the identification of possible remedial measures
潛在的使用領域（Potential Areas of Use(s)）	
當情況不允許使用一個更廣泛技術，則在分析既有系統或危害之優先順序時， PHA 可能是很有用的。這可用於產品、製程及設施之設計，亦可評估一般產品類型、次為產品分類及後為特殊產品之危害。PHA 是最普遍使用於一個計畫之開發的初期。那時候關於細部設計或作業程序都只有很少的資訊。因此，這常常會是進一步研究的一個前導。典型地，在 PHA 中確認之危害，將與像在本節中規定之其他風險管理工具一起，進一步加以評價。	PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.
I.8 風險分級及篩選（Risk Ranking and Filtering）	
風險分級及篩選是將風險比較與分級的工具。複雜系統之風險分級典型地需要對每一風險之多樣的定量和定性因素加以評估。這個工具包含視需要，將一個基本風險問題分解成許多構成要素，以捕捉在此風險中所涉及之因素。這些因素結合成一個單一的相對風險分數，而後可用以將風險分級。“篩選器”是以對風險分數進行加權或減去的形式存在，可用為將風險分級改變尺度或使風險分級合適於管理或政策	Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks.

目標。	"Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.
潛在的使用領域（Potential Areas of Use(s)）	
風險分級及過濾可用於將製造場所排定優先順序，以供主管機關或工業界檢查/稽核。於風險組合與其需被管理的潛在後果之多樣化，且難以使用單一工具進行比較的情況時，風險分級方法尤其有效。當管理上需要在相同組織架構內，評估定量及定性評價之風險時，風險分級是有用的。	Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.
I.9 輔助性統計工具 （Supporting Statistical Tools）	
統計工具可支持及促進品質風險管理。它們可進行有效的數據評價，幫助決定數據套組的重要性，並促成更可靠的決策。下面提供在製藥工業普遍使用之一些主要的統計工具清單：	Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:
(i) 管制圖，例如：	(i) Control Charts, for example:
- 允收管制圖 (參見 ISO 7966)；	-Acceptance Control Charts (see ISO 7966)
- 具有算術平均值和警告限量的管制圖 (參見 ISO 7873)；	-Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
- 累積總和圖 (ISO 7871);	-Cumulative Sum Charts (see ISO 7871)
- Shewhart 管制圖(參見 ISO 8258)；	-Shewhart Control Charts (see ISO 8258)
- 加權移動平均。	-Weighted Moving Average
(ii) 實驗設計（DOE）；	(ii) Design of Experiments (DOE)
(iii)直方圖；	(iii) Histograms
(iv) Pareto 圖；	(iv) Pareto Charts
(v) 製程能力分析。	(v) Process Capability Analysis