

1 **PROCESS CHANGE EVALUATION FRAMEWORK FOR ALLOGENEIC CELL**
2 **THERAPIES: IMPACT ON DRUG DEVELOPMENT, MANUFACTURING AND**
3 **COMMERCIALISATION**

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26

27 **Abstract**

28 **Aims:** Some allogeneic cell therapies requiring a high dose of cells for large indication
29 groups demand a change in cell expansion technology, from planar units for the early
30 development phases to microcarriers in single-use bioreactors for the market phase. The aim
31 was to model the optimal timing for making this change. **Materials and Methods:** A
32 development lifecycle cash flow framework was created to examine the implications of
33 process changes to microcarrier cultures at different stages of a cell therapy's lifecycle.
34 **Results:** The analysis performed under assumptions used in the framework predicted that
35 making this switch earlier in development is optimal from a total expected out-of-pocket cost
36 perspective. From a risk-adjusted net present value (rNPV) view, switching at phase 1 is also
37 economically competitive but a post-approval switch can offer the highest rNPV as the cost
38 of switching is offset by initial market penetration with planar technologies. **Conclusions:**
39 The framework can facilitate early decision-making during process development.

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41 **Keywords:** allogeneic cell therapy manufacture, process change, bioprocess economics, cost
42 of goods, drug development costs, cash flow

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48 **Introduction**

49 Approximately 40% of cell therapies in development are allogeneic (i.e. universal rather than
50 patient-specific) [1, 2, 3]. The worldwide stem cell therapy market is projected to grow at a
51 compound annual growth rate of 39.5% from 2015 to 2020 and is predicted to reach \$330
52 million by 2020 [4]. The growing number of allogeneic cell therapy products in later-stage
53 clinical trials is heralding a new era for the cell therapy sector. Hurdles firms face in scaling
54 up manufacturing of these cell therapy products, however, remain a key challenge for the
55 industry as it expands [5, 6, 7].

56 For most allogeneic cell therapy products in development or on the market, cell
57 expansion is carried out using either planar technologies such as T-flasks or multi-layer
58 stacked vessels (e.g. Cell Factories (Nunc, ThermoFischer Scientific, Waltham, MA) or Cell-
59 STACKs (Corning Incorporated Life Sciences, Tewksbury, MA)). This practice can be
60 attributed to in-house expertise as well as their ease of scale-up and direct translation from T-
61 flasks or 1-2 layer vessels due to their similar cell growth platform. In contrast, microcarrier
62 cultures have a greater scalability potential, incorporate automation and control and are hence
63 more suited to large-scale commercialisation. Recently, the successful culture of stem cells
64 on microcarriers that were long-established for the culturing of adherent cells in suspension
65 culture for vaccine production has also been demonstrated [8,9] and opened up the
66 opportunity to the use of more scalable three-dimensional microcarrier-based single-use
67 bioreactors.

68 However, making process changes is complicated by the fact that proving
69 comparability can be difficult with existing characterisation methods for cell therapies. Thus,
70 the ability to demonstrate product equivalence following modifications in the manufacturing
71 process is dependent on developing robust manufacturing processes capable of producing cell

72 therapy products with reproducible critical quality attributes [10]. The main challenge is to
73 set process boundaries such that the product is delivered to high quality, safety and efficacy,
74 taking into account variation in master cell banks for allogeneic cell therapies. This effort
75 should be done while maintaining a low cost of goods and a low cost of validation [10]. Even
76 minimal expansion in cell culture can cause potential alterations in cells that may only be
77 determined by later testing of the cell's structural, biological and functional properties [10,
78 11, 12]. Significant challenges remain, however, in gaining a better understanding of
79 mechanisms of action, characterising the product's critical quality attributes and how changes
80 in manufacturing processes can affect these [10].

81 Trade-offs managers face in making manufacturing process decisions in the
82 development of allogeneic cell therapies are similar to those faced by managers in the
83 biopharmaceutical industry. In the latter, manufacturing decisions made during the early
84 stages of research and development have been found to be pivotal decisions with long-lasting
85 consequences for a project's commercial feasibility such as market impact and changes in
86 public policy [13]. On the one hand, making changes to manufacturing processes later on in
87 the product development pathway results in increased risks of development delays, for
88 example because firms may be required to run additional clinical trials to demonstrate
89 product equivalence [14]. On the other hand, finalising manufacturing processes early on in
90 the development process may be economically unattractive due to high failure rates at this
91 stage of the process.

92 Previous cost analyses have shown that microcarrier cultures offer cost of goods
93 benefits that challenge the established position of planar technologies and, for large lot sizes,
94 they are the only feasible technology option [15]. From a downstream perspective, single-use
95 tangential flow filtration has been shown to be more cost-effective for smaller lot sizes and
96 fluidised bed centrifugation has been shown to be the only feasible option for very large lot

97 sizes [16]. However, models that incorporate both cost of goods and drug development costs,
98 as well as reimbursement profiles and risks, have not been presented in this sector. This paper
99 extends the cost of goods analyses for whole processes to consider whether the cost of goods
100 savings with microcarrier-based processes outweigh the cost of drug development. This
101 analysis was achieved by developing a lifecycle cash flow framework to investigate the cost,
102 risk, and project valuation implications of upstream process changes to more scalable
103 expansion technologies at different stages of a cell therapy's development pathway. A case
104 study is outlined that focuses on the impact of using standard planar processes throughout all
105 the clinical phases of development through to market, versus switching to microcarrier-based
106 single-use bioreactors at different points in the lifecycle.

107 The lower costs of commercial manufacturing with microcarrier systems were
108 weighed-up against costs for activities such as process development, process characterisation,
109 technology transfer and comparability studies, as well as time-delays and risks. To estimate
110 the impact of process changes, it is also necessary to account for the final product's revenue
111 in the future, the cost and time required before market launch, and risks along the product
112 development pathway [17]. Hence, the process change evaluation framework comprised three
113 models. The first was a cost of goods model to determine clinical and commercial
114 manufacturing costs. The second was a cost of the development model that combined clinical
115 manufacturing cost of goods with process development, technology transfer, and
116 comparability costs. The third was a development lifecycle cash flow model utilizing the risk-
117 adjusted net present value method to estimate a project's valuation. This integrated
118 framework was used to provide a holistic assessment of the financial implications of process
119 changes at different stages of the development pathway. This type of analysis can smooth the
120 progress of manufacturing decisions during process development and be used to lower the
121 risk of process changes during a product's development cycle.

122 **Materials and Methods**

123 The process change evaluation framework comprised three key models to determine the cost
124 of goods, the cost of drug development and project valuation using net present value. The
125 time required for process changes and the impact of risk were also incorporated.

126 **Cost of goods tool description**

127 A bioprocess economics and optimization model was developed to determine the cost of
128 goods values for different process flowsheets that spanned cell expansion through to volume
129 reduction and filling. A decisional-support tool considering whole bioprocessing for
130 manufacturing a generic allogeneic mesenchymal stromal cell was developed [15, 16]. The
131 model was designed to address the challenge of identifying the most cost-effective upstream,
132 downstream and fill-finish technologies and their sizes for cell therapies across a range of
133 doses, demands, and lots sizes. The model was developed in C# with the .NET framework
134 (Microsoft¹ Visual Studio 2010, Microsoft Corporation, Redmond, WA) linked to
135 Microsoft[®] Access (Microsoft[®] Corporation, Redmond, WA). The bioprocess economics
136 model, together with the input database, established process flowsheets under process and
137 technology-specific constraints, and according to resource consumption and size of
138 equipment. Once the optimal upstream processing (USP) technology was fixed, the
139 downstream processing (DSP) cost of goods per dose ($COG_{DSP}/dose$) was determined for a
140 particular flowsheet. The overall process COG/dose was determined by the sum of the annual
141 direct operating costs (i.e. materials, labor and quality control, (QC)) and indirect costs
142 (facility-dependent fixed capital investment depreciation and maintenance costs) divided by
143 the annual product output in the number of doses/year. Further details of the cost of goods
144 model for upstream and downstream cell therapy processes can be found in Simaria et al. [15]
145 and Hassan et al. [16].

146 **Cost of development tool description**

147 A framework for determining the costs of development activities was created and
148 implemented in Microsoft® Excel (Microsoft® Corporation, Redmond, WA). Table 1
149 summarizes assumptions about different activities that occur in the project’s development
150 pathway and the cost basis of calculations used in this study to estimate the total cost of these
151 activities. Figure 1 shows the model components used for this analysis. Both process
152 development and technology transfer activities were assessed on a full-time equivalent (FTE)
153 basis. For stability studies, the cost per test was considered as the sum of the material and
154 labor costs for the assay, and the facility-dependent indirect cost per assay, divided by the
155 total number of assay equipment uses per year.

156 Process performance qualification (PPQ) batches, manufacturing costs and comparability and
157 bioequivalence costs were calculated according to manufacturing costs using the decisional
158 tool. Estimations of *in vitro* and *in vivo* testing for comparability and bioequivalence costs
159 were also included. Clinical trial costs were estimated according to clinical trial cost per
160 patient and the number of patients for each trial phase.

161 **Cell therapy project valuation tool description**

162 The cell therapy valuation model was developed in Microsoft® Excel (Microsoft®
163 Corporation, Redmond, WA). The tool produces estimates of a project’s cash flows based on
164 project parameters provided by the user. User inputs included parameters relating to the
165 development stage of the project, the allogeneic or autologous nature of the product, dosage
166 per treatment, clinical application, planned process technologies, proposed product price,
167 expected market uptake, the cost of capital, tax rate, staff requirements, and assumptions
168 about a range of costs. The tool makes these estimates based on default values that the user

169 may override with project-specific values. The project valuation is calculated using the risk-
170 adjusted Net Present Value (rNPV) valuation method, by discounting future cash flows by a
171 discount rate that reflects the project's riskiness and the firm's cost of capital. rNPV is a
172 profitability indicator that must be positive to justify the investment made, and the higher this
173 value is the better project outcome. For rNPV of a cell therapy project estimation, the tool
174 also utilises a database with information on clinical trial development times and failure rates
175 of all 592 commercial cell therapy projects that entered development from 1981 until the end
176 of 2011. Based on information about development times for each subsequent development
177 stage, and failure rates of similar projects to the one for which parameters are provided, the
178 tool estimates the expected duration of subsequent development stages and the rate that is
179 used to discount future cash flows and to calculate the project's rNPV. The parameters that
180 are used to identify similar projects are the product type (i.e. allogeneic versus autologous),
181 and the stage of development of the project (i.e. pre-clinical, stage 1, 2, or 3). Accordingly,
182 the discount rate used for the rNPV is a project-specific discount rate that, apart from being
183 based on the firm's cost of capital that is provided by the user, is based on the riskiness and
184 the expected development times for a particular project. Payback time was calculated as the
185 initial investment before market entry divided by the average annual cash flows after market
186 entry.

