38. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.	38. 動物組織や微生物の培養に従事した作業員は、同様な作業に付く場合を除いて、厳密で、明確に規定された手順に従わない限り無菌作業区域に入室してはならない。
39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiologicalhazard should be decided by a designated competent person.	39. 作業員については高い水準の衛生と清浄度が必須である。無菌製品の製造に携わる作業員は異常な数或いは種類の汚染物質の放出を生ずるような状態をいつでも報告するよう指導されなければならない;そのような状態を検知するために定期的なチェックを行うことが望ましい。過度の微生物学的ハザードをもたらす可能性のある作業員に対して取るべき対応については、指定された責任者が決定しなければならない。
40. Wristwatches, make-up and jewellery should not be worn in clean areas.	40. 腕時計、化粧、装身具は清浄区域では身に着けてはならない。
41. Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.	41. 作業衣の交換及び手洗いは、更衣からの汚染を最小限にする、或いは、清浄区域への汚染物の持ち込みを最小限にする為に作成した手順書に従い、実施しなければならない。
42. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.	42. 作業衣とその質は従事する工程と作業区域のグレードに対して適切でなければならない。製品への汚染を防止するような方法で着用しなければならない。
43 The description of clothing required for each grade is given below:	43.各グレードで要求される作業衣について以下に記述する。
· Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.	グレードD: 頭髪、該当する場合はあごひげを覆わなければならない。一般的な保護衣、適切な靴或いはオーバーシューズを着用しなければならない。清浄区域外からの汚染を避けるための対策をとらなければならない。
· Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.	グレードC: 頭髪と該当する場合はあごひげ及び口ひげを覆わなければならない。つなぎ、或いはツーピースの作業衣で、手首が絞られていて、ハイネックのもの、適切な靴或いはオーバーシューズを着用しなければならない。それらは繊維或いは塵を放出しないこと。

· Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.	グレードA/B: 頭巾は頭髪及び該当する場合にはあごひげ及び口ひげを完全に覆うとともに、すそが無塵衣の襟の中に完全に入るようにしなければならない。水滴の放出を防止するための顔面マスクを着用し、粉をつけていないゴム或いはプラスチック製の手袋、そして滅菌或いは消毒した履物を着用すること。ズボンの裾は履物の中に、上着の袖は手袋の中に入れること。保護衣は実質的に繊維や塵を放出しないともに、体から放出される塵を外に出さないものでなければならない。
44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.	44. 屋外用の着衣はグレードB及びCの区域に通じる更衣室には持ち込んではならない。グレードA/Bの区域の作業員には、清浄で無菌の(滅菌された、或いは適切に消毒された)保護衣を作業セッション毎に配布しなければならない。手袋は作業中定期的に消毒すること。マスクと手袋は最低限、作業セッション毎に交換すること。
45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.	45. 清浄区域の作業着は後で放出される可能性のある汚染物質を付着させないように洗濯し、取り扱うこと。洗濯及びその後の取り扱いは文書化された手順に従うこと。作業着の洗濯は別の設備で行うことが望ましい。作業衣の不適切な取り扱いは繊維にダメージを与え、塵の放出のリスクを増加させる。
PREMISES	建物
46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.	46. 清浄区域における全ての露出表面は粒子、微生物等の発散或いは蓄積を防止し、洗剤、消毒剤を繰り返し使用しても耐えうる平滑で傷んだり破けにくいものでなければならない。
47. To reduce accumulation of dust and to facilitate cleaning there should be nouncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.	47. 塵の蓄積を防止し、洗浄し易くする為、清掃できない凹みを無くさなければならない。又、また庇、棚、戸棚、設備は最小限としなければならない。ドアは、そのような洗浄できない凹みを避けるデザインにしなければならない。この理由から、引き戸を設置することは好ましくない。
48. False ceilings should be sealed to prevent contamination from the space above them.	48. 天井の欠陥(ひび、隙間等)は上部からの汚染防止のため封止しなければならない。
49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.	49. パイプ、ダクト等のユーティリティーは凹み、隙間、清掃困難な表面を生じない様に設置しなければならない。

50. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.	50. 無菌操作を行うグレードA/Bの区域では流し及び排水口は禁止。他の区域で設置する場合は、流しあるいは設備と排水口との間に空気遮断装置を設置すること。 低グレードの区域の床の排水口は逆流防止用のトラップあるいは水封を設置すること。
51. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and parrticulatecontamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.	51. 更衣室はエアーロックとして設計されていなければならない。 保護衣への菌及び塵による汚染防止のため更衣の段階ごとに物理的に区分しなければならない。これらの部屋はフィルターを通した空気を供給してフラッシングすること。更衣室の最終段階は非作業時の状態でこれから入室する区域と同じグレードでなければならない。入室と退出で別の更衣室とすることが望ましい。通常、手の洗浄設備は更衣室の初めの段階のみに限定しなければならない。
52. Both airlock doors should not be opened simultaneously. An interlocking system ora visual and/or audible warnign system should be operated to prevent the opening of more than one door at a time.	52. エアーロックのドアは両側同時に開いてはならない。同時に1つ以上のドアの開放を防止するためにインターロッキングシステム或いは視覚的、及び/又は聴覚的同時開放警報システムを設置すること。
53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactiveor live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.	53. フィルターを通した空気を供給することで、周囲のグレードの低い区域に対し、陽圧を保持し、常に空気の流れの上流側でいなければならず、そして効果的な区域の清浄化が実施されなければならない。(非作業時、作業時の状態を含める。)隣接したグレードの異なる区域間の差圧は10－15パスカル(ガイダンス値である)であること。 製品及び製品接触面が暴露する高リスク区域の保護に特別な注意を払うこと。 病原性物質、高毒性物質、放射性物質、生ウイルス、微生物等を扱う区域については空気の供給、差圧等については通常とは異なる基準が必要である。作業によっては施設の除染或いは排出空気の除染が必要である。
54. It should be demonstrated that air-flow patterns do not present a contaminationrisk, e.g. care should be taken to ensure that air flows do not distribute particles from a particlegenerating person, operation or machine to a zone of higher product risk.	54. エアフローパターンが汚染のリスクを含んでいないことを示すこと－発塵する作業員、作業、機器、から塵を製品汚染リスクの高い側の区域に拡散しない気流パターンであることを保証しなければならない。
55. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.	55. 空気の供給に異常をきたした場合の警報システムを設置すること。 差圧管理が重要な箇所には差圧計を設置すること。 これらの差圧は定期的に記録するか、他の方法で文書化すること。
EQUIPMENT	設備

