皮膚表面黏合用之組織黏合劑與傷口閉合裝置臨床前測試基準

Pre-clinical Testing Guidance for Tissue Adhesive with Adjunct Wound Closure Device for Topical Approximation of Skin

112.02

【說明】

1. **本測試基準係提供醫療器材商辦理產品查驗登記時，臨床前測試應檢附資料及進行項目之建議，未包含臨床證據等其他資料之要求，醫療器材查驗登記申請案仍應符合相關法規。製造業者亦應依個案產品結構、材質及宣稱效能提出完整驗證評估（含臨床前測試及/或臨床證據等）之資料。**
2. **本測試基準依據現行之參考資料制定，惟科技發展日新月異，法規更新未逮處，為確保國人健康安全，審查人員將視產品宣稱效能、結構與設計之安全性及功能性，要求製造業者提供本測試基準所列項目外之驗證評估（含臨床前測試及/或臨床證據）資料；另本測試基準將不定期更新。**
3. **臨床前測試資料應包括檢驗規格(含各測試項目之合格範圍及其制定依據)、方法、原始檢驗紀錄及檢驗成績書。**
4. **如製造業者未進行表列測試項目，應檢附相關文獻或科學性評估報告，以證實產品仍具有相等之安全及功能。**
5. **各項測試如本測試基準或表列之參考方法未訂有規格者，由各製造業者自行制定規格；如本測試基準或表列參考方法已訂有規格，惟製造業者另訂不同規格者，應檢附相關文獻或科學性評估報告以說明訂定規格之依據。**
6. **製造業者使用之測試方法如與本測試基準所列參考方法不同，但(1)具同等性者，應檢附製造業者測試方法供審核；(2)如不具同等性，應檢附製造業者測試方法及相關文獻或科學性評估報告以說明該測試方法制定之依據。**
7. **如表列參考資料有修訂、廢止或被其它標準取代，製造業者得參照新版標準進行測試。**

一、 本基準適用之醫療器材範圍(Scope)

皮膚表面黏合用之組織黏合劑與傷口閉合裝置為外用醫療器材(topical application)，將邊緣整齊之手術傷口黏合。適用於此類醫療器材之手術傷口包含微創手術傷口(minimally invasive surgery)、及經過完整清潔處理之一般撕裂傷口(trauma-induced lacerations)。此器材可以與深部真皮層縫合裝置(deep dermal stitches)合併使用，但不可取代其作用。傷口閉合裝置配合液體組織黏合劑，暫時性沿著傷口邊緣確保傷口接合。分級：第二等級。

本基準不適用於黏合內部組織或血管，如：大血管(large vessels)術後之黏合、硬腦膜密封(dural sealants)與眼組織黏合等。

本基準亦不適用於含藥或生物成分的產品。

二、 本基準適用醫療器材之衛生福利部公告分類分級品項(Regulation number)及其鑑別(Identification)

公告品項: I.4011 皮膚表面黏合用之組織黏合劑與傷口閉合裝置(Tissue adhesive with adjunct wound closure device for topical approximation of skin)

風險等級: 2

鑑　　別:皮膚表面黏合用之組織黏合劑與傷口閉合裝置用於皮膚手術傷口(包括微創手術的穿刺、

簡易且經徹底清潔的撕裂性外傷)之黏合，可以與深部真皮層縫合裝置(deep dermal stitches)合併使用，但不可取代其作用。此外，傷口閉合裝置可配合液體組織黏合劑，暫時性沿著傷口邊緣確保傷口接合。

三、 產品敘述及規格(Product description and specification)

1. 黏合劑之化學組成(Chemistry)：成品各材料組成之化學名稱(含化學文摘社(CAS)編號及商品名)、結構式、化學式與分子量、原料來源和純度、聚合起始劑(polymerization initiator)之化性鑑定和純度、成品穩定劑(product stabilizer)之化性鑑定和純度、成品聚合反應流程說明。
2. 黏合劑之材質特性(Material characteristics of the adhesive)：黏度(Viscosity)、聚合殘留成份分析(Analysis of residual content)、純度(Purity)、濕度(Moisture)、凝固時間(Setting time)、致熱原性(Pyrogenicity)與無菌性(Sterility)。
3. 傷口閉合裝置之材質特性(Material characteristics of the adjunct wound closure device)：外觀(Appearance)、材質(Material)、尺寸(Dimension)(如有孔洞設計，應提供孔洞大小)、組件汙染物殘留(component contamination)、結構(Construction)、致熱原性(Pyrogenicity)與無菌性(Sterility)。
4. 保存期限及保存條件(溫度、濕度、光線等)。
5. 滅菌方式。

四、安全性及功能性試驗資料(Safety and performance data)