187 **Case Study Setup**

188 A case study was set up that addressed a key challenge faced by cell therapy manufacturers
189 related to understanding the financial implications of continuing to use standard planar
190 processes throughout all the clinical phases of development through to market, versus
191 switching to more cost-effective and scalable microcarrier-based single-use bioreactors either
192 at early or late phases of development or post-approval.

193 The case study focused on an allogeneic mesenchymal stromal cell (MSC) candidate with a
194 single-dose administration of 2×10^8 cells. The manufacturing scales were determined based
195 on the demand for clinical trial patient numbers considered representative for allogeneic cell
196 therapies and overage (e.g. to cover stability tests). Commercial scale demand scenarios of
197 10,000, 50,000 and 100,000 patients were explored. Table 2 summarises the different
198 manufacturing process change scenarios of the case studies and specifies the different points
199 of switching from planar to microcarrier-based technologies for these scenarios. For phase 3,
200 although it is possible to use a smaller single-use bioreactor than 100L, it was assumed that it
201 was best to keep this scale the same as commercial scale. Similarly, although it is possible to
202 use a smaller bioreactor than 50L at phase 2, it was necessary to use this size of the bioreactor
203 to allow for appropriate scale-up of mesenchymal stem cells to 100L at phase 3. It was
204 assumed that volume reduction was performed by tangential flow filtration and that the
205 product was cryopreserved.

206 The microcarrier scenarios explored were based on the adoption of non-porous xeno-free
207 microcarriers with a surface area of $2930 \text{ cm}^2/\text{g}$ and a microcarrier concentration of 6.3 g/L in
208 the culture. Synthetic-coated microcarriers were assumed since expansion folds that were
209 comparable to those coated with collagen have been recently reported for mesenchymal stem
210 cells [18]. In addition, serum-free media was assumed. Together, these represented a more
211 favourable regulatory compliant approach.

212 The method of estimation of process development and technology transfer costs, in this case
213 study, is demonstrated in Appendix 1, and that for the cost of stability studies is illustrated in
214 Appendix 2. For process development and technology transfer activities, it was assumed that
215 for every unit of FTE year workload, the cost incurred to the company was \$250,000. Thus,
216 the cost in each phase was equal to the product of the total duration of activity in the phase in
217 years, the cost per FTE and the total number of FTE's. Table 5 shows cost estimates for

218 product stability testing, comparability and bioequivalence tests, PPQ batches,
219 manufacturing, and clinical trials. For stability studies, stability tests were performed at 0, 3,
220 6, 9, 12, 18, 24, 36 and 48 months, or for fewer time points depending on which assays were
221 considered [11]. It was assumed that stability studies start at phase 1, and are repeated if there
222 is a process change. It was also assumed that these studies would also be performed on PPQ
223 batches (3 different lots from 3 different donors). Stability tests were carried out on overage
224 of material produced for clinical trials and PPQ batches. For planar processes, this overage at
225 phase 1, 2 and 3 was 8, 3, and 80×10^7 cells/lot respectively, as the amount of cells produced
226 by the optimal technology was greater than the amount of required for clinical studies. For
227 microcarrier-based single-use bioreactors (MC-SUB) processes, the overage at phase 1, 2 and
228 3 was 1, 9 and 20×10^9 cells/lot respectively. In general, the more cells required for trials, the
229 greater the overage produced by optimal technologies. For PPQ batches completed before US
230 Food and Drug Administration (FDA) approval and comparability batches performed in the
231 event of a process change, it was assumed that this was done using three separate lots at the
232 same scale as the forthcoming market scale upon initial market entry. For comparability tests,
233 additional assay tests were accounted for that each cost around \$0.25 million, and *in vivo*
234 studies in 10 animals for an initial \$0.4 million, assuming a good surrogate model was
235 available.

236 For manufacturing costs, it was assumed that there were three manufacturing lots for Phase 1,
237 three lots for Phase 2, 18 lots for Phase 3 and 100 lots for market production.

238 For clinical trials, the number of patients in phase 1, 2 and 3 trials were set as 15, 32 and 240,
239 respectively. It was assumed that a process change necessitates a bridging study with an
240 additional 15 patients. Clinical trial costs per patient were harder to determine due to different
241 trends reported in the literature; examples for biopharmaceuticals in literature tended to
242 suggest clinical costs per patient increase with the phase of development [19] whereas other

243 sources suggest clinical costs per patient often decrease with phase [20]. For our case study,
244 we used the example in [21] where costs per patient for oncology drugs increases from phase
245 1 to phase 2 from \$45,200 to \$69,700 and then to \$74,800 at phase 3 (excluding overheads,
246 Appendix 3). Overhead costs related to clinical trials were included in this analysis
247 (Appendix 3). A decreasing overhead cost as a percentage of the total clinical trials cost was
248 assumed at 15%, 9%, 2% of the total clinical trial cost in phase 1, 2, and 3 respectively.

249 Regarding the post-approval commercialisation of the product, the cell therapy product was
250 assumed to be marketed for seven years at a price of \$10,000 per treatment to a market of
251 10,000, 50,000, or 100,000 patients. A market penetration of 40% was assumed in the first
252 year after launch, 80% in the second year after launch, and 100% after the third year. Sales
253 and marketing costs are assumed to be 30% of costs of goods sold, in line with similar costs
254 that are typical for biopharmaceuticals [22]. A corporate tax rate of 24% was assumed.

255 Capital investment was accounted for in the cash flow, and it was assumed that a
256 manufacturing facility would be built for market production, with construction commencing
257 three years before market launch.

258 Finally, cash flows were discounted using an assumed cost of capital rate of 10%, as well as
259 the risk of failure of the project. These risks were quantified based on information from the
260 cell therapy valuation tool on median failure rates for allogeneic cell therapy projects; For a
261 generic allogeneic cell therapy product, the chance the project progresses to phase 2, 3 and
262 FDA approval stage was estimated to be 87%, 55%, and 36% respectively.

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266 **Monte Carlo analysis**

267 Monte Carlo analysis was used to capture the impact of uncertainties on the key metrics. The
268 Monte Carlo analysis was conducted using Palisade @Risk[®] 6 software (Palisade
269 Corporation, NY, USA). A triangular distribution was assumed for all variable parameters.
270 Factors to vary were determined from sensitivity analyses. For total expected out-of-pocket
271 costs, variables included process development effort for microcarrier-based single-use
272 bioreactors (including both process development and technology transfer costs), the total cost
273 of PPQ batches, the cost of comparability and bioequivalence, and clinical trial costs, each
274 varied by $\pm 50\%$. The clinical phase transition probabilities were assigned triangular
275 distributions with minimum, most likely and maximum values based on our findings. These
276 included a triangular distribution Tr (77%, 87%, 93%) for the probability of entering phase 2,
277 Tr (45%, 55%, 92%) for entering phase 3, and Tr (30%, 36%, 65%) for entering FDA
278 approval stage. For rNPV, triangular probability distributions were assigned to the
279 commercial COG/dose at $\pm 30\%$, market size at $\pm 30\%$, selling price with Tr (8,000, 10,000,
280 25,000), corporate tax rate with Tr (17%, 24%, 40%), and discount value with Tr (8%, 10%,
281 25%). For the post-approval switch, due to possible regulatory hurdles associated with the
282 late switch, the probability of entering FDA approval stage and market was altered by $\pm 30\%$,
283 i.e. Tr (25%, 36%, 47%). Two-sample T-tests were performed on the resulting data to
284 establish whether there was a statistically significant difference between the results for
285 processes involving microcarrier-based single-use bioreactors and the base case (planar
286 process). This analysis was done using OriginPro 9.1.0, Origin Lab Corporation,
287 Northampton, MA, USA.

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289

290 **Results and Discussion**

291 The process change evaluation framework was used to assess the impact of technology
292 switches from planar to microcarrier-based single-use bioreactors at different stages in the
293 cell therapy product development pathway (i.e. phase 1, 2, 3 or post-FDA approval). The key
294 economic outputs related to out-of-pocket costs during drug development and net present
295 value or project valuation were initially evaluated deterministically. Scenario analyses are
296 presented to highlight the combinations of business factors that influence the ranking of the
297 solutions. The impact of the risk of making process technology changes and uncertainties in
298 their performance was also analysed.

299

300 **Drug development cost perspective on process change evaluation**

301 The impact of market size and expansion technology choice on the commercial cost of goods
302 per dose (COG/dose) was analysed. Figure 2a compares the commercial COG/dose for a
303 market size of 10,000, 50,000 or 100,000 patients, where cell expansion is either performed
304 by planar 40-layer cell factories to produce the allogeneic cell therapy product or using 100L
305 microcarrier-based single-use bioreactor(s) for cell expansion. This figure illustrates that the
306 commercial COG/dose for MC-SUB processes are significantly reduced compare to that for
307 planar processes, 40% cheaper for a market size or 10,000, or 70% cheaper for a market size
308 of 50,000 or 100,000 patients.

309 The effect of phase of development and point at which the technology switch is made, on
310 development costs, PPQ batches, manufacturing costs and clinical trial costs were also
311 assessed. Figure 2b shows the expected out-of-pocket costs across each phase of product
312 development with activity breakdowns. This parameter is calculated by summing the total
313 cost in each phase multiplied by the probability of transition into each phase. This figure

314 shows that Phase 3 and FDA approval stages are the most expensive steps in the product
315 development cycle. This can be attributed to the high clinical trial costs at Phase 3, and the
316 expensive PPQ batches at the FDA approval stage. Figure 2c shows that starting in
317 microcarrier-based single-use bioreactors (MC-SUBs) is best from a development
318 perspective. The reason for this is that PPQ batches are significantly lower than sticking with
319 planar processes (PL) or switching to MC-SUBs post-approval (MC-PA) where the product is
320 commercially produced in planar vessels in the PL scenario and for the first year in the
321 market in MC-PA scenario. Also, since the product is already produced in microcarrier-based
322 single-use bioreactors from Phase 1 in MC-P1, the development costs should be lower than if
323 the switch from planar vessels is made during subsequent stages (a change to MC-SUBs at
324 phase 3 (MC-P3) and a change to MC-SUBs at phase 2 (MC-P2)).