56. A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).	56. コンベアベルトは、自己滅菌装置が装着されてない限り、グレードAの区域とグレートB及びそれ以下のグレードの区域との間の仕切りを貫通してはならない。(例、トンネル滅菌機)
57. As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.	57. 設備、装着物、及び付帯設備は、可能な限り操作、維持管理、修理等を清浄区域外からできるよう設計し、設置すること。 それらの滅菌が必要な場合は、完全に組み立てが終了してから行うこと。
58. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.	58. 設備の維持管理作業を清浄区域内で実施し、その作業中に当該区域の清浄度基準を維持できない場合、製造作業を再開する前に、状況に応じて清掃、消毒、滅菌等適切に行うこと。
59. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70° C.	59. 水製造及び供給システムは適切な品質の水の信頼できる供給源として適切に設計され、維持管理されなければならない。システムは設計能力を越えて運転しないこと。注射用水の製造、貯蔵、配送の際は、例えば70度を超える温度で常時循環する等の方法により、微生物の生育を防止しなければならない。
60. All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.	60. 滅菌設備、空調設備、濾過設備、空気のベントフィルター、ガスフィルター、水処理・製造・貯蔵分配設備、等の全ての設備はバリデーション及び計画的維持管理の対象とすること。(修理・点検からの)正常使用への復帰は承認を得なければならない。
SANITATION	消毒
61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.	61. 清浄区域の消毒は特別に重要であり、文書化されたプログラムに従って行うこと。 消毒剤を使用する場合は2種類以上使用すること。耐性菌の発生を検出するため、定期的にモニタリングを行うこと。
62. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.	62. 消毒剤及び洗剤について菌の汚染に関するモニタリングを行うこと。希釈したものは予め清浄にした容器内に収納し、滅菌しない場合は規定された期限内の保管に限定すること。 グレードA及びBの区域内で使用する消毒剤及び洗剤は使用前には無菌であること。
63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.	63. 清浄区域の燻蒸は手の届かない部分の微生物汚染を低減させるのに有用であろう。

PROCESSING	工程
64. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.	64. 滅菌前の段階を含めて全ての作業段階を通じて汚染を最小限にする注意を払うこと。
65. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of deadorganisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.	65. 微生物由来の製剤は他の医薬品の製造に使用する区域で製造或いは充てんを行わないこと。ただし、死滅した微生物やバクテリアの抽出物等は、不活化した後であれば他の無菌医薬品と同じ施設内で充てんしてもよい。
66. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill).Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.	66. 無菌の工程のバリデーションには栄養培地を使用したプロセスシミュレーションテスト(培地充てん)を含めること。培地の選択は製品の剤形、培地の選択性、清澄度、濃度、及び滅菌の適合性を考慮して行うこと。
67. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.	67. プロセスシュミレーションは当該製品の通常の無菌製造工程にできるだけ類似させ、そして、その後の重要工程を全て含めること。 また、ワーストケースのみならず、通常の作業時にも起こり得る様々な種類の介入について考慮しなければならない。
68. Process simulation tests should be performed as initial validation with threeconsecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should berepeated twice a year per shift and process.	68. 培地充てんは当該製品の工業化生産開始時の製造シフト毎に連続して成功した3ロットを実施し、その後規定された間隔、及び空調システム、設備、工程、シフト数等の重要な変更がある度に繰り返すこと。 通常、培地充てんはシフト毎、工程毎に年2回実施すること。
69. The number of containers used for media fills should be sufficient to enable avalid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:	69. 充てんする本数は有意な評価を行うのに充分な数であること。 バッチサイズが小さな品目については、充てん本数は最低バッチサイズと同じであること。 目標は菌の生育がゼロである、そして以下の点が適用される。
· When filling fewer than 5000 units, no contaminated units should be detected.	・充てん本数が5000本未満の場合は汚染容器が有ってはならない。
· When filling 5,000 to 10,000 units:	・充てんが5000と10000の間の場合:
a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;	a)一容器が汚染されていた場合、究明を行い、培地充てんを繰り返す事を考慮すること

b) Two (2) contaminated units are considered cause for revalidation, following investigation.	b)二容器が汚染されていた場合、究明を行った後再バリデーションを行う
· When filling more than 10,000 units:	・10000本を超える場合：
a) One (1) contaminated unit should result in an investigation;	a)一容器が汚染されていたら究明を行う
b) Two (2) contaminated units are considered cause for revalidation, following investigation.1	b)二容器が汚染されていたら究明の後再バリデーションを行う
70. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.	70. いかなる充てん本数であっても、微生物汚染が間歇的に発生する場合は究明すべき低レベルでの汚染があることを示している。 実質的汚染が発生した場合には、前回正常であった培地充てん以降に製造したバッチについて、無菌性保証への影響への究明を行わなければならない。
71. Care should be taken that any validation does not compromise the processes.	71. バリデーションが工程に悪影響を及ぼさないよう注意すること。
72. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.	72. 水源、水処理設備、及び処理された水は化学的、微生物学的、また該当する場合はエンドトキシンの汚染について定期的にモニタリングしなければならない。モニタリングの結果及び、何らかの処置を行った場合は記録を取らなければならない。
73. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.	73. 清浄区域において、特に無菌操作を行っている際は行動は最小限に控えること。作業員の動きは、過剰な塵と微生物の放出を防止するため抑制し、手順に従うこと。 着用している無塵衣の特性により(蒸れやすいので)室内の温度と湿度は不快なほど高くないようにすること。
74. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.	74. 出発原料の微生物汚染を最小限とすること。モニタリングにより微生物の規格の必要性が示された場合は出発原料の規格に含めること。
75. Containers and materials liable to generate fibres should be minimised in clean areas.	75. 繊維を発生する可能性のある容器或いは材質は清浄区域では最小限としなければならない。
76. Where appropriate, measures should be taken to minimise the particulatecontamination of the end product.	76. 該当する場合は最終製品の塵による汚染への防止対策をとらなければならない。
77. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.	77. 容器構成部品(ゴム栓、キャップ等)、容器、設備(製品接触部品)は最終清浄化の後は再汚染されないよう取り扱わなければならない。

78. The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be minimised and subject to a time-limit appropriate to the storage conditions.	78. 容器構成部品、容器、設備について、洗浄・乾燥と滅菌の間隔及び滅菌と製造での使用との間隔は最小限にすると共に、保管条件に対して適切に設定された時間制限に従わなければならない。
79. The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.	79. 薬液の調製開始から滅菌或いはろ過滅菌までの時間は最小限とすること。各品目ごとに、薬液の組成と保管条件を考慮した最大許容時間を設定しなければならない
80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should beperformed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a microorganism-retaining filter, if possible sited immediately before filling.	80. 滅菌前のバイオバーデン(薬液の生菌数試験)をモニターすること。 滅菌直前の薬液について工程規格を設定すること、規格は適用する滅菌法の効率に依存する。 バイオバーデンアッセイは無菌工程で製造される製品についても、最終滅菌製品についても実施すること。 オーバーキル滅菌パラメータが設定されている最終滅菌製品については、バイオバーデンは適切に設定された間隔で実施しても良い。 パラメトリックリリースのシステムに於いては、バイオバーデンアッセイは全ロットについて実施し、工程管理試験として考慮すること。該当する場合には、エンドトキシンのレベルをモニターしなければならない。 全ての薬液、特に大容量点滴用注射液の場合は、可能な場合充てん直前の位置に設置された除菌フィルターを通さなければならない。
81. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases should be passed through micro-organism retentive filters.	81. 無菌操作を実施する区域で必要な容器の部材、容器、設備は壁に隙間なく設置されたダブルドアの滅菌機で滅菌し、無菌作業区域に搬入するか、或いは同等の汚染防止操作手順を実施しなければならない。 不燃性ガスは除菌フィルターを通さなければならない。
82. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.	82. いかなる新しい工程もその効果についてバリデーションを実施しなければならない。又、過去の実績に基づいて、設定された間隔で、その効果を検証しなければならない。又。 工程或いは設備に明確な変更が行われた際にも、再度バリデーションを行うこと。
STERILISATION	滅菌

