

# Electronic Batch Record System (EBRS) Roll Out at Takeda Ireland Limited

the road from concept to realised benefits



## Introduction

**This case study outlines the introduction of a multi-plant Electronic Batch Record System (EBRS) at Takeda Ireland Ltd to replace legacy paper based systems in alignment with an Operational Excellence strategy. The emphasis of this study is the strategic planning and project management considerations to take the EBRS from concept to realisation, the business benefits reaped, and how these benefits contribute towards operational excellence. In addition, mention is given to some key challenges to this and any large multi-plant EBRS programme.**

Takeda Ireland Limited, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, ranked no. 15<sup>1</sup> in the global pharmaceutical market, manufactures solid oral dosage forms for global distribution, and is thus bound by stringent international regulatory standards for pharmaceutical production. The EBRS introduction programme replaced legacy paper based batch record systems in four plants covering bulk granule, capsule, intermediate granules, and tablet manufacture in addition to multiple drug product packaging lines. The context for the programme was a Takeda operational excellence drive necessitating computerised automation to advance cost reduction, productivity, and regulatory compliance.

Project Management for the EBRS programme was provided by Systematic I.S. Strategies Ltd (Systematic), an independent provider of information and execution systems project management and consulting services to the regulated life sciences sector. The decision to utilise Systematic Project Management expertise was based on a desire by Takeda to retain project control, while recognising the need for independent experience based planning and project management.

"The outcome of a complicated and high risk project like installing an eBRS application in a 24x5/24 x7 shift multi-plant campus is characterized by asking correct questions and making correct decisions from day 1. Who is going to do it, how will it be done are fundamental concerns - but also fundamental errors if answered poorly. If I have any advice to give is deliberate long and hard, choose wisely, plan carefully and involve the services of Systematic all along the way"

... Paul Blunnie, Plant Director, Takeda Ireland Ltd.

## Facility Overview

Takeda Ireland Limited (TIL) comprises of an API plant in Grange Castle and a Finished Product facility in Bray County Wicklow. The TIL 16,500m<sup>2</sup> multi-plant solid oral dosage facility in Bray is the focus of this study. It was established in 1997 and is Takeda's main Pharmaceutical production base for the European and U.S. markets. Approximately 4,000 product batches (2,500 bulk, 1,500 packed, including 10,000 intermediate batches) are produced annually<sup>2</sup> for a range of products to treat diabetes, hypertension, peptic ulcer, and insomnia. The facility is comprised of four distinct plants producing and packaging bulk granules, capsules, and tablets for global distribution (USA, Europe, Asia, Pacific, and Japan).

## Software Application & Infrastructure

Prior to the EBRS programme, TIL utilised the XFP Manufacturing Execution System (MES) from Elan Software Systems (more recently acquired by Siemens) for weigh/dispense automation and materials flow control from warehouse into production. Controlling dispensing operations had been a historic priority due to the high volume of dispensing operations on site. The MES is integrated to SAP ERP for inventory control and a Laboratory Information Management System (Labware LIMS) for materials sampling. To optimise existing investment, the XFP MES was chosen as the platform for the EBRS application, and Elan provided software related services for the programme. Various other suppliers provided technical support for IT infrastructure, at-plant computers and peripherals, and customised stainless steel components.

In preparation for the EBRS programme, a significant MES server and network infrastructure upgrade was necessary to accommodate the need for high electronic data security, GMP data integrity, and business continuity needs necessary for any EBRS application. The revised "EBRS ready" infrastructure comprised an upgraded Citrix farm to host the MES application, a number of module specific application servers, an MES database cluster, expanded Storage Area Network (SAN), and new business continuity components including disaster recovery and data backup components. The infrastructure is deployed on a qualified/secure network, with validated testing and production instances in addition to development environments. This infrastructure serves a Citrix based EBRS deployment running on plant based mobile rugged PC's, rugged wireless barcode scanners, barcode printers, and networked at-plant document scanners.