325 From Figure 2c, it can be seen that non-clinical costs for cell therapy were found to be around
326 60% of the total drug development costs. This proportion differs to biologics where non-
327 clinical costs are typically around 20-30% of the total drug development costs [23,24]. This
328 difference is mainly due to the much lower total clinical trial costs for cell therapy versus
329 biologics, due to fewer patient numbers required in phase 1 to 3 trials. (The data in Figure 2c
330 is shown in Appendix 4).

331 **Lifecycle profitability perspective on process change evaluation**

332 The economic output of lifecycle profitability was assessed with market size and point at
333 which the technology switch is made. Profitability was assessed with risk-adjusted net
334 present value, rNPV, and a high and positive rNPV value was indicative of an enhanced
335 project outcome. Figure 2d shows that from a lifecycle profitability perspective using the
336 rNPV metric, switching to microcarrier-based single-use bioreactors (MC-SUBs) post-
337 approval should be optimal. This figure shows that the rNPV for MC-PA was four-fold

338 greater than the standard planar process at a market size of 10,000 patients, 1.5 fold greater at
339 a market size of 50,000 patients, and 1.4 fold greater at a market size of 100,000 patients. The
340 higher rNPV can be attributed to the fact that there are no delays associated with market entry
341 since the costs for new expansion technology development are incurred while sales start with
342 the product made using planar vessels in the first year of market penetration. (It was assumed
343 that 40% of the target market is penetrated in the first year of launch). The case in which the
344 product is manufactured using planar vessels throughout its lifecycle is the least favourable
345 from an rNPV perspective, indicating a switch to the more scalable MC-SUBs at any stage in
346 the development lifecycle is better than not making a switch. The difference in rNPV
347 between the case where the process starts in MC-SUBs (MC-P1) and the case where
348 expansion is always planar (PL) is less marked than expected; a three-fold difference in rNPV
349 at a market size of 10,000 patients, and a 1.3 fold rNPV difference at a market size of 50,000
350 and 100,000 patients. This finding was due to the assumed total number of years on the
351 market of 7 years excluding delays. At two years on the market, with a market size of 50,000
352 patients, excluding delays, the rNPV of MC-P1, (using MC-SUBs throughout, starting in
353 phase 1), is double that of PL (staying with planar technologies throughout). At a market size
354 of 10,000 patients, payback time is lowest for PL (11.5 years) and MC-P1 (11.6 years). At the
355 higher market size of 50,000 patients, payback time is lowest for MC-PA, (10.5 years) and
356 PL (10.8 years). At the highest market size of 100,000 patients, however, payback time is
357 shortest for MC-PA (10.4 years), MC-P1 (10.8 years) and PL (10.8 years). For all market
358 sizes, the intermediate switches to MC-SUBs at phase 2 or 3 have the longest payback time.

359 **Sensitivity analysis**

360 The sensitivity of total expected-out-of-pocket costs to various parameters was analysed.
361 Figure 3 illustrates the sensitivity analyses results for a target market size of 50,000 patients
362 (base case). The graphs in Figures 3 a, b, and c show that total expected-out-of-pocket cost

363 (TEOPC) is most sensitive to PPQ batches, and clinical trial costs for all cases. Also, TEOPC
364 is also sensitive to comparability costs if the process change is made later in the development
365 phase i.e. at phase 3 or post-approval. Figures 3 d and e show that rNPV is, however, most
366 sensitive to selling price, market size, and discount rate, with similar profiles for all cases
367 involving microcarrier-based single-use bioreactors. In addition to these factors, for the
368 planar process, rNPV is also quite sensitive to COG/dose and fixed capital investment due to
369 the high associated manufacturing cost related to using this technology at commercial scale
370 of 50,000 patients, (Figure 3d).

371

372 **Scenario analyses: effect on the ranking of cases with respect to cost and rNPV**

373 This section describes the results of the different scenario analyses so as to gain greater
374 insight into the critical levels of key technical, clinical and commercial features of cell
375 therapy development that lead to a switch in the rankings of the process change cases.

376 ***Impact of process development effort on expected out-of-pocket costs***

377 The impact of being able to reduce the extra process development effort required with
378 microcarrier cultures on the ranking of cases was explored for different market sizes (Figures
379 4a and b). Here process development effort includes process development, technology
380 transfer, stability, comparability and clinical trials costs associated with microcarrier-based
381 cell cultures. In reality, current process development efforts associated with MC-SUBs can be
382 improved by using further advanced microcarriers that combine a high-surface area for high
383 growth levels of mesenchymal stem cells, with ease of recovery to minimise losses after
384 expansion and trypsinisation. Also, to improved microcarrier development, this could include
385 enhanced protocols for cell recovery from the microcarriers from microcarrier suppliers.

386 Other factors that could reduce current development efforts associated with this are the
387 incorporation of the design of experiments statistical tool and the use of ultra-scale down
388 techniques [25-27] such as small-scale bioreactors and automation, for rapid screening and
389 optimisation.

390 Figure 4 illustrates that overall, switching post-approval remains more costly regarding total
391 expected out-of-pocket costs irrespective of any decreases in process development effort and
392 market size. However, for the cases of switching to MC-SUBs at Phases 1-3, reductions in
393 process development effort relative to the base case assumption can have an impact on their
394 ranking compared to the standard planar approach. More specifically, in this case study, for
395 these pre-approval switches to MC-SUBs to have equally competitive or lower out-of-pocket
396 costs to the planar process, the process development effort needs to drop by 25-50% for a
397 market size of 10,000 patients (Figure 4a) and 5-25% for 50,000 patients (Figure 4b). In
398 contrast, for a larger market size of 100,000 patients, the early pre-approval switch cases (MC
399 P1, MC P2) can tolerate up to a 25% increase in process development effort above the base
400 case assumption and still be competitive with the planar case, (data not shown).

401 *Impact of COG/dose on rNPV*

402 The impact of commercial COG/dose for planar and microcarrier-based cell cultures and
403 market size on the ranking of cases with regards to profitability expressed as rNPV was
404 performed. Figure 4c shows the results for a market size of 10,000 patients. At this low
405 market size, switching post-approval or starting in MC-SUBs has the highest rNPV, and
406 planar processes the lowest. A 50% increase in COG/dose for MC-SUBs makes starting in
407 MC-SUBs or switching to MC-SUBs post-approval slightly less competitive than the planar
408 process. If however, the market size is increased to 50,000 (Figure 4d), switching to MC-
409 SUBs post-approval, has the highest rNPV always and sticking to planar processes, the

410 lowest. A change in commercial COG/dose has no effect on the ranking of the cases. At a
411 market size of 100,000 patients, the trends for impact on COG/dose on rNPV were similar to
412 50,000 patients, (data not shown).

413 *COG/dose and market size*

414 Figures 5 a-c show two-way sensitivity analyses to show the effect of commercial COG/dose
415 and market size on the % change in rNPV relative to planar processes for a late to early
416 switch, i.e. MC-PA (Figure 5a), MC-P3 (Figure 5b) and MC-P1 (Figure 5c). Light grey
417 regions on these charts are representative of areas where the rNPV for MC-SUB processes are
418 greater than that for traditional planar processes and are thus preferable approaches. These
419 figures show that switching to MC-SUBs post-approval, or starting in MC-SUBs offers the
420 greatest window of flexibility to account for variation in market size and commercial
421 COG/dose for MC-SUBs. For MC-PA, the cost of switching occurs during the first year of
422 market penetration, (with the planar process in Year 1 of launch). MC-P1 offers lower PPQ
423 costs. When the switch is made at phase 3 (Figure 5b) or 2 (data not shown), the operating
424 window for switching to MC-SUBs is smaller due to the greater cost of development if the
425 change occurs at this late stage. This indicates that late phase switches are more sensitive to
426 the market size and the relative difference in the COG/dose between MC-SUBs and planar
427 systems. For example, if the MC-SUBs COG/dose turns out to be over 50% higher than
428 originally anticipated, then the switch to MC-SUBs becomes unfavourable if the market size
429 is also below ~40,000 patients in the late stage MC-P3 scenario (Figure 5b). In contrast, the
430 critical market size drops to ~20,000 patients in the MC-PA and MC-P1 scenarios at 50%
431 higher COG values for MC-SUBs (Figure 5a and c). Hence, the attractiveness of the switch,
432 as measured by rNPV, is largely unaffected by COG/dose and market size changes for the
433 post-approval and early phase scenarios.

434 ***Market size and selling price***

435 Figures 5 d-f show the effect of variation in market size and selling price on the percentage
436 change in rNPV relative to that for planar processes, with the light grey regions representing
437 areas where rNPV is greater using MC-SUB processes than the standard planar process. This
438 type of analysis is useful in demonstrating that if the selling price is increased beyond the
439 base case of \$10,000 per dose, a post-approval switch will still have a greater rNPV than that
440 for planar processes. For example, at a higher selling price of \$25,000 per dose, the model
441 results predict that a post-approval switch would have a favourable rNPV relative to planar
442 processes, while starting in MC-SUBs would give an equally competitive rNPV to planar
443 processes, but intermediate switches at phase 3 or phase 2 (data not shown) would result in a
444 lower rNPV in comparison to planar processes.

445 ***COG/dose and drug development effort***

446 Figures 2d and 5 have shown that MC-PA, followed by MC-P1 are the optimal cases
447 from a lifecycle profitability (rNPV) perspective. Figure 6 assesses whether MC-PA and MC-
448 P1 remain optimal solutions in terms of the highest rNPV when total process development for
449 MC-SUBs, market size and commercial COG/dose for MC-SUBs are varied. Figures 6a-c
450 show the effect of a change in the process development effort needed for switching to MC-
451 SUBs and the commercial COG/dose for MC-SUBs on the window where switching to MC-
452 SUBs wins over sticking to planar systems. The window where $rNPV_{MC} > rNPV_{PL}$ is
453 indicated by the light grey region of these plots for scenarios where the switch is made
454 progressively earlier and for a market size of 10,000 patients (Figures 6a-c) or 50,000 patients
455 (Figures 6d-f). Here total process development effort for MC-SUBs includes process
456 development, technology transfer, stability, comparability and extra clinical trials associated
457 with making a process change. For commercial production, the cost of goods for

458 microcarrier-based single-use bioreactors (COG_{MC}) was lower than the cost of goods for
459 planar vessels (COG_{PL}).

460 Figure 6 illustrates that if the COG difference between the MC and PL systems is
461 greater than anticipated (e.g. % change in $COG_{MC}/dose = -20\%$) then the MC-PA and MC-P1
462 options still win over sticking to planar systems irrespective of the cost of development and
463 market size. However, if the microcarrier options prove more costly to operate than assumed
464 (e.g. % change in $COG_{MC}/dose = +20\%$) then the decision to switch to microcarriers in
465 bioreactors becomes sensitive to the cost of development at the lower market size of 10,000
466 patients.. If this COG increase is accompanied by increases in process development cost in
467 the order of 20%, then the planar options win in terms of overall profitability for the MC-PA
468 and MC-P1 scenarios (Figures 6a and c). .In contrast, switching at phase 3 (MC-P3) is only
469 favourable if the process development effort for MC-SUBs can be reduced by ~40% for cases
470 where the $COG_{MC}/dose$ is higher than expected by 20% (Figure 6b),

471 Figures 6d-f show that for a market size of 50,000 patients, switching to MC-SUBs is
472 better than planar processes from an rNPV perspective irrespective of the timing of the
473 change, the cost of development or the COG/dose, as indicated by the wide windows of
474 operation.

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477 **Robustness of each process change strategy**

478 The study was extended to characterize the variability in the total expected out-of-pocket
479 costs and rNPV values caused by fluctuations in technical, clinical and commercial variables.
480 The following discussion highlights the key findings from this analysis and assesses the
481 robustness of the process change strategies.

482 Figure 7a shows frequency distribution plots generated from the Monte Carlo analysis,
483 illustrating total expected out-of-pocket cost under uncertainty of the probability of entering
484 the next phase of trials or FDA approval stage, including the costs of process development,
485 technology transfer, clinical trials, comparability and bioequivalence, and PPQ batches.
486 Options with the lowest mean costs and narrowest distributions, and hence less risk, are
487 preferred. This figure indicates that the widest distribution in total expected out-of-pocket
488 cost is for a post-approval switch, suggesting that this option has the highest likelihood of
489 exceeding a particular cost budget. This distribution suggests that if a switch is to be made, an
490 earlier switch to MC-SUBs would be less of a risk from a budget perspective. Two-paired T-
491 tests ($p < 0.05$) established that the total expected out-of-pocket cost distributions for MC-
492 SUB processes were significantly lower (MC-P1, MC-P2) or higher (MC-P3, MC-PA) than
493 the planar process. Hence, the ranking of best to worst process with respect to total expected
494 out-of-pocket costs, under conditions of uncertainty and risk, are MC-P1, MC-P2, PL, MC-
495 P3, and MC-PA. This ranking was similar to deterministic values in Figure 2c where
496 uncertainty was unaccounted. Figure 7b shows similar plots for rNPV under the uncertainty
497 of market size, selling price, commercial COG/dose, tax rate and discount value, and the
498 profiles and variation in rNPV are similar regardless of the case. For the post-approval switch
499 (MC-PA), uncertainty in transition to market phase was introduced to account for potential
500 regulatory hurdles introduced by the late switch. Two-paired T-Tests showed that the cases
501 where the switch occurs post-approval or starting in MC-SUBs have significantly higher
502 rNPVs ($p < 0.05$) than the planar process. However, there was no statistical difference
503 between the planar process and switching to MC-SUBs at phase 2 or phase 3. The ranking of
504 processes with respect to highest to lowest rNPV when and uncertainty is taken into account
505 are switching to MC-SUBs post-approval and starting in MC-SUBs as equally optimal,
506 followed by planar processes or switching at phase 2 or at phase 3. This is similar to

507 deterministic risk-adjusted rNPV values in Figure 2d where switching to MC-SUBs post-
508 approval was optimal, followed by starting in MC-SUBs. Although more development work
509 with microcarriers is needed, starting in MC-SUBs may be more optimal than a later switch
510 as there is a lower associated risk of the cells being biologically different concerning
511 functionality in three-dimensional cultures, than in planar, two-dimensional cultures.

512 This analysis was performed for a case study examining allogeneic mesenchymal stromal
513 cells, and thus, we anticipate that different trends could be seen for autologous mesenchymal
514 stromal cells (MSCs), and for other cell types such as pluripotent cells, which also include a
515 differentiation step. Furthermore, this analysis assumed that 3D culture of MSCs was on
516 microcarriers in single-use bioreactors. Studies are showing that MSCs grown as aggregates
517 in suspension in bioreactors may give comparable or better growth conditions than planar
518 systems [28, 29]. Future research would determine whether this would have an impact on the
519 cost and profit implications examined in this case study, as well as on the ranking of the
520 optimal time to switch to 3D culture. Overall this analysis can help to determine the effect of
521 timely process changes on total development costs, rNPV, associated risk, and variation in
522 critical factors. As more cell therapy products are commercially produced at larger scales
523 using newer microcarrier-based single-use bioreactor technologies, successes, failures and a
524 more developed regulation pathway will help to determine the success of key manufacturing
525 processes and business models.

526 **Conclusions**

527 For the commercial production of allogeneic mesenchymal stromal cells for some high dose
528 indications such as graft-versus-host disease (GvHD) or cardiac disease, a switch in cell
529 expansion technologies from traditional planar technologies, such as cell factories, to more
530 scalable microcarrier-based single-use bioreactors, may be necessary. A process change
531 framework was applied to a case study assessing a dose of 2×10^7 cells per patient for a

532 market size of 10,000, 50,000 and 100,000 patients. In addition to manufacturing costs, costs
533 of process development, technology transfer, clinical trials, and comparability were assessed.
534 Implications of different manufacturing process technology strategies were analyzed for total
535 expected out-of-pocket costs and the project's profitability (rNPV). In our assessment and
536 under the assumptions used in the framework, intermediate switches at phase 2 or phase 3
537 were less favourable than either using microcarrier-based single-use bioreactors throughout,
538 starting in phase 1, or making the switch post-approval. However, in our assessment, it was
539 always better to switch than never to switch. If the scenario of starting in single-use
540 bioreactors is compared to switching post-approval, a post-approval switch is more
541 advantageous from a profitability perspective, and in the possible event that the selling price
542 is significantly higher than assumed (£10,000 per treatment). Starting in microcarrier-based
543 single-use bioreactors overall is more favourable due to the lower total expected-out of-
544 pocket costs, and the fact that that rNPV is not much less than a post-approval switch.
545 Moreover, such a strategy allows for wider unexpected changes in process development
546 effort for microcarrier-based single-use bioreactors, bridging study size, market size and
547 commercial COG/dose. Overall, there should be less risk of a wide variation in total costs
548 when the switch to microcarrier-based single-use bioreactors is made early at phase 1, rather
549 than at the post-approval stage. This analysis can help to manage better the risks associated
550 with process changes at different stages of the product's development lifecycle.

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558 **Executive summary**

559 **Production of commercial allogeneic mesenchymal stem cells**

- 560 • Allogeneic mesenchymal stem cells produced at commercial scale for some high dose
561 indications may necessitate a process change from traditional planar cell expansion
562 technologies to microcarrier-based single-use bioreactors.

563 **Decisional tool**

- 564 • A decisional tool comprising a process change evaluation framework, was developed
565 for a case study assessing a dose of 2×10^7 cells per patient for a market size of
566 10,000, 50,000 and 100,000 patients.
- 567 • Total expected out-of-pocket costs including manufacturing costs, and costs of
568 process development, technology transfer, clinical trials, and comparability were
569 included.
- 570 • rNPV was also assessed to compare switching at phase 1, 2, 3 or post-approval.

571

572 **Conclusion**

- 573 • The results of this analysis are dependent on the assumptions used in the framework.

- 574 • Switching to microcarrier-based single-use bioreactors at the beginning of phase 2 or
575 phase 3 are financially less favorable compared to switching at the beginning, phase I
576 or after approval (if bioequivalence can be shown).
- 577 • But, switching is always better than never switching.
- 578 • A post-approval switch gives the highest rNPV, and is more robust to significant
579 increases in selling price.
- 580 • Starting in microcarrier-based single-use bioreactors overall is the best approach due
581 to its lower total expected-out of-pocket cost, a high rNPV, and is less susceptible to
582 changes in process development effort for microcarrier-based single-use bioreactors,
583 bridging study size, market size and commercial COG/dose.

584 **Abbreviations**

585 CF-10: 10-layer cell factories

586 CF-40: 40-layer cell factories

587 COG/dose: Cost of goods per dose

588 $COG_{DSP}/dose$: Downstream processing cost of goods per dose

589 COG_{MC} : cost of goods for microcarrier-based single-use bioreactors

590 $COG_{MC}/dose$: cost of goods for microcarrier-based single-use bioreactors per dose

591 COG_{PL} : cost of goods for planar vessels

592 $COG_{PL}/dose$: cost of goods for planar vessels per dose

593 DSP: Downstream processing

594 ELISA: enzyme-linked immunosorbent assay

595 FDA: Food and drug administration (US)

596 GvHD: Graft-versus-host disease

597 FTE: Full-time equivalent

598 MC-PA: Change to MC-SUB post-approval

599 MC-P1: MC-SUBs throughout (starting in phase 1)
600 MC-P2: Change to MC-SUB at Phase 2
601 MC-P3: Change to MC-SUB at Phase 3
602 MC-SUB: microcarrier-based single-use bioreactor
603 MSC: mesenchymal stromal cell
604 PD: process development
605 Ph: Phase of clinical trial
606 PL: planar vessels
607 PLE: process limit evaluation
608 PPQ batches: Process Performance Qualification batches
609 R&D: research and development
610 QA: Quality assurance
611 QC: Quality control
612 rNPV: Risk adjusted net present value
613 $rNPV_{MC}$: risk-adjusted net present value for microcarrier-based single-use bioreactors
614 $rNPV_{PL}$: risk-adjusted net present value for planar vessels
615 TEOPC: total expected-out-of-pocket cost
616 Sterility USP: Sterility, United States Pharmacopeia
617 Tr: triangular distribution (in Monte Carlo analysis)
618 USP: Upstream processing
619

620 **Acknowledgements**

621 Financial support from the Technology Strategy Board (UK) and Lonza is gratefully
622 acknowledged. Constructive feedback and technical advice from industrial experts at Lonza
623 is gratefully acknowledged. UCL hosts the EPSRC Centre for Innovative Manufacturing in
624 Emergent Macromolecular Therapies with an academic network and a consortium of
625 industrial and government users.

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703

Table 1: Assumptions of activities that occur in a product’s development lifecycle, phases of the lifecycle in which these activities are performed, and the cost basis of calculations used in this case study to estimate the total cost of these activities. Ph: clinical trial phase; FTE: full-time equivalent workload; FDA app: Food and drug administration approval; PPQ: Process performance qualification; COG: cost of goods; CPP: critical process parameter; PLE: process limit evaluation.

	Process Development	Comparability & Bioequivalence	Technology Transfer	Process performance qualification	Product stability	Clinical material production	Clinical trials
Assumptions of activities involved	Cell characterisation, Assay development, Assay qualification, Process optimisation, Equipment validation	<i>In vitro</i> (assay cost) and <i>in vivo</i> (animal model surrogate). If process change: additional but fewer lots at the same scale using the old process to demonstrate equivalence in clinic. Process is then locked.	Identification of 5-10 CPPs and performing PLE studies, Documentation, Training	3 PPQ batches	Stability tests & assays (use conformance batches as want shelf life to be as long as possible).	Engineering runs, Clinical production	Clinical trial costs, Extra clinical trial cost if process change
When occurs	Ph 1/2/3 (& FDA app if there is a post-approval change)	At the stage of process change for comparability/bioequivalence & <i>in vitro</i> testing & at Ph 1 for <i>in vivo</i> testing	Ph 1/2/3/FDA app	FDA app	Starts at Phase 1, repeated if there is a change and done again at FDA app stage (final process)	Ph1/2/3	Ph1/2/3 (& FDA app if there is a post-approval change)
Cost basis	FTE	Cost per dose for additional batches using the old process & assumed <i>in vitro/in vivo</i> cost	FTE	COG/dose (includes assay validation cost as QC cost)	Assay cost (includes material cost, labour cost, Indirect cost)	COG/dose	Clinical trial cost per patient

Table 2: Cell expansion technologies used in each case and phase for allogeneic mesenchymal stromal cell therapy manufacturing. Downstream processing steps are assumed to be tangential flow filtration followed by cryovial filling for cryopreservation in all cases. CF-10: 10 layer cell factories; CF-40: 40-layer cell factories; MC-SUB: microcarrier-based single-use bioreactors.

	Phase 1	Phase 2	Phase 3	Market size (number of patients, x1000)	FDA approval & Market
PL: Planar technologies throughout	10 x CF-10	20 x CF-10	8 x CF-40	10	48 x CF-40
				50	232 CF-40
				100	464 CF-40
MC-PA: Change to MC-SUB post-approval	10 x CF-10	20 x CF-10	8 x CF-40	10	1x 100L MC-SUB
				50	2x 100L MC-SUB
				100	4x 100L MC-SUB
MC-P3: Change to MC-SUB at Phase 3	10 x CF-10	20 x CF-10	1x 100L MC-SUB	10	1x 100L MC-SUB
				50	2x 100L MC-SUB
				100	4x 100L MC-SUB
MC-P2: Change to MC-SUB at Phase 2	10 x CF-10	1x 50L MC-SUB	1x 100L MC-SUB	10	1x 100L MC-SUB
				50	2x 100L MC-SUB
				100	4x 100L MC-SUB
MC-P1: MC-SUBs throughout (starting in phase 1)	1x 10L MC-SUB	1x 50L MC-SUB	1x 100L MC-SUB	10	1x 100L MC-SUB
				50	2x 100L MC-SUB
				100	4x 100L MC-SUB

Table 3: Estimated costs in \$ millions of product development, technology transfer, comparability and bioequivalence tests, process performance qualification (PPQ) batches, product stability testing, manufacturing, and clinical trials. Cost estimations were as in Table 1. Product development and technology transfer costs were estimated on a fixed time equivalent (FTE) basis, and example calculations are in Appendix 4. Stability costs were based on assay costs shown in Appendix 1. Data is shown for market sizes of 10,000, 50,000 or 100,000 patients. Any changes due to market increase to 50,000 are shown in round brackets, and any changes due to a market increase to 100,000 are shown in square brackets, if applicable. PL: planar throughout; MC-PA: Change to MC-SUB post-approval; MC-P1: using MC-SUBs throughout, starting at phase 1; MC-P2: Change to MC-SUB at Phase 2; MC-P3: Change to MC-SUB at Phase 3; MC-SUB: microcarrier-based single-use bioreactor.

		Phase 1	Phase 2	Phase 3	FDA approval/Market
Process Development	PL	0.5	0.5	1.5	
	MC-PA	0.5	0.5	1.5	5
	MC-P3	0.5	0.5	3	
	MC-P2	0.5	3	3	
	MC-P1	1.25	3	3	
Technology Transfer	PL	0.5	0.5	1.5	2
	MC-PA	0.5	0.5	1.5	5
	MC-P3	0.5	0.5	1.5	5
	MC-P2	0.5	1.5	1.5	5
	MC-P1	0.75	1.5	1.5	5
Comparability & bioequivalence	PL	0.4			
	MC-PA	0.4			9.71 (13.55) [26.23]
	MC-P3	0.4		9.71 (13.55) [26.05]	
	MC-P2	0.4	2.07		
	MC-P1	0.4			
PPQ batches	PL				12.8 (37.7) [73.1]
	MC-PA				15.9 (32.2) [62.5]
	MC-P3				9.5 (13.3) [26.0]
	MC-P2				9.5 (13.3) [26.0]
	MC-P1				9.5 (13.3) [26.0]
Product stability	PL	0.05	0.04	0	0.27
	MC-PA	0.05	0.04	0	0.53
	MC-P3	0.05	0.04	0.07	0.27
	MC-P2	0.05	0.1	0	0.26
	MC-P1	0.05	0.04	0	0.27
	MC-PA	1.15	1.23	4.55	
	MC-P3	1.15	1.23	5.65	
	MC-P2	1.15	1.82	5.65	
MC-P1	1.22	1.82	5.65		
Clinical trials	PL	0.78	2.44	18.23	
	MC-PA	0.78	2.44	18.23	1.22
	MC-P3	0.78	2.44	19.45	
	MC-P2	0.78	3.58	18.23	
	MC-P1	0.78	2.44	18.23	

Decisional tool for process change evaluation							
		DEVELOPMENT	MANUFACTURING	CLINICAL TRIALS	MARKET		
KEY MODEL INPUTS	Per Phase:	<ul style="list-style-type: none"> Process development FTE Technology transfer FTE Comparability (<i>in vitro</i> & <i>in vivo</i> testing requirements) Stability assay requirements Duration 	Per Phase:	<ul style="list-style-type: none"> Demand Material requirement Labour requirement QC requirement Indirect overheads Number of PPQ batches Resource unit costs Duration 	Per Phase:	<ul style="list-style-type: none"> Clinical trial cost per patient Number of patients Duration Phase transition probability Dose 	<ul style="list-style-type: none"> Market size Selling price Sales curve Sales & marketing costs Discount rate
	COST METRICS	Development cost per phase:	<ul style="list-style-type: none"> Process development cost Tech transfer cost Comparability cost Stability assay cost 	Manufacturing cost:	<ul style="list-style-type: none"> Capital investment Clinical manufacturing cost PPQ batch cost Commercial cost of goods (COG) 	Clinical trial cost per phase	
		Expected total cost of development					
		Expected out-of-pocket cost per phase					
PROFIT METRICS	<ul style="list-style-type: none"> Reimbursement Risk adjusted net present value (rNPV) Payback time 						

Figure 1: Process change model structure. Tech transfer: Technology transfer; PPQ: Process performance qualification.

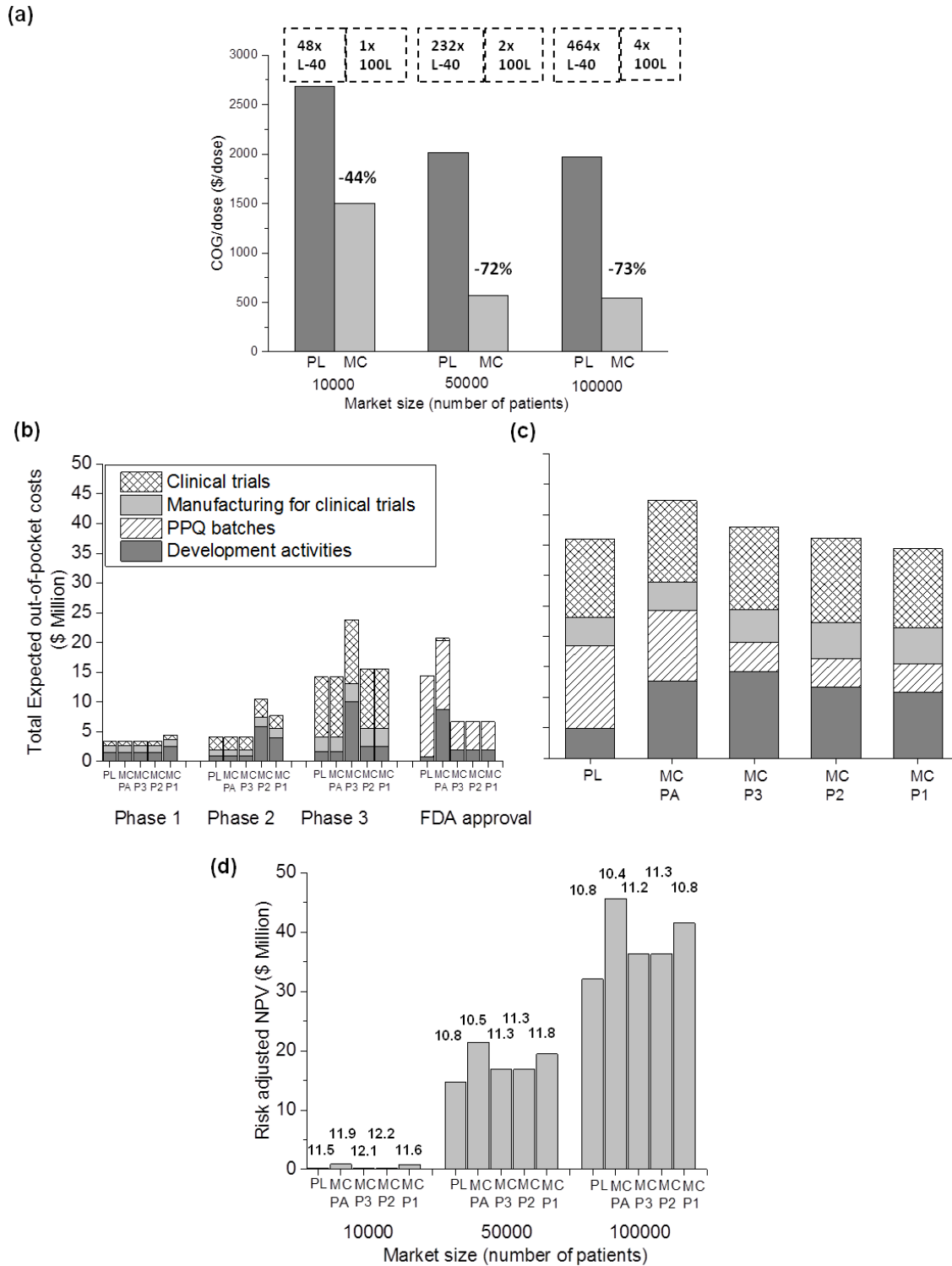


Figure 2: Assuming a dose of 200 million mesenchymal stromal cells, a) commercial cost of goods per dose (COG/dose) for an assumed market of 10,000, 50,000 and 100,000 patients, for a manufacturing process where cell expansion is performed by planar 40-layer cell factories, versus cell expansion in 100L microcarrier-based single-use bioreactors. b) For a market size of 50,000 patients, expected out-of pocket costs across phase and c) total expected out-of-pocket costs with activity breakdowns for planar process (PL), change to microcarrier-based SUB process post-approval (MC PA), change to MC-SUBs at phase 3 (MC P3), change to MC-SUBs at phase 2 (MC P2), or using MC-SUBs throughout, starting in phase 1 (MC P1). d) Risk adjusted net present value for these cases. Payback time in years is shown above the bars.