・83. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European (or other relevant) Pharmacopoeia or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.	83. 全ての滅菌工程にバリデーションを実施しなければならない。適用される滅菌法が欧州(あるいは関連する)薬局方の最新版に記載されていない場合や、適用される製品が単純な水溶液或いは油性液でない場合は特別な注意を要する。 可能な場合は加熱滅菌を選択すること。何れの場合も滅菌工程は製造販売承認に従わなければならない。
84. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.	84. いかなる滅菌法を適用する場合においても、当該製品に適していること、滅菌する各載荷形態毎の全ての部分において、滅菌庫内の全ての部分で必要とする滅菌条件を達成するための効果を有していることを物理的測定及びバイオロジカルインジケーターにより示さなければならない。工程の有効性を最低年一回の規定した間隔で、又設備に重大な変更が行われた際に検証しなければならない。結果について記録を残さなければならない。
85. For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.	85. 有効に滅菌する為、被滅菌物全体が必要な条件にさらされること、そして工程がこの点を達成するように設計されていなければならない。
86. Validated loading patterns should be established for all sterilisation processes.	86. 全ての滅菌工程についてバリデーションで検証された載荷形態を確立しなければならない。
87. Biological indicators should be considered as an additional method for monitoring the sterilisation.They should be stored and used according to the manufacturer's intstructions, and their quality checked by possitive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.	87. 滅菌のモニタリングの別の方法としてバイオロジカルインジケータを考慮すること。 それらの製造業者の指示に従って保管、使用し、陽性対照を用いてそれらの品質をチェックすること。 バイオロジカルインジケータを使用する場合はそれから微生物汚染を起こさないよう厳重な注意をすること。
88. There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.	88. 滅菌前と滅菌済みの製品を明確に区別するための方策がなければならない。製品或いは構成部品を入れたバスケット、トレー、或いは他の運搬用具には個々に物質名、バッチ番号、滅菌前或いは滅菌済み、といった表示を行わなければならない。オートクレーブテープ等を滅菌工程を受けたか否かの指示用具として使用しても良いが、それらはロットが実際に無菌であることを示す程の信頼性を有しない。
89. Sterilization records should be available for each sterilisation run. They should be approved as part of the batch release procedure.	89. 各滅菌工程毎に滅菌記録がなくてはならない。それらはバッチの出荷判定の一部として承認されなければならない。
STERILIZATION BY HEAT	加熱滅菌

90. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.	90. 加熱滅菌の各サイクルを時間/温度チャートに充分大きいスケールで記録するか、或いはその他の機器によって充分な正確度と精度をもって記録しなければならない。 温度制御と記録のための温度センサーの位置はバリデーションの過程で決定し、該当する場合は、同じ位置に配置した2番目の独立したセンサーと対比して確認しなければならない。
91. Chemical or biological indicators may also be used, but should not take the place of physical measurements.	91. 化学的或いはバイオロジカルインジケーターを使用しても良いが、物理学的測定に代替することはできない。
92. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.	92. 滅菌時間の計測を開始する前に載荷全体が必要な温度に達するために充分な時間をかけなければならない。この時間は、被滅菌物の各載荷形態毎に定めなければならない。
93. After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.	93. 加熱滅菌サイクルの高温相が終了後の冷却過程において、被滅菌物の汚染に対して注意を払わなければならない。リークのある容器の使用が阻止される場合を除き、全ての製品に接する冷却用流体及びガスは滅菌しなければならない。
MOIST HEAT	湿熱滅菌
94. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.	94. 滅菌工程のモニターは温度と圧力の両方を用いること。制御機器は通常モニタリング機器及び記録チャートと独立していること。自働制御及びモニタリング装置が用いられている場合は重要工程要求項目が達成されていることを保証するためバリデーションを実施すること。システム及び滅菌サイクルの異常はシステムにより登録されると共に作業者が観察しなければならない。独立した温度指示器の読みは、滅菌サイクルの間に記録計チャートと対比して日常的に確認すること。チャンバーの底部にドレーンがある滅菌機については、滅菌期間中この部分の温度を記録する必要があるであろう。滅菌サイクルの一部として真空減圧フェーズがある場合は頻繁にリークテストを実施しなければならない。
95. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.	95. 密封容器中の製品以外の場合、被滅菌物は空気の除去と蒸気の透過は可能であるが、再汚染を防止できる材質で包装しなければならない。投入した被滅菌物の全ての部位が必要な温度で必要な時間滅菌剤と接触しなければならない。

96. Care should be taken to ensure that steam used for sterilisation is of suitablequality and does not contain additives at a level which could cause contamination of product or equipment.	96. 滅菌に使用する蒸気は適切な品質であり、製品或いは設備に汚染を生じさせる量の付加物を含まないよう注意しなければならない。
DRY HEAT	乾熱滅菌
97. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.	97. 工程においては、チャンバー内で空気が循環し、非無菌の空気が侵入するのを防止するため陽圧を保持しなければならない。供給空気はHEPAフィルターを通すこと。この工程が脱パイロジェンを意図する場合は、バリデーションの一環としてエンドトキシンチャレンジ試験を実施すること。
STERILISATION BY RADIATION	放射線滅菌
98. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.	98. 放射線滅菌は熱感受性の強い材質や製品に適用される。多くの医薬品及び一部の包装材料は放射線感受性があるので、この滅菌法は実験により製品品質を損なうことが無いことが確認された場合のみ適用できる。紫外線照射は通常滅菌法として認められない。
99. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.	99. 滅菌工程の間照射線量を測定しなければならない。照射線量率の測定とは別に、製品により吸収された線量を定量的に示す照射量インジケータを使用すること。線量計は被滅菌物の中に充分な数を、互いに近接して挿入し、照射機の中に常に線量計があるようにすること。プラスチック製の線量計を用いる場合は、校正の有効期限内に使用すること。線量計の吸収線量は照射後速やかに読み取ること。
100. Biological indicators may be used as an additional control	100. バイオロジカルインジケーターは追加的な管理方法として使用することができる。
101. Validation procedures should ensure that the effects of variations in density of the packages are considered.	101. バリデーションの手順は、包装材料の密度の変動の影響が考慮されることを確実にしなければならない。
102. Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.	102. 被滅菌物を取り扱う手順は、照射前と済みのものの混同を防止するようになっていること。照射前と済みのものを識別するために、放射線感応変色ディスクを各包装ごとに使用すること。
103. The total radiation dose should be administered within a predetermined time span.	103. 総照射線量を予め決められた時間枠内に投与すること。
STERILISATION WITH ETHYLENE OXIDE	エチレンオキサイドガスによる滅菌

104. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.	104. この滅菌法は他に現実的方法がない場合のみ適用すること。工程バリデーションの過程で、滅菌による製品品質へのダメージが無いこと、脱ガスにおける条件と時間が、製品特性に応じて規定された残留ガス及び滅菌ガスの反応生成物の許容濃度以下になることを示すこと。
105. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.	105. ガスと微生物の直接接触が必須である。結晶や乾燥蛋白等の物質内に封入された微生物が存在しないよう注意が必要である。包装材料の性質と量が当該工程に多大に影響する。
106. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.	106. ガスへの暴露の前に、被滅菌物を滅菌条件で要求される温度と湿度に平衡しておかなければならない。 この状態に達するまでの時間は、滅菌までの時間を最小にしなければならないという必要性と相反しているが、それらのバランスをとらなければならない。
107. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.	107. 滅菌サイクル毎に、適切なバイオロジカルインジケーターを、投入した被滅菌物全体に分布させた適切な数のテストピースを用いてモニタリングすること。その結果は、バッチレコードの一部としなければならない。
108. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.	108. サイクル終了までの時間、滅菌工程中のチャンバー内の圧力、温度、湿度、ガス濃度、使用したガスの総量を滅菌サイクル毎に記録すること。 圧力と温度はサイクル全体を通じてチャートに記録すること。その結果は、バッチレコードの一部としなければならない。
109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.	109. 滅菌終了後は、被滅菌物は換気された環境で、残留ガスと滅菌ガスの反応生成物を規定されたレベルまで下げるため管理して保管すること。この工程はバリデーションを実施しなければならない。
FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR CONTAINER	容器における滅菌が不可能な医薬品のろ過
110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.	110. 最終容器内での滅菌が可能な場合、ろ過だけで充分であるとはみなされない。現在利用可能な方法では、蒸気滅菌が望ましい方法である。製品が最終容器内で滅菌できない場合は、溶液又は液体を公称孔径0.22ミクロン(又はこれ未満)或いは同等な除菌能力を有する無菌のフィルターでろ過し、あらかじめ滅菌した容器に充てんすることができる。これらのフィルターは大部分の細菌及び真菌を除去することができるが、ウィルス又はマイコプラズマを全て除去することは出来ない。ろ過滅菌工程を、ある程度の熱処理によって補完することを考慮しなければならない。

111. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.	111. 他の滅菌工程と比較してろ過滅菌法はリスクが高いため、滅菌した除菌フィルターによる更に2度目のろ過を充填直前に行うことが推奨される。最終無菌ろ過は、可能な限り充てんポイントに近い所で行わなければならない。
112. Flibre-shedding characteristics of filters should be minimal.	112. フィルターからの繊維の発生は最小限としなければならない。
113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.	113. 滅菌フィルターの完全性は、使用開始前に検証しなければならない。そして、バブルポイント、ディフュシブ・フロー、プレッシャーホールド試験等の適切な方法を使用して、使用直後に確認しなければならない。既知量のバルク液のろ過に要する時間と、フィルターを通過させるために使用する圧力差は、バリデーション中に決定しなければならない。通常製造中にこれらの数値からの重大な差異があれば記録し、調査しなければならない。これらのチェック結果はバッチ記録の一部に包含すること。重要なガスフィルター及びエアベントフィルターの完全性は、使用後に確認 すること。その他のフィルターの完全性は適切な間隔で確認しなければならない。
114. The same filter should not be used for more than one working day unless such use has been validated.	114. バリデーションで検証されていない限り、同一のフィルターを一作業日を超えて使用してはならない。
115. The filter should not affect the product by removal of ingredients from it or by release of substances into it.	115. フィルターは、製品の成分を除去(吸着あるいは反応により)したり、製品中に物質を放出する等により、製品に影響を及ぼさないようにすること。
FINISHING OF STERILE PRODUCTS	無菌医薬品の最終化工程
116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.	116. 半打栓した凍結乾燥製品は栓が完全に挿入されるまでは常にグレードAの環境下に保持しなければならない。
117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.	117. 容器は適切なバリデーション済みの方法で密封すること。 ガラス或いはプラスチック製のアンプル等の溶閉された容器は100%完全性試験を実施しなければならない。その他の種類の容器については抜き取りサンプルについて適切な方法で完全性の確認を行わなければならない。
118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.	118. 無菌的に充てんされたバイアルの容器栓システムは打栓されたバイアルにアルミキャップが巻き締めされるまでは完全性は十分でない。 そのためキャップの巻き締めは栓を挿入したら可及的速やかに実施しなければならない。
119. As the equipment used to crimp vial caps can generate large quantities of nonviable particulates, the equipment should be located at a separate station equipped with adequate air extraction.	119. 巻き締め機は大量の発塵をする設備であるので、適切な排気システムを備えた区分された場所に設置しなければならない。

120. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.	120. バイアルのキャップ巻き締めは滅菌されたキャップを用いて無菌工程として実施しても良いし、無菌重要区域外でクリーンプロセスとして実施しても良い。 後者のアプローチを採用した場合、無菌工程区域から出るまではグレードAで保護さる、その後もキャップが巻き閉められるまではグレードAの空気供給下で保護されなければならない。
121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.	121. 栓がない、或いは正しい位置にないバイアルは巻き締め前に取り除かなければならない。 巻き締めステーションで人の介入が必要な場合、バイアルに直接接触しないよう、また微生物汚染を最小限とするための適切な技術を適用しなければならない。
122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.	122. アクセス制限バリア(RABS)やアイソレータは要求される条件を実現するために有用であり、巻き締め作業への人の直接介入を最小とするために有用である。
123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.	123. 減圧下で密封された容器は、予め設定した期間の後、減圧を保持しているか確認する為の試験を実施しなければならない。
124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.	124. 充てんした注射剤は異物とその他の欠陥について個装ごとに検査しなければならない。目視検査の場合は、照度と背景について管理された適切な条件下で行うこと。 目視検査員は定期視力検査を受け、眼鏡着用の場合は眼鏡を装着して視力検査を受け、又検査中は頻繁に休憩を与えられなければならない。他の外観検査法を用いる場合は、その工程にバリデーションを実施し、検査装置は定期的に性能を確認しなければならない。 それらの結果を記録しなければならない。
QUALITY CONTROL	品質管理
125. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.	125. 最終製品の無菌試験は、無菌性を保証する一連の管理手段の一番後で実施するものという位置づけである。 無菌試験法は当該製品についてバリデーションを実施しなければならない。
126. In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.	126. パラメトリックリリースが承認されている場合は製造工程全体のバリデーションとモニタリングに特別な注意を払わなければならない。
127. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:	127. 無菌試験用サンプルはバッチ全体を代表するものでなければならない、しかし特に、バッチの中でも汚染のリスクが高いと思われる部分から採取したサンプルも含めること、即ち
a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;	a 無菌的に充てんされた製品については、サンプルは充てん開始時と終了時のもの、及びいかなる重大な介入の後のものも含むこと。

b) for products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.	b 最終滅菌工程による製品は滅菌機に投入された製品の中の、最も温度の低いと思われる位置からサンプルを採取することを考慮すること。

European Journal of Parenteral & Pharmaceutical Sciences 2007; **12**(2): 39-46

Particle and microbial airborne dispersion from people

W Whyte and M Hejab
University of Glasgow, Glasgow, Scotland, UK.

The airborne dispersion of particles from 55 people (30 females and 25 males) was measured. The dispersion per minute of microbe carrying particles (MCPs) averaged 2,400 when wearing personal indoor clothing, and 177 when wearing cleanroom garments. One exceptional person, whose dispersal rates were not included in these results, dispersed 11,000 per minute when wearing cleanroom garments. The dispersion rate of particles ≥5μm per minute averaged 332,000 when wearing indoor clothing, and 37,300 when wearing cleanroom garments. The dispersion rate of particles ≥0.5μm per minute averaged 2,130,000 when wearing indoor clothing, and 1,020,000 when wearing cleanroom garments. The dispersion rates for particles and MCPs were higher in males than females. Depending on the method used, the average equivalent particle diameter of the MCPs was 9μm or 18μm.

There was no situation where the dispersion of MCPs was not accompanied by substantial numbers of both ≥0.5μm and ≥5.0μm airborne particles, and there appears to be little advantage in measuring particles ≥5.0μm when using airborne particle counting to indirectly monitor the dispersion of MCPs. When wearing cleanroom garments, the ratio of ≥0.5μm particles to MCPs was found to average 5,800:1, and for ≥5.0μm particles it was 210:1.

Key words: Particle; microbial, airborne, dispersion, people

Introduction

Microbes in cleanroom air are almost exclusively derived from personnel within the room. People shed one outermost layer of epithelial cells every 24 hours, this amounting to about 10^9 cells per day[1]. Skin cells are approximately 33μm x 44μm in surface area and about 3 to 5μm thick, and may be found in the environment either as whole cells or fragments, the median size across the surface being about 20μm, with 7-10% less than 10μm[1]. Micro-organisms grow on the cells and glands of the skin and are dispersed into the air on skin detritus. These particles are therefore often called microbe carrying particles (MCPs). MCPs will vary in size, shape, and density, and it is conventional to consider the size of particles in terms of equivalent particle diameter, which is the size of a sphere of unit density that has the same aerodynamic properties as the particle being considered. It therefore follows that a skin cell, which has a surface diameter of about 20μm but a thickness of 3 to 5μm is likely to have an equivalent particle diameter below 20μ. Noble, Lidwell and Kingston[2], and Whyte[3], have investigated the equivalent particle diameter of MCPs dispersed from people, and Whyte, Green and Albisu[4] have compiled these results and reported that the average size is about 12μm, with 1% below 1μm, 25% below 7μm, 25% above 24μm, and 5% above 50μm. This size distribution shows that if non viable particles ≥0.5μm were sampled by use of a particle counter then 100% of MCPs would be counted and, if particles ≥5.0μm were sampled, it can be calculated using the method given in Whyte, Green and Albisu's paper that about 83% of the MCPs would be counted.

MCPs and inert particles are kept at a low concentration in cleanroom air. This is done by supplying HEPA filtered air and by minimising the dispersion from people by use of occlusive clothing. From a knowledge of the dispersion rate of MCPs and particles, as well as the air supply to a room, the likely airborne concentration in a cleanroom can be calculated, this method being described by Whyte[5], and Ljungqvist and Reinmüller[6].

The reduction of the dispersion of MCPs by cleanroom garments has been reported by Whyte and Bailey[7], who have also reported on the reduction of the dispersion of particles[8]. Reinmüller and Ljungqvist[9] have also published information on this topic. However, these and similar dispersion studies have been carried out on one person, or on small groups of people. Additional information is required to establish the rates of dispersal of MCPs and total particles by the normal population, and on the ratio of total particles to MCPs, and differences in dispersion rates between males and females.

Annex 1 (2003) of the European Commission Guide to Good Manufacturing Practice (EC GGMP)[10] gives information on concentrations of airborne particles and microbes that should not be exceeded in cleanrooms where sterile pharmaceutical products are manufactured. Airborne MCPs

Corresponding author: W Whyte, James Watt Building South, University of Glasgow, Glasgow, G12 8QQ, UK. Telephone: 0141 330 3699; Fax: 0141 330 3501; Email: w.whyte@mech.gla.ac.uk

must be controlled in cleanrooms, or they may deposit into pharmaceutical products. However, the requirement for controlling inert airborne particles is less clear. Although an occasional inert particle will deposit from the air into containers, the particle deposition into containers has been studied in several pharmaceutical manufacturing cleanrooms, and shown to be insignificant with respect to the regulatory limits set[11, 12], and unlikely to harm patients who receive the product[13]. Particles found in containers after manufacture do not come from air but from containers and stoppers[11]. It is even less clear why airborne particles ≥5μm should be measured in pharmaceutical cleanrooms, especially as their concentration is so low as to be below accurate and reliable measurement. The FDA Guidance (2004)[14] does not have such a requirement. Informal discussions with the European Medicines Agency have suggested that they consider that because particles ≥5μm are closer in size to MCPs than ≥0.5μm particles, they need to be monitored. It has also been suggested that particles ≥5μm can be found with no accompanying particles ≥0.5μm, and therefore need to be independently counted. These suggestions require investigation.

Measurement of particle and microbial dispersion from people

The measurement of airborne particles and microbe carrying particles was carried out in a dispersal chamber. This is the same design as was used in a series of studies starting in 1976[15]. It has the advantage over previous designs as the airborne dispersion rate, i.e. number per minute, can be measured.

Description of dispersal chamber

The dispersal chamber where a person exercised is shown in **Figure 1**. It was 0.68m x 0.52m x 2m high and was made of metal frame covered with clear plastic sheet. Air was supplied at the top of the chamber and passed through a HEPA filter (a) into the chamber. Air was normally supplied at just over 700L/min, and balanced by the removal of air by a high-volume bacterial sampler (Casella slit sampler) operating at 700L/min, and an airborne particle counter operating at 2.83L/min, at sampling port (c). A slight positive pressure was maintained inside the chamber to ensure that no contamination entered the chamber from outside. This outward flow was checked by an anemometer at the exhaust ports (d).

Personnel tested and clothing worn

Testing was carried out on 55 people (30 females and 25 males). All of the females worked within a cleanroom of a pharmaceutical manufacturing company. So did the majority of men, but to make the numbers more even, some male technicians from Glasgow University were tested. Each subject was tested while wearing the following two types of clothing:

1 Personal indoor clothing: Trousers were worn by all subjects except 6 females, who wore skirts. A blouse, shirt, or T shirt was also worn, and clean plastic overshoes were worn over shoes.

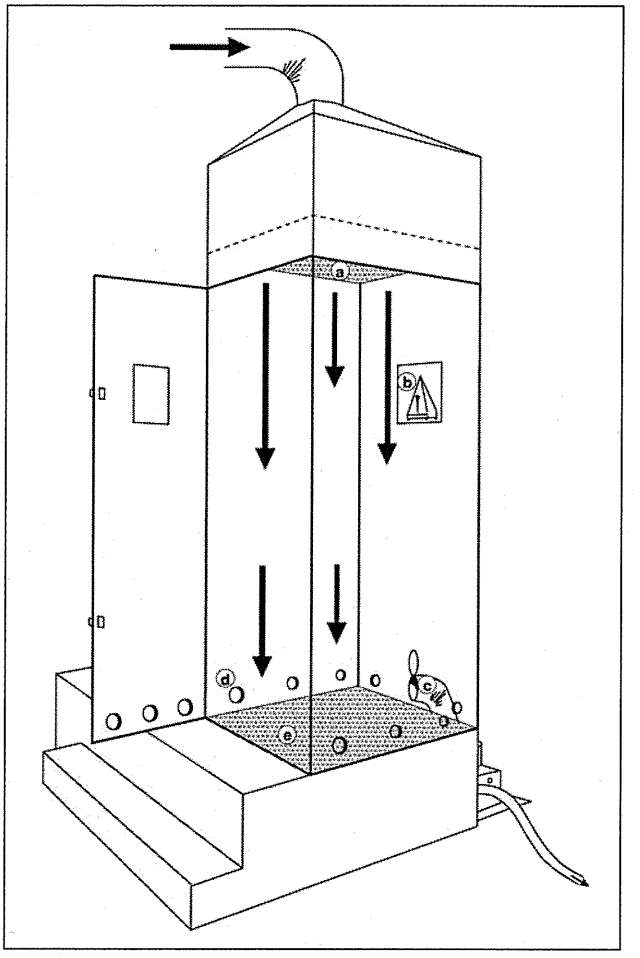

Figure 1. Dispersal chamber.

2 Cleanroom garments, manufactured from woven polyester fabric, were worn on top of the person's indoor clothing. It has been shown that the dispersion rate is dependant on whether the cleanroom clothing is new, or washed and sterilised[9]. The garments were supplied by the pharmaceutical company and it was not clear how often they had been worn. It was certain that none of the garments were new, and the average use was much greater than 50 times. The polyester fabric was tested for pore diameter according to the method laid down in the IEST Recommended Practice 003.3[16]. This test is a good indicator of the filtration and occlusive properties of the fabric, which was shown to have a pore diameter of 25μm. A coverall was worn and its trouser bottoms were covered by knee-length boots. The subject also wore disposable latex gloves, disposable mask and woven polyester hood, the hood being tucked into the neck of the coverall, leaving only the eye area uncovered.

Dispersal chamber test procedure

The test procedure was as follows:

1 The steps leading into the chamber were disinfected.
2 The particle counter, which was used to count particles ≥0.5μm and ≥5.0μm, was switched on and the fan speed increased to its maximum to flush the chamber and reduce the airborne particle count to practically zero.

3 The subject, wearing the required clothing entered the chamber. The door was then closed. The floor of the chamber was covered with a foam mat (e) dipped in disinfectant and wrung out. This ensured that a minimal amount of particle and microbial contamination was re-dispersed from the floor during exercise.
4 The subject stood at rest until the total particle count reduced to practically zero, and became steady.
5 The air supply was then reduced to just over 700L/min.
6 The subject started marching to the beat of a metronome (1 beat/s), while swinging one arm, and then the other, up to their shoulder. The metronome was visible to the person, its position (b) being shown in **Figure 1**.
7 After the first minute of the exercise, the bacterial air sampler, which had a sampling rate of 700L/min, was switched on and off for between 30s and 4 min, depending on the likely dispersion rate. Males wearing their personal indoor clothing were tested for 30s, and when wearing cleanroom clothing they were tested for 2 minutes. Females wearing their personal indoor clothing were tested for 1 minute, and for 4 minutes when wearing cleanroom clothing.
8 MCPs were deposited onto plates containing tryptone soya agar (Oxoid Ltd) supplemented with 0.5% polysorbate 80 to aid the growth of lypophylic skin bacteria. The plates were incubated aerobically for 48 hrs at 37°C before counting the bacterial colonies. To minimise errors, plates were incubated before use and checked for sterility.
9 The particle counter simultaneously recorded the concentrations of the total particles greater, or equal to, 0.5µm and 5.0µm during the exercise.
10 After exercising, the person left the chamber, and the air supply was increased to a maximum to flush the chamber.

Calculation of the dispersion rate

The chamber was designed to give a downflow of unidirectional air. This ensured that during exercise the concentration of airborne contamination came quickly up to a maximum plateau concentration. Tests were carried out that established the airborne contamination took one minute to reach a maximum. This was used as the time when microbial and particle sampling began. Assuming the concentration of airborne dispersion reached a steady state i.e. the dispersion of particles is balanced by their removal, the dispersion of airborne contamination per minute can be calculated by use of the following equation:

$$D = C \times Q/S$$

Where,
D = Total number of MCPs, or particles, dispersed per minute
C = Total number of airborne contaminants measured by the microbial sampler, or particle counter, per minute
Q = air supply rate to chamber (700L/min)
S = sampling rate of microbial sampler (700L/min), or particle counter (2.8L/min)

In the case of the MCPs, the volume of the air supplied to, and removed from, the chamber by the slit sampler can be assumed to be the same, and hence the equation simplifies to the following:

$$D = C$$

In the case of the particle sampler, the sampling rate was 2.83L/min, and the particle dispersion per minute calculated as follows:

$$D = C \times 700/2.8$$

Sampling efficiency of the microbial sampling method

As can be seen in **Figure 1**, the airborne sampler was connected at the bottom of the chamber by a 10cm diameter duct. Because of the height of the sampler's intake and the distance of the chamber from the floor, the duct had to turn through 90° in a short distance. The duct's sharp turn was likely to cause losses due to impaction of the MCPs. Some preliminary tests were carried out to ascertain these losses, and they were thought to be about 25% of the total. It was also known that some microbial samplers have low collection efficiency[17], and therefore some collection losses were likely when using the Casella slit sampler. When tested in comparison to other samplers, the Andersen sampler is normally found to be the most efficient sampler available[17], especially when its entrance cone is removed[18] and it has been suggested as the sampler by which the efficiency of other samplers should be assessed[19,20]. However, the Casella sampler was chosen in preference to the Anderson sampler because of its much higher air sampling rate, which enabled low dispersion rates to be measured.