<sup>1</sup> Source: IMS Health, World review 2010 (net sales ranking, fiscal 2009)

<sup>2</sup> Batch throughput at time of EBRS commissioning for each plant

## EBRS Roll Out at Takeda Ireland Limited

### Strategic Planning – Business Objectives

A critical element in the planning phase was to definitively identify the EBRS business objectives. Having established a steering committee involving all operational department managers, head of functions, and the system sponsor (a board level representative with operations responsibility), six key EBRS business objectives were agreed as the first collective task of the steering committee. These are summarised below:

1. Significant reduction in batch review effort
2. Significant reduction in batch review cycle time (from production completion to batch approval)
3. Improvements in batch Right First Time (RFT)
4. Reduction of inefficient paper batch file handling and storage systems
5. Facilitate more flexible batch review locations. The context of this is that some batches needed be reviewed in situ at the point of production due to the health & safety risks of removing batch files to uncontrolled areas of the facility (e.g. QA open plan spaces). This, combined with the inefficient practice of sequentially passing batch files between numerous reviewers, was identified as a process that needed more flexibility.
6. Provide centralised, instantaneous, batch reporting and monitoring

Unambiguous agreement of business objectives among stakeholders is a critical milestone in the planning stage as all detailed user requirements must relate to at least one of these objectives, and these objectives bring clarity of thought to often complicated design decisions later in the project. Furthermore, clear objectives from the outset are a must if system payback is to be measured. Although there are other known benefits to EBRS introduction (in addition to the above stated objectives), most conspicuously those benefits found within the heart of production operations, the above were considered to be the critical factors regarding business bottlenecks at the time of project conception.

### Strategic Planning – EBRS Scope

EBRS, like many manufacturing systems, exists on a continuum from basic MES components to fully automated EBRS integrated to all production equipment, typically through SCADA (Supervisory Control And Data Acquisition) or DCS (Distributed Control System) interfaces. Hence, a key output from the planning stage was a clear statement of the general scope of EBRS as it applies to the facility in question. Due to technical constraints in the SCADA environment and the desire to consume EBRS in bite sized chunks, the 80-20 rule was applied (80% of the effects/gains from 20% of the causes/effort) and the scope of EBRS was agreed as predominately “paper on glass” with only critical plant based weighing equipment to be integrated to EBRS. In this case, “Paper On Glass” means that the information captured on paper based manufacturing instructions (MI’s) is replaced by electronic equivalents. This does not mean that EBRS merely

transcribes each piece of information on a paper form into a manually typed field on a computerised form (i.e. “paper on glass” does not equate to “electronic paper”). In reality, a significant amount of hand written information on paper batch files is auto-populated within EBRS through automated data retrieval, calculations, systems integration, and barcode scanning. The local definition of EBRS was “a computer based system that drives the manufacturing of a production batch, streamlines batch review, and maintains an electronic record of the batch and associated quality information in a validated and compliant environment”.

### Strategic Planning – Roll Out Strategy

Due to the novelty of EBRS within the organisation and a desire to verify business returns before committing to a multi-plant roll-out, the decision was made to pilot EBRS in Plant 1 of four (see Table 1) before addressing subsequent plants. Although classed as a “pilot”, the scope of this plant represented a significant share of the overall EBRS environment. The strategy was then, contingent on the actual benefits yielded from Plant 1, to implement EBRS sequentially for the other plants, while ensuring that the requisite benefits were yielded between plant roll-outs. Each plant rollout was managed as an individual project within the programme (i.e. the Phase 1 to 4 projects).

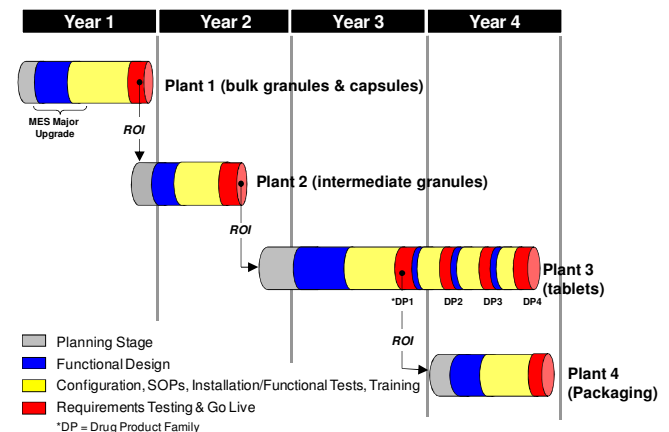


Figure 1: EBRS Programme Schedule

The general Project Management approach was consistent for each phase, adhering to industry good practices for computerised systems in the pharmaceutical and associated industries (GAMP4 and 5) through a detailed project implementation approach provided by Systematic. However, the EBRS design process and go-live strategy differed according to process complexity, product variability, and batch throughput of each plant (see “Implementation Approach” below). As the project was contingent on business returns, it was critical that schedule milestones (most notably go-live events) were planned to optimise Return On Investment (ROI) for each phase. Hence, schedule and budget adherence, in addition to measurable scope adherence, were key indicators for subsequent phase approvals.

## Team Assembly

Due to industry trends towards configurable MES/ EBRS applications (in contrast to code intensive solutions), and the reality that EBRS is a process enabler, EBR design must be driven by users who are experienced in the nuances of the manufacturing process. For this reason, it is a critical success factor for any such project that the project team includes the right user Subject Matter Experts (SME's) in terms of detailed process knowledge, peer respect, and project/team focus. The EBRS project team comprised the management based steering committee and three core team components; (1) an EBR process design team of SME's working closely with the supplier technical consultants, (2) a technical support team including IT and System Administration skill sets, and (3) a quality team comprising validation, regulatory compliance, Qualified Person representatives, and training coordinators. The individuals filling team roles changed for each programme phase, but the overall team template remained consistent throughout the programme. It is noteworthy that computer systems aptitude, while useful, was not a prerequisite for EBR design SME's throughout the programme. This skill set became more relevant in latter project phases as supplier involvement in EBR design decreased and site representatives were empowered to configure EBRS internally. As the majority of the project team were TIL SME's, seconded as a project capital cost, detailed resource drawdown planning and stress testing in the planning stage was a critical factor in ensuring adherence to project costs (and thus adherence to projected ROI). Figure 2 shows the internal team utilisation pattern, quantified as Full Time Equivalents (%FTE) for the single (plant 1, 2, & 4) and multiple drug-product plant (plant 3) projects. The shape of this curve is highly dependent on the design strategy and verification approach adapted. A key goal is to minimise resources, and thus cost, by designing generic reusable EBR components early in the project so subsequent product go-live events are increasingly less resource intensive (see also "Issues Affecting Deployment Approach" below).

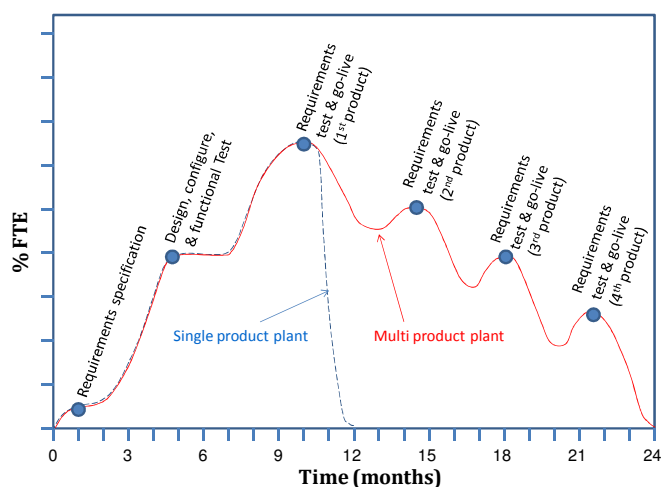


Figure 2: Team Utilisation Pattern

## Implementation Approach

**Best Practices:** The EBRS implementation life cycle adhered to GAMP guidelines (Good Automated Manufacturing Practice). Phase 1 and 2 aligned with GAMP 4 (guide for the validation of automated systems), while Phase 3 and 4 aligned with the more recently published GAMP 5 (a risk based approach to compliant GxP computerised systems). GAMP is not a prescriptive method or standard, rather it provides for pragmatic guidance, approaches, and tools for computerised systems practitioners. Hence, it must be applied with judgement and experience if it is to be both cost effective and robust as a real world project tool. The business objectives, system description, project organisation model, quality environment (supplier and internal), and qualification / verification requirements remained relatively consistent throughout all four programme phases. However, differences in the complexities of each plant, evolving industry best practice guidelines, and changes in the balance of project contribution between TIL and supplier as the programme progressed meant that the implementation process needed to be flexible. To achieve this, a separate quality and project plan was developed by Systematic for each project phase. This plan, analogous to a detailed project charter with an added quality dimension, specifies in detail the goals, implementation and verification approach, team organisation, schedule, project quality controls, deliverables, and key dependencies for each programme phase. Due to the necessity for all stakeholders and contributors to familiarise with this plan, TIL adapted this as a formal company SOP for the lifetime of the project, reviewed and approved by the steering committee and supplier.