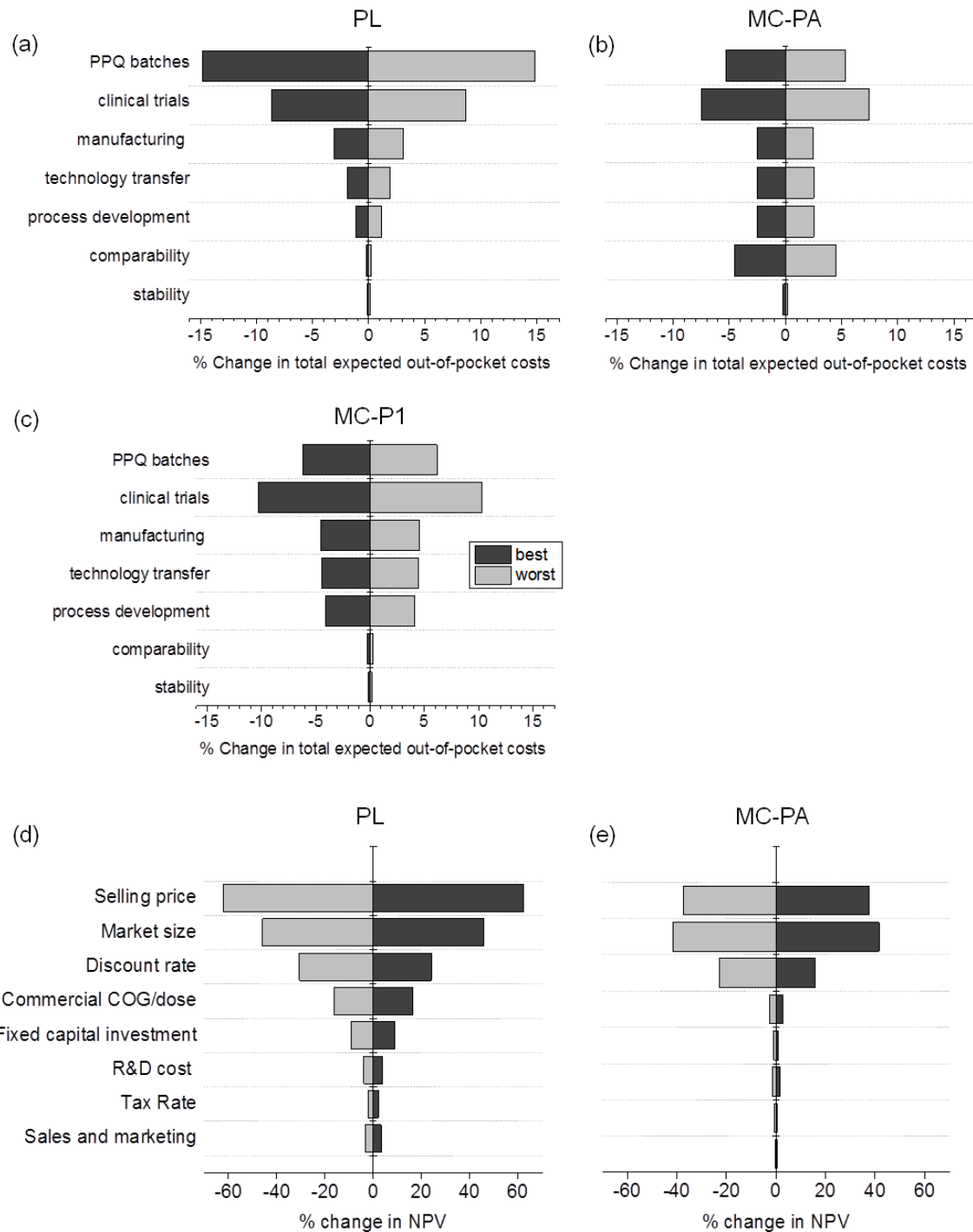


Figure 3: For a target market size of 50,000 patients (base case), Sensitivity analyses with respect to total expected-out-of-pocket costs to reach approval for **a)** planar technologies throughout, PL, **b)** change to microcarrier-based SUB process post-approval, MC-PA, or **c)** using microcarrier-based SUBs throughout, starting in phase 1, MC-P1. The sensitivity analysis plot for a change to MC-SUBs at phase 3 was similar to a change to MC-SUBs post-approval (data not shown). The sensitivity analysis plot for a change to MC-SUBs at phase 2 was similar to using MC-SUBs throughout, starting in phase 1 (data not shown). Sensitivity analyses with respect to risk adjusted rNPV for **d)** planar technologies throughout, PL, **e)** change to microcarrier-based SUB process post-approval, MC-PA. A change to microcarrier-based SUBs at phase 3, phase 2, or Phase 1 had similar profiles to the post-approval change (data not shown). PPQ: process performance qualification; COG/dose: cost of goods per dose; R&D: research and development.

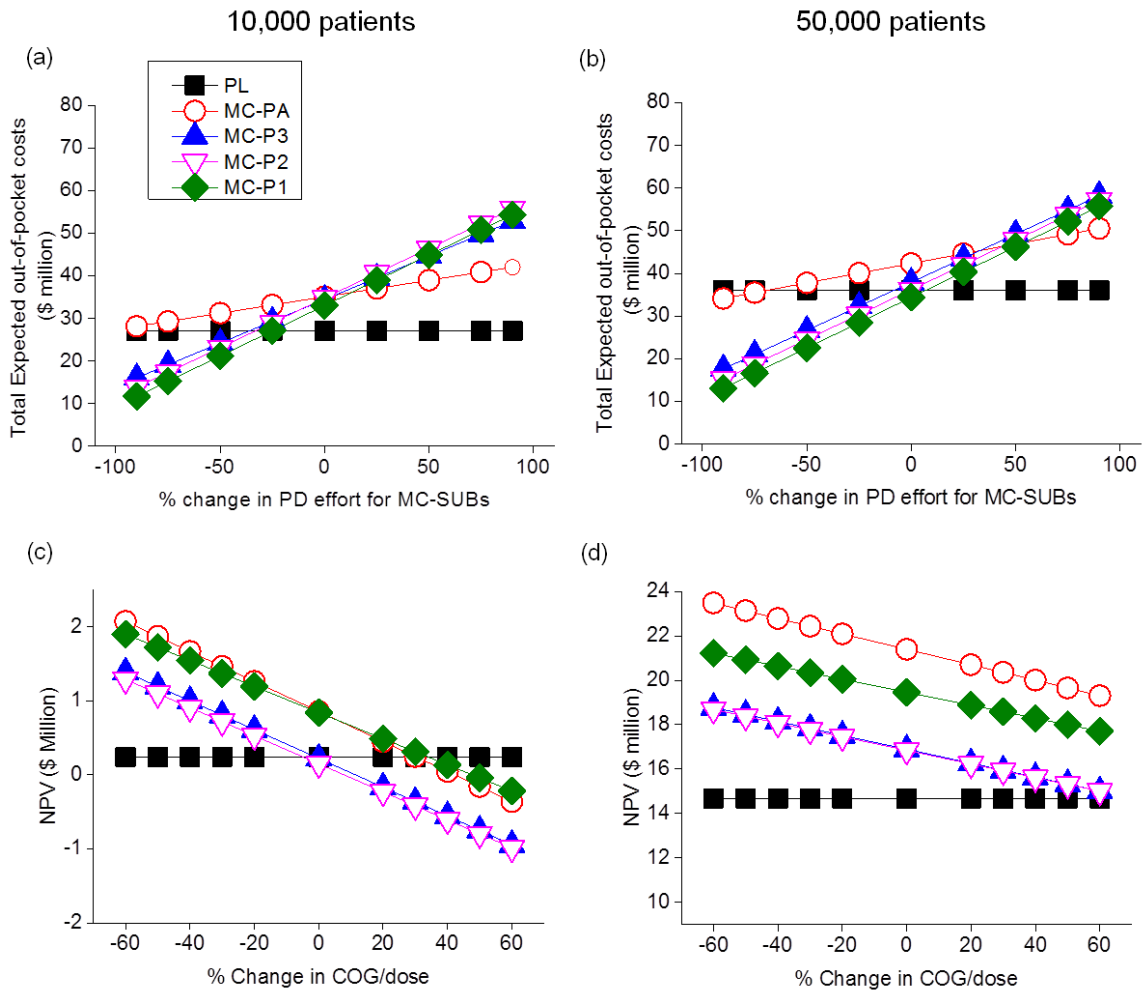


Figure 4: The impact of a change in process development effort needed for microcarrier-based cell cultures on the ranking of cases with respect to total expected out-of-pocket costs for a market size of **a)** 10,000 and **b)** 50,000 patients. Here total process development effort includes process development, technology transfer, stability, comparability and extra clinical trials associated with making a process change. The impact of commercial COG/dose for microcarrier-based cell cultures on the ranking of cases with respect to total rNPV for a market size of **c)** 10,000 and **d)** 50,000 patients. In this analysis it is assumed that the COG/dose for planar processes is fixed and that for MC-SUBs is varied. MC-SUB: microcarrier-based single-use bioreactor; COG/dose: cost of goods per dose; rNPV: risk-adjusted net present value; PL: planar technologies throughout; MC-PA: change to MC-SUBs post-approval; MC-P3: change to MC-SUBs at phase 3; MC-P2: change to MC-SUBs at phase 2; MC-P1: MC-SUBs throughout (starting in Phase 1).