項目	規格、需求及/或應進行測試	參考方法
1.生物相容性評估 (Biocompatibility Evaluation)	(1)細胞毒性(Cytotoxicity) (2)致敏性(Sensitization) (3)刺激或皮內刺激性(Irritation/Intracutaneous reactivity) (4)急性毒性(Acute systemic toxicity) (5)亞急性毒性(Subacute toxicity) (6)植入性(Implantation) 若產品屬新材質者，將視個案另評估組織黏合劑材質降解產物安全性評估。	ISO 10993-1:2018[1] ISO 10993-3:2014[2] ISO 10993-5:2009[3] ISO 10993-6:2016[4] ISO 10993-9:2009[5] ISO 10993-10:2010[6] ISO 10993-11:2017[7] ISO 10993-12:2012[8] ISO 10993-13:2010[9]
2.滅菌確效 (Sterilization Validation)	進行滅菌確效(Sterilization validation)應確保SAL(Sterility assurance level)小於 10^{-6}，依產品滅菌方式標準。	依產品滅菌方式選擇適合參照之標準： ISO 17665-1:2006[10] ISO 11135-1:2007[11] ISO 11137-1:2006 [12] ISO 11137-2:2006[13] ISO 11137-3:2006[14]
3.熱原試驗 (Pyrogen test)	如製造業者宣稱產品為無熱原(non-pyrogenic)，應進行熱原試驗並符合其宣稱。	依各國藥典規定
4.功能性試驗	(1) 黏合劑聚合後之黏合力(Adhesive strength of the final	FDA Guidance(2010)[15]

(Performance test)	polymerized device):如提供下列之評估結果。 i. 抗拉強度(Tensile strength) ii. 抗拉/交疊剪力強度(Tensile or overlap shear strength) iii. 剝離黏著強度(Peel adhesion strength) iv. 衝擊強度(Impact strength) (2) 黏合劑之降解率(Degradation rate): 如產品降解過程中有下列副產物，應進行其之含量檢驗。 i. 配方添加劑(Formulation additive) ii. 單體不純物(Monomer impurities) iii. 降解產物(Degradation products) (3) 黏合劑之聚合反應產熱(Heat of polymerization study)。 (4) 傷口閉合裝置組件之力學強度(Strength of the skin adjunct wound closure device component): 如提供下列之評估結果。 i. 剝離測試(Peel testing) ii. 持拉測試(Creep testing) iii. 抗拉測試(Tensile testing)	ASTM D3330/D3330M-04(2018)[16] ASTM D3654/D3654M-06(2019)[17] ASTM D882-18[18] ASTM F2255-05(2015)[19] ASTM F2256-05(2015)[20] ASTM F2258-05(2015)[21] ASTM F2458-05(2015)[22]
5.架儲期(Shelf life)	以最終產品為測試標的，進行真實時間安定性試驗(real time stability testing)或加速架儲期試驗(accelerated shelf life testing)，確保產品於有效期間之安全與功效性。	依各製造業者規定 ASTM F1980(2021) [23] FDA Guidance(2010)[15]

五、參考文獻 (References)

1. ISO 10993-1:2018 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.
2. ISO 10993-3:2014 Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.
3. ISO 10993-5:2009 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.
4. ISO 10993-6:2016 Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.
5. ISO 10993-9:2009 Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products.
6. ISO 10993-10:2010 Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.
7. ISO 10993-11:2017 Biological evaluation of medical devices — Part 11: Tests for systemic toxicity.
8. ISO 10993-12:2012 Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.

9. ISO 10993-13:2010 Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices.
10. ISO 17665-1:2006 Sterilization of health care products —Moist heat —Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.
11. ISO 11135-1:2006 Sterilization of health care products —Ethylene oxide —Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.
12. ISO 11137-1:2006 Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.
13. ISO 11137-2:2006 Sterilization of health care products —Radiation —Part 2: Establishing the sterilization dose.
14. ISO 11137-3:2006 Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects.
15. Guidance for Industry and FDA Staff Class II Special Controls Guidance Document: Tissue Adhesive with Adjunct Wound Closure Device Intended for the Topical Approximation of Skin (2010).
16. ASTM D3330/D3330M-04(2018) Standard Test Method for Peel Adhesion of Pressure-Sensitive Tape.
17. ASTM D3654/D3654M-06(2019) Standard Test Methods for Shear Adhesion of Pressure-Sensitive Tapes.
18. ASTM D882-18 Standard Test Method For Tensile Properties Of Thin Plastic Sheeting.
19. ASTM F2255-05(2015) Standard Test Method for Strength Properties of Tissue Adhesives in Lap-Shear by Tension Loading.
20. ASTM F2256-05(2015) Standard Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension Loading.
21. ASTM F2258-05 F2258-05(2015) Standard Test Method for Strength Properties of Tissue Adhesives in Tension.
22. ASTM F2458-05(2015) Standard Test Method for Wound Closure Strength of Tissue Adhesives and Sealants.
23. ASTM F1980 (2021) Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices.