A.L. 485 ta' l-2004

ATT TA' L-2003 DWAR IL-MEDIĊINI (ATT NRU. III TA' L- 2003)

Regolamenti ta' l-2004 dwar il-Prattika Tajba tal-Manifattura ta' Prodotti Mediċinali u ta' Prodotti Mediċinali Investigattivi għall-Użu mill-Bniedem.

BIS-SAĦĦA tas-setgħat mogħtija bl-artikolu 106 ta' l-Att ta' l-2003 dwar il-Mediċini, il-Ministru tas-Saħħa, l-Anzjani u Kura fil-Komunità għamel dawn ir-regolamenti li ġejjin:-

Titolu.

1. It-titolu ta' dawn ir-regolamenti hu Regolamenti ta' l-2004 dwar il-Prattika Tajba ta' Prodotti Mediċinali u ta' Prodotti Mediċinali Investigattivi għall-Użu mill-Bniedem.

Skop.

2. Dawn ir-regolamenti, li jittrasponu d-Direttiva 2003/94/KE jistabbilixxu prinċipju u linji gwida ta' prattika tajba għall-manifattura ta' prodotti mediċinali u prodotti mediċinali investigattivi għall-użu mill-bniedem.

Tifsiriet.

3. Għall-finijiet ta' dawn ir- regolamenti u kemm-il darba r-rabta tal-kliem ma tkunx teħtieġ xort'oħra:-

"assikurazzjoni ta' kwalità farmaċewtika" tfisser is-somma totali ta' l-arranġamenti organizzati magħmula bi skop li jiġi żgurat li l-prodotti mediċinali jew il-prodotti mediċinali investigattivi huma tal-kwalità meħtieġa għall-użu intiż għalihom;

"*blinding*" tfisser it-tibdil għal skop ta' mmaskjar ta' l-identità tal-prodott tal-mediċina investigattiva skond l-istruzzjonijiet ta' l-isponsor;

"manifattur" tfisser kull persuna imdaħħla f'attivitajiet li dwarhom tkun meħtieġa l-liċenza msemmija fir-Regolamenti ta' l-2004 dwar il-Manifattura ta' Prodotti Mediċinali għall-Użu tal-Bniedem, ta' l-avviż legali 143;

"persuna kwalifikata" tfisser kull persuna li tkun kwalifikata kif provdut fir-regolament 9 tar-Regolamenti ta' l-2004 dwar il-Manifattura ta' Prodotti Mediċinali għall-Użu tal-Bniedem, ta' l-avviż legali 143;

"prattika tajba tal-manifattura" tfisser li l-parti ta' l-assikurazzjoni tal-kwalità li tiżgura li l-prodotti huma konsistentement prodotti u kkontrollati skond il-livelli ta' kwalità meħtieġa għall-użu intiż għalihom;

"prodott mediċinali"tfisser kull prodott kif definit fl-Artikolu 1(2) tad-Direttiva 2001/83/KE;

"prodotti mediinali investigattiv" tfisser forma farmaewtika ta' sostanza ta' sostanza attiva jew *placebo* li jkun qed jiġi eżaminat jew użat bħala riferenza fi prova klinika, inklużi prodotti li diġà għandhom awtorizzazjoni għal-tqegħid fis-suq imma li jsir l-użu jew l-assemblaġġ tagħhom (formulati jew pakkeġġati) f'manjiera differenti mill-forma awtorizzata, jew meta dawn jiġu użati għal indikazzjoni mhux awtorizzata, jew użati biex tinkiseb aktar informazzjoni dwar il-forma awtorizzata;

"*unblinding*" tfisser il-kxif ta' l-identità moħbija jew immaskjata ta' prodott li qabel kienet moħbija.

Ispezzjonijiet.

4. (1) L-Awtorità għandha, permezz ta' spezzjonijiet ripetuti fil-każ ta' mediċinali għall-użu mill-bniedem u permezz ta' ispezzjonijiet fil-każ ta' prodotti mediċinali investigattivi, tiżgura li l-manifatturi jirrispettaw il-prinċipji u linji gwida ta' prattika tajba ta' manifattura stipulata b'dawn ir-regolamenti.