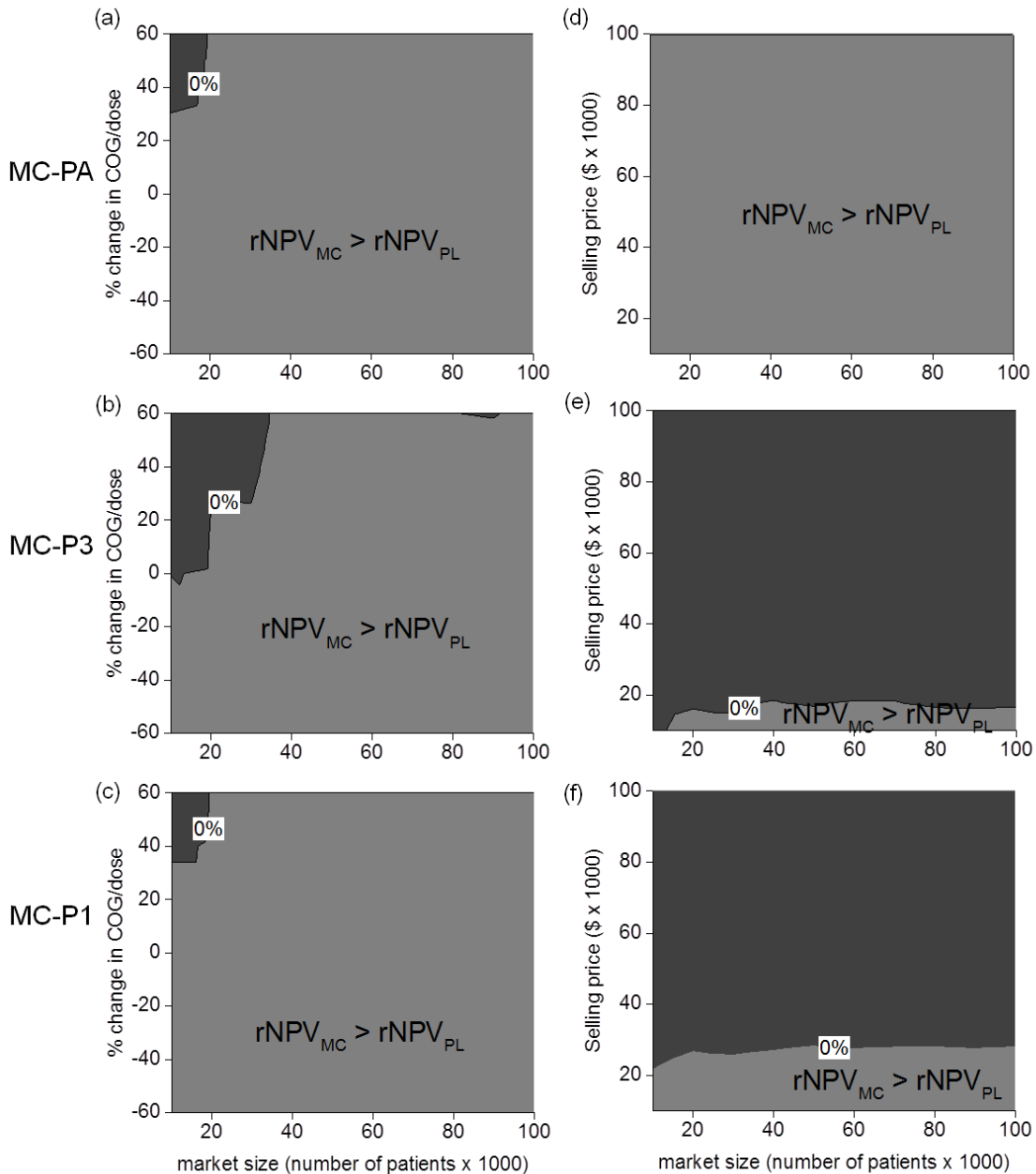


Figure 5: Two-way analyses to show the effect of commercial COG/dose for MC-SUBs and market size on the % change in rNPV relative to planar processes for switching to microcarrier-based SUBs (a) post-approval, MC-PA, (b) at phase 3, MC-P3 (similar to phase 2, data not shown), and (c) at phase 1, MC-P1; Two-way analyses to show the effect of market size and selling price on the % change in rNPV relative to planar processes for switching to microcarrier-based SUBs (d) post-approval, MC-PA, (e) at phase 3, MC-P3 (similar to phase 2, data not shown), and (f) at phase 1, MC-P1. Dark grey regions indicates windows of operation that favours sticking with planar processes, and light grey regions labelled $rNPV_{MC} > rNPV_{PL}$ represent windows of operation that favours switching to MC-SUBs, where rNPV is risk adjusted net present value, MC is microcarrier-based single-use bioreactors and PL are planar vessels.

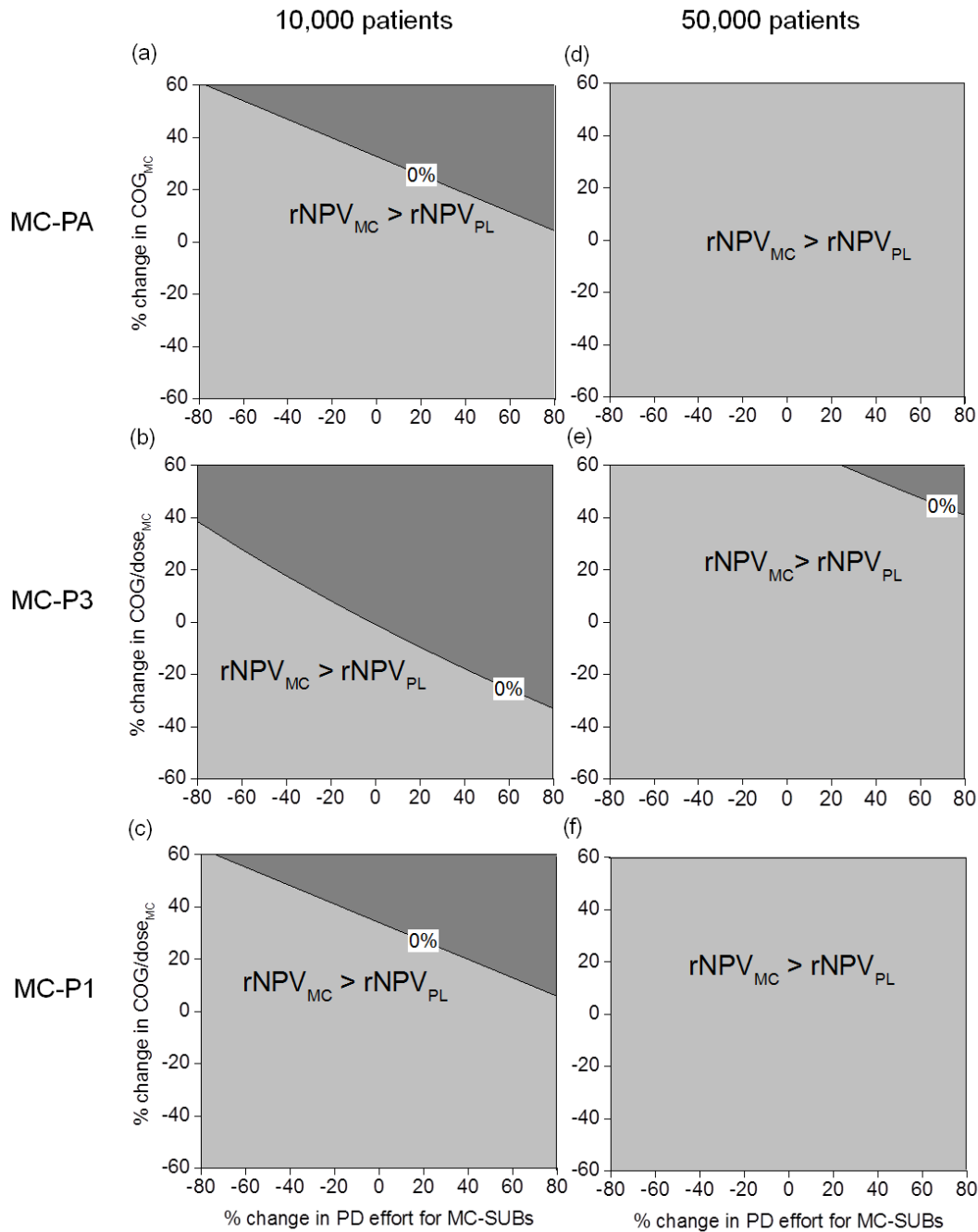


Figure 6: Two-way analyses to show the effect of % change in total process development effort for microcarrier-based cell cultures (MC-SUBs) and % change in COG_{MC} on the percentage change in $rNPV$ relative to planar processes for switching to MC-SUBs. Here total process development effort includes process development, technology transfer, stability, comparability and extra clinical trials associated with making a process change. Dark grey regions indicates windows of operation that favours sticking with planar processes, and light grey regions labelled $rNPV_{MC} > rNPV_{PL}$ represent windows of operation that favours switching to MC-SUBs. Results shown for a market size of 10,000 patients for switching to MC-SUBs a) post-approval, b) at phase 3 (similar to phase 2, data not shown), c) at phase 1, and for a market size of 50,000 patients for switching to MC-SUBs d) post-approval, e) at phase 3 (similar to phase 2, data not shown), f) at phase 1. (For a market size of 100,000 patients, the results were very similar to 50,000 patients, data not shown). MC-PA: change to MC-SUBs post-approval; MC-P3: change to MC-SUBs at phase 3; MC-P2: change to MC-SUBs at phase 2; MC-P1: MC-SUBs throughout (starting in Phase 1).