To ascertain the combined losses from the intake duct and the air sampler, a series of experiments using 20 people (11 females and 9 males) compared the counts from two Anderson samplers (without their entrance cones) placed on the floor of the dispersal chamber, with the attached Casella slit sampler. Indoor clothing was worn and the average count obtained from the slit sampler was 524/min, and 1366/min from the Andersen sampler. This gives a ratio between the two counts of 2.6:1, and this ratio was used to recalculate the count obtained from the slit sampler i.e. the counts from the slit sampler were multiplied by 2.6.

Results of particle and microbial dispersion in chamber

All of the results in this section are given to 3 significant places. The results given in this section do not include the exceptionally high dispersion rate of MCPs obtained from one person. This is discussed in the next section of this paper.

Shown in **Figure 2** is the dispersion rate per minute of MCPs, particles ≥0.5µm, and ≥5µm, obtained from 55 people wearing cleanroom garments. The counts on the left are from females, and those on the right are males.

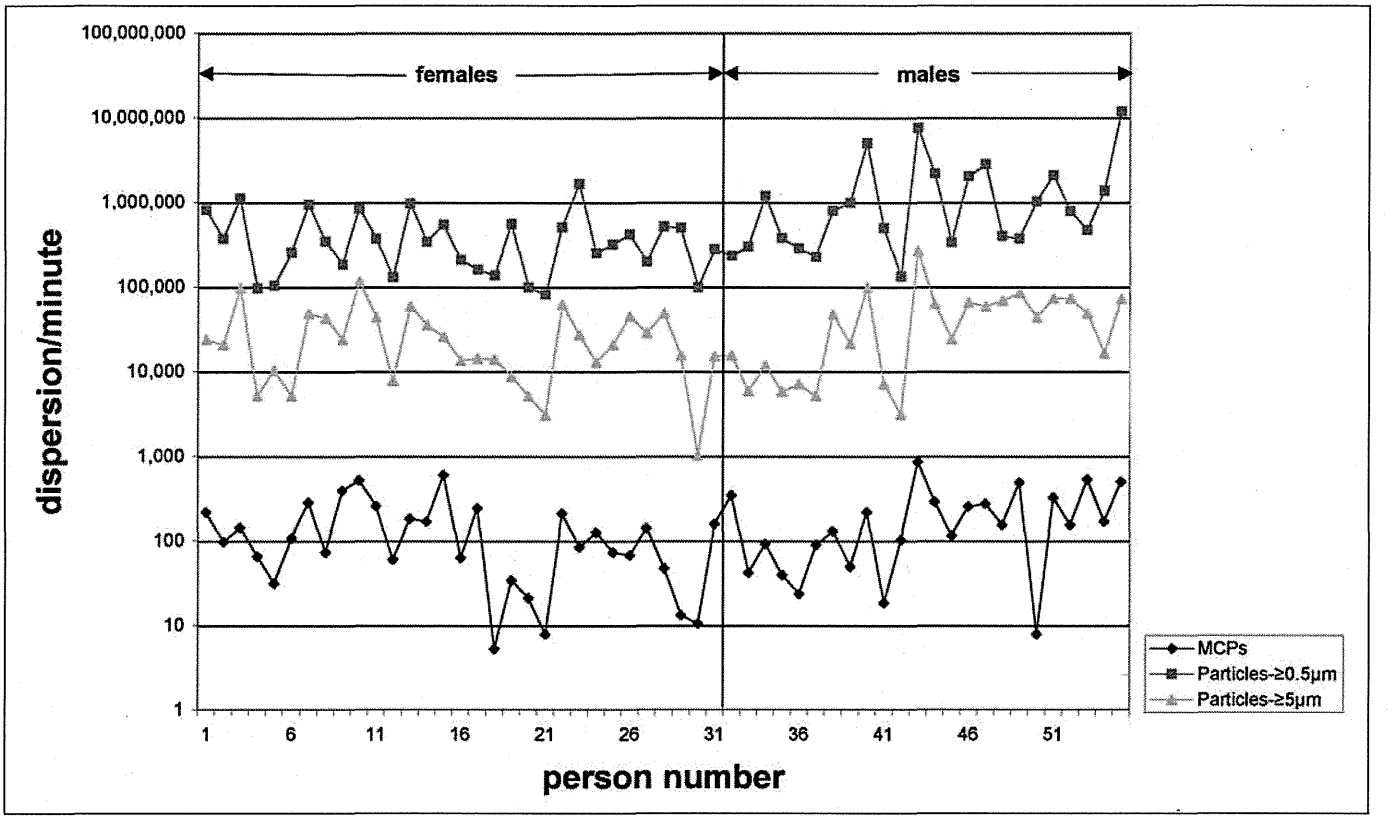

Figure 2. Dispersion of MCPs and particles from 55 people wearing cleanroom garments. Dispersal rates are arranged to show the rates from 30 females on the left and 25 males on the right.

Shown in **Figure 3** is a plot of both the number of particles ≥0.5µm and ≥5µm dispersed per minute from the 55 people in comparison to the dispersal rate of MCPs from the same people.

Given in **Table 1** are the average and range of the dispersion of MCPs per minute. These results are also given for males and females wearing both their normal indoor clothing and cleanroom garments.

Given in **Table 2** are the average and range of counts of the dispersion per minute of particles ≥0.5µm and ≥5µm.

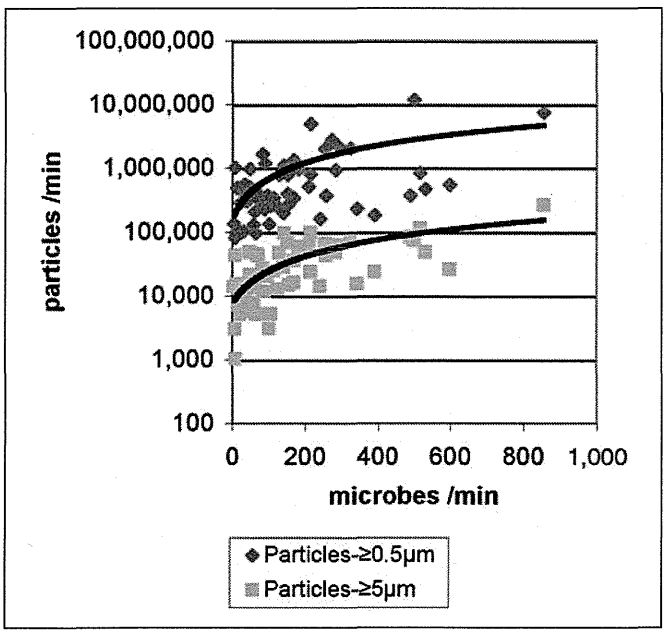

Figure 3. Relation of MCPs to ≥0.5µm and ≥5µm particles.