(2) L-Awtorità għandha tieħu wkoll in konsiderazzjoni il-kompilazzjoni, pubblikata mill-Kummissjoni, ta' proċeduri tal-Komunità dwar spezzjonijiet u l-iskambju ta' informazzjoni.

(3) Għall-interpretazzjoni tal-prinċipji u linji gwida ta' prattika tajba ta'manifattura, l-Awtorità u l-manifatturi għandhom jieħdu in konsiderazzjoni l-linji gwida dettaljati li jirreferi għalihom it-tieni paragrafu ta' l-Artiklu 47 tad-Direttiva 2001/83/KE pubblikata mill-Kummissjoni fil-"Gwida għal prattika tajba ta' manifattura għall-prodotti mediċinali u għall-prodotti mediċinali investigattivi".

Konformità ma' prattika tajba ta' manifattura.

5. (1) Il-manifattur għandu jiżgura li l-operazzjonijiet ta' manifattura, inklużi dawk ta' prodotti mediċinali intiżi biss għall-esportazzjoni, isiru skond prattika tajba ta'manifattura u l-awtorizzazjoni ta' manifattura .

(2) L-importatur għandu jiżgura li:

(a) fil-każ ta' prodotti mediċinali u prodotti mediċinali investigattivi importati minn pajjiżi terzi, dawn jkunu ġew manifatturati skond il-livelli li huma mill-anqas ekwivalenti għal livelli ta' prattika tajba ta' manifattura stabbiliti mill-Komunità;

(b) fil-każ ta' prodotti mediċinali, dawk il-prodotti kienu mmanifatturati minn manifatturi li huma awtorizzati li jimmanifatturaw; u

(c) fil-każ ta' prodotti mediċinali investigattivi, dawk il-prodotti ġew manifatturati minn manifattur li jkun ġie avżat lill-awtoritajiet kompetenti u aċċettat minnhom għal dak l-iskop.

Qbil ma' l-awtorizzazzjoni għat-tqegħid fis-suq.

6. (1) Il-manifattur għandu jiżgura li l-operazzjonijiet kollha ta' manifattura ta' prodotti mediċinali soġġetti għall-awtorizzazzjoni għat-tqegħid fis-suq jkunu qegħdin isiru skond l-informazzjoni mogħtija fl-applikazzjoni għall-awtorizzazjoni għat-tqegħid fis-suq kif aċċettata mill-Awtorità dwar il-Liċenzi.

(2) Fil-każ ta'prodotti mediċinali investigattivi, il-manifattur, għandu jiżgura li kull operazzjoni ta' manifattura ssir skond l-informazzjoni mogħtija mill-isponsor kif provdut fir-Regolamenti ta' l-2004 dwar il-Provi Kliniċi, u kif aċċettati mill-Awtorità dwar il-Liċenzji.

(3) Il-manifattur għandu regolarment jirrevedi il-metodi ta' manifattura tiegħu skond kull progress xjentifiku u tekniku u l-iżvilupp tal-prodott mediċinali investigattiv.

(4) Jekk tkun meħtieġa varjazzjoni fil-faxxiklu ta' l-awtorizazzjoni għat-tqegħid fis-suq jew emenda fit-talba li hemm provdut dwarha fir-Regolamenti ta' l-2004 dwar il-Provi Kliniċi, għandha tiġi ppreżentata applikazzjoni għall-modifika lill-Awtorità.

Sistema ta' assikurazzjoni ta' kwalità.

7. Il-manifattur għandu jistabbilixxi u jimplimenta sistema ta' assikurazzjoni effettiva tal-kwalità farmaċewtika li tinvolvi parteċipazzjoni attiva tad-diriġenza u l-persunal tad-dipartimenti differenti.

Persunal.

8. (1) Il-manifattur għandu jiżgura li:-

(a) jkun hemm f'kull sit ta' manifattura għadd biż-żejjed ta' nies kompetenti u kwalifikati kif imiss għad- disposizzjoni tiegħu biex jilħaq l-iskop ta' assikurazzjoni tal-kwalità farmaċewtika;

(b) id-doveri tal-persunal tad- diriġenza u dak superviżorju, inklużi l-persuni kwalifikati, responsabbli għall-implementazzjoni u li jħaddmu prattika tajba ta' manifattura, ikunu definiti fid-deskrizzjoni tad-doveri tagħhom;

(c) ir-relazzjonijiet ġenarkiċi tal-persunal tal-manifattur għandhom ikunu definiti f'mappa organizzattiva;

(d) il-mapep organizzattivi u deskrizzjonijiet tad-doveri għandhom ikunu approvati skond il-proċeduri interni tal-manifattur;

(e) il-persunal jkollu awtorita biż-zejjed biex jesegwixxu d-doveri kollha b'mod korrett;

(f) il-persunal għandu jkollu taħriġ tal-bidu li jitkompla jaġġorna ruħu maż-żmien u l-effettività tat-taħriġ għandha tkun verifikata, u tkun tkopri partikolarment it-teorija u l-applikazzjoni tal-kunċett ta' assikurazzjoni ta' kwalità u ta' prattika tajba ta' manifattura, u, fejn ikun hemm bżonn, il-ħtiġijiet partikolari għall-manifattura tal-prodotti mediċinali investigattivi;

(g) il-programmi ta' iġjene adottati għall-esekuzzjoni ta' attivitajiet għandhom jiġu stabbiliti u osservati u dawk il-programmi għandhom b'mod partikolari, jinkludu proċeduri relatati kemm mas-saħħa, mal-prattika tal-iġjene u ma' l-ilbies tal-persunal.

Bini u attrezzar.

9. (1) Il-bini u l-attrezzar għall-manifattura għandhom ikunu jinstabu, mfassla, mibnija, adattati u miżmumin f'kundizzjoni hekk li jkunu jissodisfaw l-operazzjonijiet li jkunu hemm intiżi li jsiru.

(2) Il-bini u l-attrezzaturi għall-manifattura għandhom jiġu mqegħda, mfassla u mħaddma b'mod tali li jimminimizzaw ir-riskju ta' żbalji u li jippermettu tindif u manutenzjoni effettivi biex iwarrbu kull kontaminazzjoni, kontaminazzjoni minn naħa għal oħra u b'mod ġenerali, effetti avversi fuq il-kwalità tal-prodott.

(3) Il-bini u l-attrezzaturi li jkunu ser jiġu użati għal operazzjonijiet ta' manifattura, li huma meħtieġa għall-kwalita' tal-prodotti, għandhom ikunu soġġetti għal kwalifika u validazzjoni adatti.

Dokumentazzjoni.

10. (1) (a) Huwa d-dmir tal-manifattur li jistabbilixxi u jżomm sistema ta' dokumentazzjoni bbażata fuq speċifikazzjonijiet, formuli ta' manifattura u struzzjonijiet ta' proċessar u pakketjar, proċeduri u records li jkopru l-operazzjonijiet ta' manifattura diversi li jsiru.

(b) Id-dokumentazzjoni għandha tkun ċara, u bla żbalji u aġġornata. Għandhom ikunu disponibbli proċeduri għal operazzjonijiet ta' manifattura ġenerali stabbiliti minn qabel, flimkien ma' dokumenti speċifiċi għall-manifattura ta' kull unità. Dawk id-dokumenti għandhom jippermettu li tiġi rintraċċata l-istorja kollha ta' kif tkun saret il-manifatturata ta' kull unità u l-bidliet introdotti waqt l-iżvilupp ta' prodott mediċinali investigattiv.

(2) (a) Għal prodott mediċinali, id- dokumentazzjoni ta' l-unita' għandha tinżamm għal mill-anqas sena wara d-data ta' skadenza ta' kull unità konċernata jew għal mill-anqas ħames snin wara - ċertifikazzjoni msemmija fir-Regolamenti ta' l-2004 dwar il-Manifattura ta' Prodotti Mediċinali għall-użu mill-Bniedem, skond liema jkun l-itwal perjodu.

(b) Fil-każ ta'prodott ta' mediċina investigattiva, id-dokumentazzjoni dwar l-unità għandha tinżamm għal mill-anqas ħames snin jew wara li jitlesta jew wara it-tmiem formali ta' l-aħħar prova klinika li fiha tkun ġiet użata l-unità. L-isponsor jew id-detentur ta' l-awtorizzazzjoni għat-tqegħid fis- suq, jekk dan jkun differenti, għandu jkun responsabbli biex jiżgura li r-records jibqgħu jinżammu skond kif inhu mitlub għal awtorizzazzjoni għat-tqegħid fis-suq skond Anness I mad-Direttiva 2001/83/KE, jekk dan ikun meħtieġ għal awtorizzazzjoni għat-tqegħid fis-suq sussegwenti.

(3) (a) Meta jintuzaw sistemi ta' proċessar ta' tagħrif elettroniku, fotografiku jew sistemi oħrajn minflok dokumenti miktubin, il-manifattur għandu qabel xejn jikkonvalida s-sistemi billi juri li dak it-tagħrif se jkun maħżun kif imiss matul il-perijodu antiċipat tal-ħażna.

(b) It-tagħrif maħżun b'dawk is-sistemi għandu jkun disponibbli f'forma leġibbli u għandu jingħata lill-awtoritajiet kompetenti meta dawn jitolbuh.

(ċ) It-tagħrif elettroniku maħżun għandu jkun protett, b' metodi bħal ma hi d-duplikazzjoni jew kopji ta' riserva u trasferimenti għal ġo sistema ta' ħażna oħra, biex l-informazzjoni la tintilef u lanqas ma ġġarrab ħsara, u li tkun tista' tiġi rintraċċata b'mezzi ta' verifika.

11. (1) (a) L-operazzjonijiet differenti tal-produzzjoni għandhom isiru skond l-istruzzjonijiet u proċeduri stabbiliti bil-quddiem skond prattika tajba ta' manifattura. Produzzjoni.

(b) Għandu jkun hemm riżorsi adegwati u suffiċjenti li jkunu disponibbli biex isiru l-kontrolli ta' waqt il-proċess ta' manifattura.

(ċ) Kull devjazzjoni fil-proċess u difett fil-prodott għandu jiġi dokumentat u investigat sew u fil-fond .

(2) Għandhom jittieħdu miżuri tekniċi jew ta' organizzazzjoni adatti biex ma' ssirx kontaminazzjoni minn oġġett għal l-ieħor u taħlit. Fil każ ta' prodotti mediċinali investigattivi għandha tingħata attenzjoni partikolari għal meta l-prodott jintmess bl-idejn matul u wara xi operazzjoni ta' *blinding*.

(3) Fil-każ ta' prodotti mediċinali, għandha tiġi validata kull manifattura ġdida jew tibdil importanti ta' proċess ta' manifattura ta' prodott mediċinali, u l-fażijiet kritiċi tal-proċess ta'manifattura għandhom ikunu rivalidati regolarment.

(4) Fil-każ ta' prodotti mediċinali investigattivi, il-proċess tal-manifattura għandu jkun validat fis-sħubija kollha tiegħu sakemm dan ikun adatt, billi jiġi kunsidrat l-istadju ta' żvilupp tal-prodott. Għandhom ikunu validati il-fażijiet kritiċi tal-proċess, bħalma hi l-isterilizzazzjoni, u l-fażijiet kollha fit-tifsil u l-iżvilupp tal-proċess ta' manifattura għandhom ikunu dokumentati kollha kemm huma.

Kontroll tal-Kwalità.

12. (1) (a) Il-manifattur għandu jistabbilixxi u jżomm sistema ta' kontroll tal-kwalità li titqiegħed taħt l-awtorità ta' persuna li jkollha l-kwalifiki meħtieġa u li tkun indipendenti mill-produzzjoni.

(b) Dik il-persuna għandu jkollha għad- disposizzjoni tagħha jew għandu jkollha aċċess għal, xi laboratorju wieħed jew aktar ta' kontroll tal-kwalità b'għadd ta' persunal biż-żejjed u li jkun attrezzat sew biex jagħmel l-eżamijiet u ittestjar meħtieġa ta' materjali tal-bidu u ta' materjal li jintuża għall-ippakkettjar u l-ittestjar ta' prodotti intermedjarji u ta' dawk li jkunu lesti.

(2) (a) Fil-każ ta' prodotti mediċinali, inklużi dawk importati minn pajjiżi terzi, jistgħu jintużaw laboratorji kontrattwali jekk dawn ikunu awtorizzati skond ir-regolament 13 ta' dawn ir-regolamenti.

(b) Fil-każ ta' prodotti mediċinali investigattivi l-isponsor għandu jiżgura li l-laboratorju kontrattwali jkun konformi ma l-kontenut tat-talba msemmija fir-Regolamenti ta' l-2004 dwar il-Provi Kliniċi, u aċċettat mill-Awtorità:

Iżda meta dawk il-prodotti jkunu importati minn pajjiżi terzi, il-kontroll analitiku ma jkunx wieħed mandatorju.

(3) Waqt il-kontroll finali tal-prodott lest, qabel ma' joħroġ għall-bejgħ jew għad-distribuzzjoni jew għall-użu fi provi kliniċi, is-

sistema tal-kontroll ta' kwalità, b'żieda mar-riżultati analitiċi, għandha tati każ, ta' kull informazzjoni essenzjali bħalma huma kondizzjonijiet tal-produzzjoni, ir-riżultati tal-kontrolli ta' waqt il-manifattura, l-eżami tad-dokumenti tal-manifattura u l-konformità tal-prodott ma' l-ispeċifikazzjonijiet tiegħu, inkluż il-prodott finali lest u ppakkjat.

(4) (a) Fil-każ tal-prodott mediċinali lest, għandhom jinżammu kampjuni ta' kull lott għal mill-anqas sena wara id-data ta' l-skadenza.

(b) Fil-każ ta' prodott mediċinali nvestigattiv, għandhom jinżammu kampjuni suffiċjenti minn kull lott tal-prodott formulat bl-ingrossa u ta' l-elementi l-aktar importanti fl-ippakkettjar użati għal kull lott tal-prodott lest għal mill-anqas sentejn wara li jkunu tlestew jew wara il-waqfien formali ta' l-aħħar prova klinika li fiha kien intuża il-lott, skond liema perjodu jkun aktar twil.

(ċ) Fil-każ ta' kampjuni ta' materjal tal-bidu, ħlief għas-solventi, gassijiet jew l-ilma, użati fil-proċess ta' manifattura, dawk il-kampjuni għandhom jinżammu għal mill-anqas sentejn wara li l-prodott ikun gie rilaxxat:

Iżda dak il-perjodu jista jitqassar jekk il-perjodu ta' stabbilità tal-materjal, kif indikat fl-speifikazzjoni rilevanti, huwa wieħed iqsar.

(d) Dawk il-kampjuni kollha għandhom jinżammu għad-disposizzjoni ta' l-awtoritajiet kompetenti.

Xogħol mgħoti barra.

13. (1) Kull operazzjoni ta'manifattura jew operazzjoni li għandha x'taqsam magħha li tingħata barra għandha tkun is-soġġett ta' ftehim bil-miktub.

(2) Il-ftehim għandu isemmi b'mod ċar ir-responsabbilitajiet ta' kull parti u għandu jagħti definizzjoni b'mod partikolari, ta' l-osservanza ta' prattika tajba ta'manifattura li trid tigi segwita u l-mod kif il-persuna kwalifikata li tkun responsabbli biex tiċċertifika kull konsenja, għandha twettaq ir-responsabilitajiet tagħha.

(3) Parti fil-ftehim ma għandiex tagħti b'appalt ix-xogħol fdat lilha taħt il-ftehim mingħajr l-awtorizzazzjoni bil-miktub tal-parti l-oħra.