**User Requirements:** A separate User Requirements Specification (URS) was developed for each plant. It is critical that the URS was accurate, complete, and clearly expressed as this document is the baseline for all aspects of implementation management from supplier response, risk assessment, design review, testing, and ultimately system acceptance. System acceptance can only be achieved among the stakeholder if the final conformance to requirements is quantifiable, thus the structure and quality of the URS is critical. For EBRS projects (as EBRS is a process enabler), the URS should be process oriented, allowing designers to map the EBRS workflows directly from the URS with additional reference to the Manufacturing Instructions.

**Issues affecting deployment approach:** The quality and project plan is the baseline "project" phase reference, while the URS is the baseline "solution" phase reference. These two planning documents were given a specific mention as they are critical determinants for project and solution success. The nature of the other project deliverables (in the concept, planning, specification, configuration, verification, reporting & release/acceptance stages) were tailored depending on the characteristics of each plant. Again, as EBRS is a process enabler, a detailed "one size fits all" deployment cycle is impractical. Some key issues which affected the deployment approach for each plant included:

## EBRS Roll Out at Takeda Ireland Limited

- Process complexity and variability (e.g. Is the process relatively new or mature, are individual processes predominately sequential or parallel, are intermediate processes dependent on each other, are there numerous or limited product codes, is the process labour intensive or machine driven, are there time sensitive tasks to be controlled, how sensitive is the process to parameter variance, frequency and understanding of process deviations)
- Are there known inefficiencies in the production process and are there opportunities for leaning out parts of the process either prior to or as part of EBRS implementation?
- Process similarity across different products (e.g. can we optimise EBR design through generic EBR workflows for multiple products that utilise the same resources?)
- Production schedule structures and batch cycle time (e.g. Campaign structures, work order inter-dependencies, shift change-overs per batch)
- Level of routine manual quality checks (e.g. check signatures, executive reviews, specification checking)
- Level of routine and exception In Process Testing (variability, location, complexity, and frequency)
- Nature and frequency of clearances and change-overs (e.g. are area clearances batch specific or batch independent)
- Historical process consistency (e.g. equipment performance consistency, downtime trends, past deviations)
- Nature and number of supplementary attachments in the batch file (are these attachments routine or by exception)
- Integration complexity (to other applications, floor scales, IPT/Bench scales, process equipment)
- In house project team experience (e.g. experience of GxP computerised systems projects, of EBRS projects, of the specific EBRS application and associated technology)
- User base experience and attitude (Is there a culture of embracing computerised automation?)
- Supplier capabilities (e.g. what do software & technical service suppliers add in terms of; software related services, knowledge of the manufacturing process, validation collateral, grasp of GMP issues, project oversight).
- In house & supplier EBRS support capabilities
- In house computerised system verification experience (As EBRS is driven by complex process workflows, testing of all potential production normal and exception case scenarios is not possible. Hence, experience in risk based verification strategies is critical).

Examples of how the above questions affected each phase roll-out approach included:

- Plant 1: EBR design approach reflected; first plant, so the solution is novel, single product, multi-process, high throughput, shippable to market. Deployed with significant supplier involvement in design, configuration, MES upgrade, and functional verification.
- Plant 2: EBR design approach reflected; labour intensive processes, single product, high throughput, broad SCADA systems, internal intermediate product. Deployed with

significant supplier involvement in design, configuration, and functional verification.

- Plant 3: EBR design approach reflected; relatively generic processes but multiple drug products, so an EBR design challenge was to design by process, making electronic batch masters generic across multiple products. This reduced EBRS masters for project effort, verification, training, and supportability reasons. Due to the number of products and the desire to attain relatively fast payback, it was decided to go-live in product stages to optimise ROI. This was a challenge as the up-front EBR workflow design was to be generic across multiple products. This phase was deployed with significant supplier involvement in design and configuration.
- Plant 4: EBR design approach reflected; multiple packaging lines, varying equipment, large item code volumes (numerous SKU's across multiple products and markets), complex and frequent set up processes, and cross trained shifts. The EBR challenge was to design generic EBR masters, driven for each drug product by item specific static data. Supplier involvement was limited to design review and custom functionality development.

**Table 1: Plant summary**

Plant	Type	Process	Product range	Characterised by
<b>Plant 1</b>	Bulk granules & capsules	Dispensing, coating, blending, encapsulation	Single	High volume bulk packed granules and capsules (>200 granule tonnes/year exported)
<b>Plant 2</b>	Intermediate granules	Dispensing, multiple RBFG granulations	Single	Similar to a scaled API plant. >200 tonnes/year intermediate used for tablets made in Plant 3.
<b>Plant 3</b>	Tablets	Dispensing, granulation, blending, compression, film coating, printing	Multiple (>40)	Campaign manufacturing, many tablet press change-overs (~40 million blisters/year)
<b>Plant 4</b>	Packaging	Blister packing, cartoning, overwrapping	Multiple (>100)	Three separate lines, (incl. primary and secondary). Imported bulk products packed in addition to those produced on site.