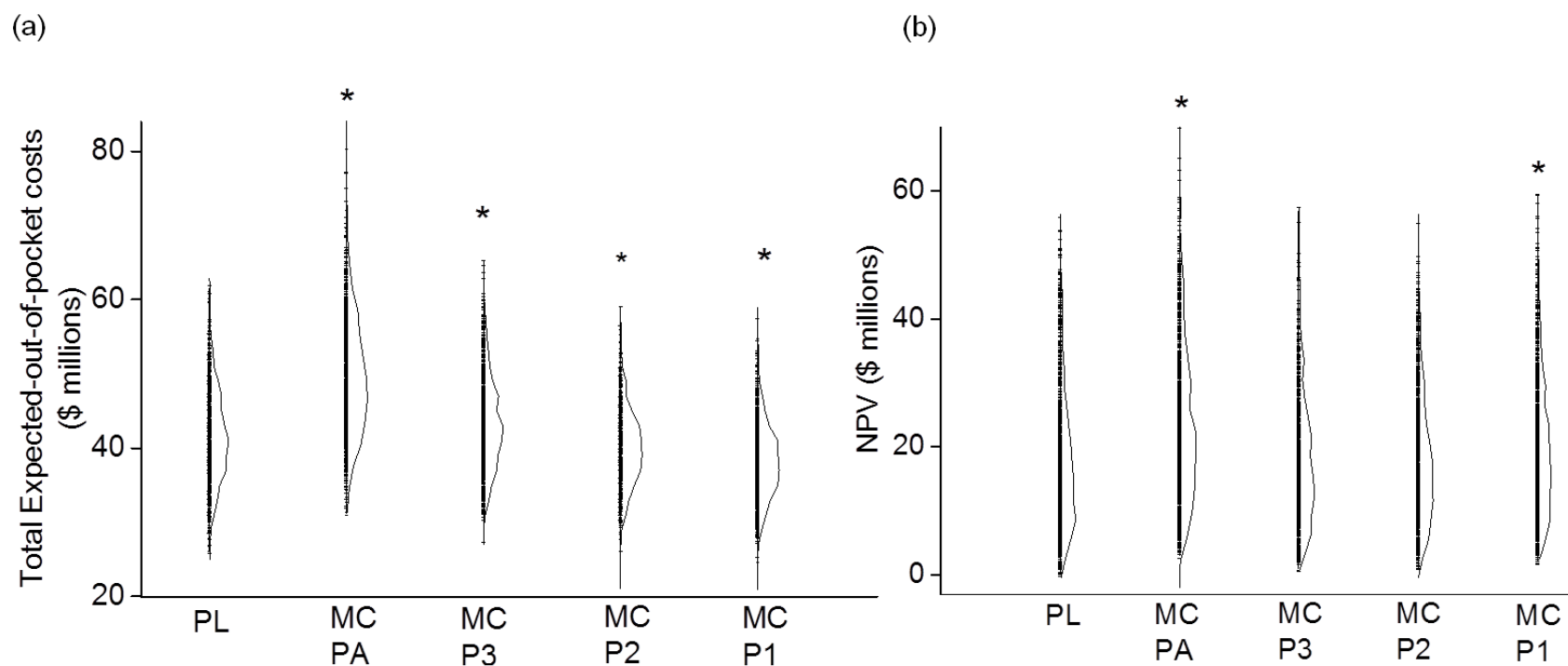


Figure 7: Frequency distribution plots for a market size of 50,000 patients, depicting (a) total expected out-of pocket cost under uncertainty of probability of entering the next phase of trials of Food and Drug administration (FDA) approval stage, process development costs (including process development and technology transfer), clinical trial costs, comparability and bioequivalence costs, and cost of process performance qualification (PPQ) batches. There was a statistically significant difference ($p < 0.05$) between all processes involving microcarrier-based single-use bioreactors (SUBs) and the planar process with (Two-paired T-test, Origin), as indicated by the asterisks above the graph. The mean \pm SD for the planar process (PL), changing to microcarrier SUB process post-approval (MC PA), change to microcarrier-SUB process at phase 3 (MC P3), change to microcarrier-SUB process at phase 2 (MC P2), and starting in microcarrier-SUB process at phase 1 (MC P1), were 41.4 ± 6.0 , 49.4 ± 7.8 , 43.2 ± 6.1 , 40.0 ± 5.0 , and 38.2 ± 5.0 respectively; (b) Risk-adjusted net present value (rNPV) under uncertainty of market size, selling price, commercial cost of goods per dose (COG/dose), tax rate and discount value, and probability of transition to the market for the post-approval switch due in order to account for unexpected potential regulatory challenges. There was a statistically significant difference ($p < 0.05$) between the processes where the switch to microcarrier-based SUBs were made post-approval or at phase 1 and the planar process (Two-paired T-test, OriginPro 9.1.0), as indicated by the asterisks above the graph. The mean \pm SD for the PL, MC PA, MC P3, MC P2, MC P1 were 17.9 ± 11.1 , 23.4 ± 12.8 , 17.7 ± 9.80 , 17.8 ± 9.9 , and 20.1 ± 11.0 respectively. PL: planar throughout; MC-PA: Change to MC-SUB post-approval; MC-P1: using MC-SUBs throughout, starting at phase 1; MC-P2: Change to MC-SUB at Phase 2; MC-P3: Change to MC-SUB at Phase 3

Appendix 1: Example calculations to estimate product development costs and technology transfer costs on an FTE basis. Assumed that on average for every unit of full-time equivalent (FTE) year workload, the cost incurred to the company is \$250K. Cost in phase is the product of total duration of activity in the phase (in years), \$250,000 and total FTE. QC: quality control; QA: quality assurance.

		Phase 1	Phase 2	Phase 3	FDA approval
Process Development (\$ millions)	Example Calculation for PL	Total FTE = 1 project manager + 3 process scientists + 1 QC/QA specialist = 5 Duration = 0.4 yrs Cost = \$250,000 x 5 x 0.4 = \$0.5 million	Total FTE = 1 project manager + 3 process scientists + 1 QC/QA specialist = 5 Duration = 0.4 yrs Cost = \$250,000 x 5 x 0.4 = \$0.5 million	Total FTE = 1 project manager + 6 process scientists + 5 QC/QA specialist = 12 Duration = 0.5 yrs Cost = \$250,000 x 12 x 0.5 = \$1.5 million	
Technology Transfer (\$ millions)	Example Calculation for PL	Total FTE = 1 project manager + 4 Technology transfer specialists + 1 Regulatory support specialist = 6 Duration = 0.3 yrs Cost = \$250,000 x 5 x 0.3 = \$0.5 million	Total FTE = 1 project manager + 5 Technology transfer specialists + 3 Regulatory support specialist = 9 Duration = 0.2 yrs Cost = \$250,000 x 5 x 0.2 = \$0.5 million	Total FTE = 1 project manager + 6 Technology transfer specialists + 2 Regulatory support specialist = 9 Duration = 0.65 yrs Cost = \$250,000 x 5 x 0.65 = \$1.5 million	Total FTE = 1 project manager + 6 Technology transfer specialists + 4 Regulatory support specialist = 11 Duration = 0.7 yrs Cost = \$250,000 x 5 x 0.7 = \$0.5 million

Appendix 2: Estimation of assays required and stability test costs in different phases of trials. The number of timepoints in different phases of trials shown below is for the case where there is no process change, and these change accordingly if there is a change, considering that the duration of phase 1, 2, and 3 trials are considered to be 1.5, 2.5 and 3 years respectively. ELISA: enzyme-linked immunosorbent assay; Sterility USP: Sterility, United States Pharmacopeia

Test	Equipment	Nr of stability timepoints			Cost per assay	Total cost of stability assays in Ph 1
		Phase 1	Phase 2	Phase 3		
Cell count & Viability	Nucleocounter	6	2	8	\$ 0.4 K	\$ 2.4 K
Sterility USP <71>	thermal cycler	2	1	3	\$ 1.9 K	\$ 3.8 K
Mycoplasma <63>	luminometer	2	1	3	\$ 1.5 K	\$ 0.7 K
Flow Markers	flow cytometer	6	2	8	\$ 1.7 K	\$ 10 K
ELISA for Endotoxin analysis	plate reader	2	1	3	\$ 3.0 K	\$ 6.0 K
ELISA for analysis of cytokines	plate reader	6	1	3	\$ 3.3 K	\$ 9.0 K
ELISA for cell-based assay	Plate reader	2	2	8	\$5.0K	\$10.0K
					Total	\$ 51 K
					Total for 3 lots	\$154K

Appendix 3: Summary of clinical trial costs per patient, cells/phase, number of assumed lots/year, and scale for planar and microcarrier-based single-use bioreactors, for a hypothetical dose of 200 million mesenchymal stromal cells per patient. It was assumed that stability studies were performed using overage produced for clinical trials. Material for *in vitro* testing in comparability and bioequivalence studies was assumed to be produced in separate batches at the scale at which the expansion technology switch was made. MC-SUB: microcarrier-based single-use bioreactors; CF-10: 10-layer cell factory; CF-40: 40-layer cell factory

	Phase 1	Phase 2	Phase 3	FDA approval	Market
Numbers of patients	15	32	240	N/A	10,000 to 100,000
Clinical trial cost per patient (excluding overheads)	45200	69700	74800	N/A	N/A
Clinical trial cost per patient (including overheads)	51867	76152	75954	N/A	N/A
Transition probability	100%	87%	55%	36%	
Cells/phase produced (Planar)	3.24×10^9	6.49×10^9	6.23×10^{10}	6.2×10^{10} to 6.0×10^{11}	2×10^{12} to $2E+13$
Cells/phase produced (MC-SUB)	6.35×10^9	3.18×10^{10}	3.81×10^{11}	6.4×10^{10} to 2.5×10^{11}	2×10^{12} to 8.5×10^{12}
Number of lots	3	3	18	3	100
Scale if Planar	10 x CF-10	20 x CF-10	8 x CF-40	48-464 CF-40	48-464 CF-40
Scale if MC-SUB	1 X 10L	1x 50L	1 x 100L	1-4 x 100L	1-4 x 100L

Appendix 4: Assuming a dose of 200 million mesenchymal stromal cells and a market size of 50,000 patients, total expected out-of-pocket costs in \$ millions with activity breakdowns for planar process (PL), and the % change of total expected out of pocket costs for change to microcarrier-based SUB process post-approval (MC PA), change at phase 3 (MC P3), change at phase 2 (MC P2), or using MC-SUBs throughout, (starting in phase 1) (MC P1), relative to the planar base case. Note expected out-of-pockets costs take into account the probability of transition to each phase.

	Development activities	PPQ batches	Manufacturing for clinical trials	Clinical trials
PL	4.8	13.6	4.7	12.9
MC-PA	+163%	-15%	+0%	+3%
MC-P3	+195%	-64%	+13%	+5%
MC-P2	+141%	-65%	+24%	+8%
MC-P1	+55%	-184%	+20%	+0%