(4) Dik il-parti għandha timxi mal-prinċipji u linji gwida ta' prattika tajba ta'manifattura u għandha toqogħod għal spezzjonijiet li jsiru mill-awtoritajiet kompetenti kif provdut fl-Att ta' l-2003 dwar il-Mediċini, u fir-Regolamenti ta' l-2004 dwar il-Provi Kliniċi.

Lmenti , ġbir lura ta' prodott mis-suq u *unblinding* f'emerġenza.

14. (1) Fil-każ ta' prodotti mediċinali, il-manifattur għandu:-

(a) jimplimenta sistema biex jirreġistra u jirrevedi l-ilmenti flimkien ma' sistema effettiva biex jiġbor lura, malajr kemm jista' jkun u f'kull ħin, prodotti mediċinali fil-firxa tad-distribuzzjoni;

(b) jirreġistra u jinvestiga kull ilment li għandu x'jaqsam ma' difett;

(c) jinforma lill-awtorità kompetenti b'kull difett li jista' jwassal għal ġbir lura mis-suq jew restrizzjoni mhux normali fuq il-forniment u, sakemm dan ikun possibbbli, jindika l-pajjiżi destinatarji. Kull ġbir lura mis-suq għandu jsir skond il-ħtiġijiet imsemmija taħt l-Att ta' l-2003 dwar il-Mediċini.

(2) Fil-każ ta' prodotti mediċinali investigattivi, il-manifattur għandu:

(a) f'kooperazzjoni ma' l-isponsor, jimplimenta sistema għar-registrazzjoni u r-reviżjoni ta' lmenti flimkien ma' sistema effettiva għall-ġbir lura mis-suq fil-pront u f' kull ħin ta' prodotti mediċinali investigattivi li jkunu diġà daħlu fil-firxa tad-distribuzzjoni;

(b) jirreġistra u jinvestiga kull ilment dwar xi difett u għandu jinforma lill-awtorità kompetenti b'kull difett li jista' jirriżulta fi l-ġbir lura mis-suq jew restrizzjoni mhux normali fuq il-forniment;

(c) jidentifika kull post ta fejn issir il-prova u, sa fejn ikun possibbli, jindika l-pajjiżi destinatarji .

(3) Fil-każ ta' prodott mediċinali investigattiv li dwaru tkun diġà inħarġet awtorizzazjoni għat-tqegħid fis-suq, il-manifattur tal-prodott mediċinali investigattiv għandu, f'kooperazzjoni ma' l-isponsor, jinforma lid-detentur ta' l-awtrorizzazjoni għat-tqegħid fis-suq b'kull difett li jista' jkun relatat mal-prodott mediċinali awtorizzat.

(4) L-isponsor għandu jimplimenta proċedura biex ikun jista' jsir *"unblinding"* ta' malajr kemm jista' jkun fuq prodotti *blinded*, meta dan ikun meħtieġ għal l-ġbir 'l lura mis-suq fil-pront kif imsemmi fis-sub regolament (2) ta' dan ir-regolament, u għandu jiżgura li dik il-proċedura tiżvela tikxef l-identità tal-prodott *blinded* daqstant biss daqs kemm ikun meħtieġ.

Awtospezzjoni.

15. Il-manifattur għandu:

(a) jagħmel awtospezzjonijet ripetuti bħala parti mis-sistema ta' assikurazzjoni ta' kwalità biex isegwi mill-qrib l-implimentazzjoni u t-twettiq ta' prattika tajba ta' manifattura u biex jipproponi miżuri korrettivi neċessarji, u

(b) jżomm records ta' awtospezzjonijiet bħal dawk u ta' kull azzjoni korrettiva li tittieħed sussegwentament.

Tikkettjar.

16. Fil-każ ta' prodott mediċinali investigattiv, l-ittikkettjar għandu jsir b'mod li jiżgura l-protezzjoni tas-suġġett u kif dan ikun jista' jinstab, biex tista' tiġi identifikata x-xorta tal-prodott u l-prova tiegħu u li biex ikun jista' jigi faċilitat l-użu korrett tal-prodott mediċinali investigattiv.