These results are also given for males and females wearing both indoor and cleanroom garments.

Given in **Table 3** is the reduction in airborne dispersion of MCPs and particles when people wore cleanroom garments over their indoor clothing.

Given in **Table 4** are the ratios of the number of particles and MCPs dispersed per minute by males compared to females. The males always gave a higher dispersion of particles. A two-sample t test was used to compare the counts obtained from the males and females. The dispersion rates of MCPs, particles ≥0.5µm, and particles ≥5µm were compared between males and females when they wore both cleanroom and indoor personnel clothing. The statistical analysis showed this difference, in all comparisons, to be highly significant i.e. $P < 0.001$.

Given in **Table 5** are the ratios of the number of particles ≥0.5µm and ≥5µm dispersed per minute, compared to the number of MCPs dispersed per minute.

Table 1. Average number and range of the dispersion rate per minute of MCPs from 55 people (25 males and 30 females)

	Indoor clothing – MCPs	Cleanroom garments – MCPs
All - averages	2,400	177
All –range	94 to 13,800	5 to 855
Females - averages	943	144
Females- range	94 to 6,630	5 to 514
Males - averages	4,160	216
Males -range	109 to 13,800	7.8 to 855

Table 2. Average number and range of the dispersion rate per minute of ≥0.5μm and ≥5μm particles from 55 people (25 males and 30 females).

	Indoor clothing		Cleanroom garments	
	particles ≥0.5μm	particles ≥5μm	particles ≥0.5μm	particles ≥5μm
All – averages	2,130,000	332,000	1,020,000	37,300
All – range	142,000–14,500,000	3,810-2,110,000	79,700-11,700,000	1,020-263,000
Females – averages	1,720,000	257,000	432,000	29,000
Females – range	142,000-11,800,000	3,810-2,110,000	79,700-1,640,000	1,020-114,000
Males – averages	2,630,000	422,000	1,720,000	47,300
Males – range	250,000-14,500,000	6,350-1,680,000	222,000-11,700,000	3,050-263,000

Table 3. Number of times reduction in airborne dispersion when cleanroom garments were worn over personnel indoor clothing

	MCPs	Particles ≥5.0μm	Particles ≥0.5μm
All	13.6	8.9	2.1
Females	6.5	8.9	4
Males	19.3	8.9	1.5

Table 4. Ratios, males: females of the number of particles and MCPs dispersed per minute.

Indoor clothing			Cleanroom garments		
MCPs	≥0.5μm	≥5μm	MCPs	≥0.5μm	≥5μm
4.4:1	1.5:1	1.6:1	1.5:1	4.0:1	1.4:1

Table 5. Ratios of the number of particles ≥0.5μm and ≥5μm dispersed per minute compared to the MCPs

Indoor clothing		Cleanroom garments	
particles ≥0.5μm	particles ≥5μm	particles ≥0.5μm	particles ≥5μm
890:1	140:1	5,800:1	210:1

Table 6. Number of MCPs dispersed per minute from two male personnel wearing indoor and cleanroom garments.

Person tested	Indoor clothing	Cleanroom garments
Prolific disperser	16,100	11,000
Control person	1,590	6

Microbial dispersion from a prolific disperser

A dispersal chamber test was carried out on one unusual individual. This was in addition to the 55 people, and only microbial dispersion was recorded. The individual had been working for some time in a cleanroom without incident. However, an unusually high percentage of microbes in the room quite suddenly appeared and were identified as *Micrococcus luteus*. The microbial flora of the skin of this person had changed so that it had become predominately *Micrococcus luteus*, and gave an uncountable concentration on the contact plate samples taken from his clothing. The cause of this change was uncertain but he had received antibiotic treatment which could have changed his skin flora. He was withdrawn from the cleanroom and tests carried out in the dispersal chamber.

Tests were carried out on the dispersion of MCPs using the method described in the previous section. These were carried out on both the person and another male, who acted as a control. Both were tested using their indoor clothing i.e. shirt and trousers, and then with cleanroom garments. The cleanroom garments consisted of sterile factory trousers and shirt, with a sterile polyester coverall on top. The coverall, hood, and full length boots were made of the same fabric and design as used in the previous set of tests carried out on 55 people. Disposable mask, polyester hood, and sterile disposable latex gloves were also worn.

Given in **Table 6** is the microbial dispersion rate obtained from the prolific disperser and the control person, when wearing personal indoor clothing and then cleanroom garments. The MCPs sampled from the prolific disperser were almost exclusively one species i.e. *Micrococcus luteus*, which was most unusual. Two tests were carried out for each clothing condition, and these were averaged. The counts were then normalised by multiplying them by 2.6 to take account of the efficiency of the microbial air sampler, as previously determined.

The control person gave microbial dispersion rates within the range of values found with the tests carried out on 55 people, but the prolific disperser gave unusually high ones. Shown in **Figure 4** is the microbial dispersion

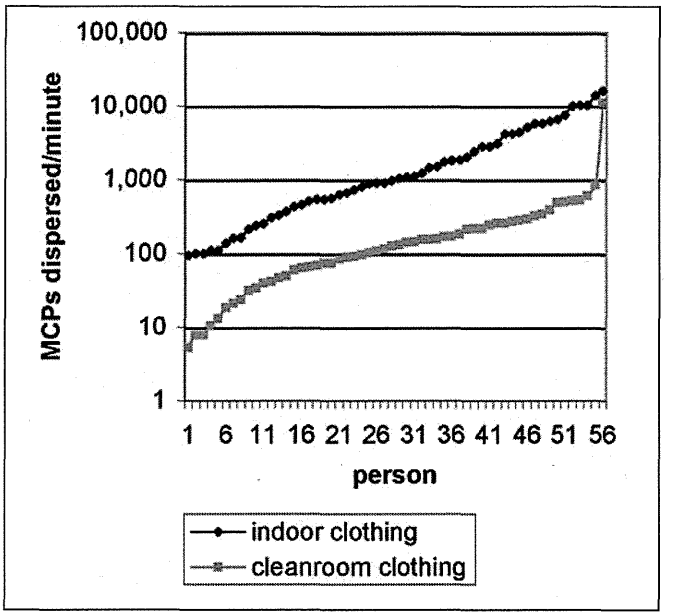

Figure 4. Dispersion of MCPs per minute from 55 people and the additional prolific disperser when wearing indoor and cleanroom garments.