L.N. 485 of 2004

MEDICINES ACT
(ACT NO. III OF 2003)

Good Manufacturing Practice in Respect of Medicinal and Investigational Medicinal Products for Human Use Regulations, 2004

IN exercise of the powers conferred by article 106 of the Medicines Act, 2003, the Minister of Health, the Elderly and Community Care has made the:-

Title.

1. The title of these regulations is the Good Manufacturing Practice in Respect of Medicinal and Investigational Medicinal Products for Human Use Regulations, 2004.

Scope.

2. These regulations, which transpose Directive 2003/94/EC, lay down the principles and guidelines of good manufacturing practice in respect of the manufacture of medicinal and investigational medicinal products for human use.

Definitions.

3. For the purposes of these regulations and unless the context otherwise requires:-

"the Authority" means the Medicines Authority;

"blinding" means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;

"good manufacturing practice" means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use;

"investigational medicinal product" means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already having a marketing authorization but which are used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

"manufacturer" means any person engaged the activities for which the licence referred to in the Manufacture of Medicinal Products for Human Use Regulations, 2004, Legal Notice 143, is required;

"medicinal product" means any product as defined in Article 1(2) of Directive 2001/83/EC;

"pharmaceutical quality assurance" means the total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use;

"qualified person" means any person who is a qualified person as provided by regulation 9 of the Manufacture of Medicinal Products for Human Use Regulations, 2004, Legal Notice 143.

"unblinding" means the disclosure of the identity of a blinded product.

Inspections.

4. (1) The Authority shall, by means of repeated inspections in the case of medicinals for human use and by means of inspections in the case of investigational medicinal products, ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by these regulations.

(2) The Authority shall also take into account the compilation, published by the Commission, of Community procedures on inspections and exchange of information.

(3) For the interpretation of the principles and guidelines of good manufacturing practice, the Authority and the manufacturers shall take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in the "Guide to good manufacturing practice for medicinal products and for investigational medicinal products".

Conformity with good manufacturing practice.

5. (1) It shall be the duty of the manufacturer to ensure that manufacturing operations, including those of medicinal products intended only for export, are carried out in accordance with good manufacturing practice and with the manufacturing authorisation.

(2) It shall be the duty of the importer to ensure that:

(a) in the case of medicinal products and investigational medicinal products imported from third countries, these have been

manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down by the Community;

(b) in the case of medicinal products , such products have been manufactured by manufacturers duly authorised for the purpose; and

(c) in the case of investigational medicinal products, such products have been manufactured by a manufacturer notified to the competent authorities and accepted by them for that purpose.

Compliance with marketing authorisation.

6. (1) It shall be the duty of the manufacturer to ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as accepted by the Licensing Authority.

(2) In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information provided by the sponsor as provided the Clinical Trials Regulations, 2004 and as accepted by the Licensing Authority.

(3) It shall be the duty of the manufacturer to review regularly his manufacturing methods in the light of scientific and technical progress and the development of the investigational medicinal product.

(4) If a variation to the marketing authorisation dossier or an amendment to the request provided for in the Clinical Trials Regulations, 2004 is necessary, the application for modification shall be submitted to the Authority.

Quality assurance system.

7. It shall be the duty of the manufacturer to establish and implement an effective pharmaceutical quality assurance system involving the active participation of the management and personnel of the different departments.

Personnel.

8. (1) It shall be the duty of the manufacturer to ensure that:

(a) there is at each manufacturing site, a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the pharmaceutical quality assurance objective;

(b) the duties of the managerial and supervisory staff, including the qualified persons, responsible for implementing and

operating good manufacturing practice, are defined in the job descriptions;

(c) the hierarchical relationships of the manufacturer's staff are defined in an organisation chart;

(d) the organisation charts and job descriptions are approved in accordance with the manufacturer's internal procedures;

(e) the staff have sufficient authority to discharge their responsibility correctly;

(f) the personnel receives initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance and good manufacturing practice, and, where appropriate, the particular requirements for the manufacture of investigational medicinal products;

(g) the hygiene programmes adapted to the activities to be carried out shall be established and observed and such programmes shall, in particular include procedures relating to health, hygiene practice and clothing of personnel.

Premises and equipment.

9. (1) Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended operations.

(2) Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.

(3) Premises and equipment to be used for manufacturing operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation.

Documentation.

10. (1) (a) It shall be the duty of the manufacturer to establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed.

(b) Documents shall be clear, free from error and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. Such set of documents shall enable the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product to be traced.

(2) (a) For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Manufacturing of Medicinal Products for Human use, Regulations 2004.

(b) In the case of an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation.

3. (a) When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage.

(b) Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request.

(c) The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained.

Production.

11. (1) (a) The different production operations shall be carried out in accordance with pre-established instructions and procedures and in accordance with good manufacturing practice.

(b) Adequate and sufficient resources shall be made available for the in-process controls.

(c) All process deviations and product defects shall be documented and thoroughly investigated.

(2) Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups. In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.

(3) In the case of medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated and the critical phases of manufacturing processes shall be regularly re-validated.

(4) In the case of investigational medicinal products, the manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development. The critical process steps, such as sterilisation, shall be validated and all steps in the design and development of the manufacturing process shall be fully documented.

Quality control.

12. (1) (a) It shall be the duty of the manufacturer to establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

(b) Such person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of the starting materials and packaging materials and the testing of intermediate and finished products.

(2) (a) In the case of medicinal products, including those imported from third countries, contract laboratories may be used if authorised in accordance with regulation 13 of these regulations.

(b) In the case of investigational medicinal products, the sponsor shall ensure that the contract laboratory complies with the content of the request referred to in the Clinical Trials Regulations, 2004 and accepted by the Authority.

Provided that when such products are imported from third countries, analytical control shall not be mandatory.

(3) During the final control of the finished product, before its release for sale or distribution or for use in clinical trials, the quality control system shall take into account, in addition to analytical results, any essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications, including the final finished pack.

(4) (a) In the case of a finished medicinal product, samples of each batch shall be retained for at least one year after the expiry date.

(b) In the case of an investigational medicinal product, sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished product batch shall be retained for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

(c) In the case of samples of starting materials, other than solvents, gases or water, used in the manufacturing process, such samples shall be retained for at least two years after the release of the product:

Provided that such period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter.

(d) All such samples shall be maintained at the disposal of the competent authorities.

Work given out.

13. (1) Any manufacturing operation or operation linked thereto which is given out shall be the subject of a written agreement.

(2) The agreement shall clearly define the responsibilities of each party and shall define, in particular, the observance of good manufacturing practice to be followed and the manner in which the qualified person responsible for certifying each batch is to discharge his responsibilities.

(3) A party to the agreement shall not subcontract any of the work entrusted to him under the agreement without written authorisation from the other party.

(4) Such party shall comply with the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities as provided by the Medicines Act, 2003 and by the Clinical Trials Regulations, 2004.

Complaints, product recall and emergency unblinding.

14. (1) The manufacturer shall, in the case of medicinal products:

(a) implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network;

(b) record and investigate any complaint concerning a defect;

(c) inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination.Any recall shall be made in accordance with the requirements referred to in the Medicines Act, 2003;

(2) In the case of investigational medicinal products, the manufacturer shall:

(a) in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products which have already entered the distribution network;

(b) record and investigate any complaint concerning a defect and shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply;

(c) identify all trial sites and, in so far as is possible, indicate the countries of destination.

(3) In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised medicinal product.

(4) It shall be the duty of the sponsor to implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall referred to in sub-regulation (2) of this regulation, and to ensure that such procedure discloses the identity of the blinded product only in so far as is necessary.

15. The manufacturer shall: Self-inspection.

(a) conduct repeated self-inspections as part of the quality assurance system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures; and

(b) maintain records of such self-inspections and any corrective action subsequently taken.

Labelling.

16. In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.

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