**The Training Challenge:** As EBRS facilitates a heavily human interactive process, user training is a critical consideration in achieving meaningful project returns. For example, significant Right First Time improvements cannot be achieved unless correct EBRS operation is second nature to all levels in terms of system usage and information entry consistency (see "Benefits" below). User education on EBRS is an ongoing activity throughout the project through user involvement in requirements definition, design reviews, testing, and general communications. A well structured, communicated, and executed formal training plan is a must as part of the project planning activities. Formal training execution at the facility reached 780 man days of training across 4 plants (averaging at 195 man days per plant), and was deployed through over 30

## EBRS Roll Out at Takeda Ireland Limited

customised training courses defined mainly by role and process. A key challenge for the training programme of a large EBR project is to train users close enough to go-live to ensure that the material is remembered and relevant on the date of go-live, and also to have enough training completed to facilitate requirements testing, which assesses training and other procedural aspects in addition to system performance (similar in principle to performance qualification). This means that the training time window must be minimised (1-3 months), while also aligning with production schedules to ensure trainee availability. The training logistical challenges are significant, and are compounded by shift cycles (24/5 and 24/7) and the need to optimise trainer skill sets; do we go with a knowledgeable process SME, an EBR software SME, or a training delivery expert? Due to real world project constraints, rarely will all of these requirements be met, so training supports and course content must address gaps in the optimum skill set. In addition, the training challenge is further compounded by the need to ensure that the various new system usage and management SOP's developed as part of the project are understood by the trainees as part of the training programme.

### System Benefits & their Role in Operational Excellence

As the EBRS programme required quantifiable ROI, prior to starting each phase/plant, "current" key performance indicators were consolidated from plant statistics (or measured where not available) to establish a benchmark for business payback analysis. The payback analysis focussed primarily on the programme business objectives (described earlier), and hence the benefits quantified related directly to these objectives. However, the study also exposed other benefits not originally stated in the formal programme business objectives. The actual benefits yielded varied across different plants due to project cost variability and plant characteristics, but all plants showed significant improvements following EBRS "go-live". For example, the quantifiable benefits shown in Figure 3 were noted following the first EBRS plant go-live, based on the initial months of data gathering from the date of go-live (most data shown is based on 4 months of data gathering):

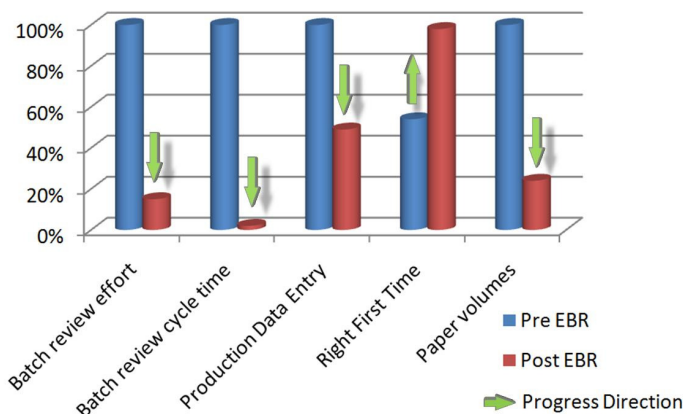


Figure 3: Quantified (normalised) EBRS Benefits

The following describes these benefits in more detail, with reference to the original business objectives (see "Strategic Planning – Business Objectives").

- Batch Review Effort:** 85% reduction in batch review effort (man hours per batch) as only exceptions to the "correct" batch need to be reviewed. This is often referred to as "batch review by exception".
- Batch Review Cycle Times:** 98% reduction in batch review cycle time (from production completion to approval), facilitating First In First Out (FIFO) batch shipment planning.
- Right First Time (RFT):** Although GMP/Document RFT was instantly improved due to automated real time tolerance checking, early EBRS procedure familiarisation among users counter-balanced this improvement (e.g. incorrectly processed alerts meant that alerts remained incomplete at batch review time). Hence, net RFT improvements were only observed after the initial 4 months of usage, and following supplementary user training. Document RFT improved thereafter to over 98%.
- Paper Volumes:** 76% reduction in paper handling and storage. Some exception paperwork remained due to the programme 80-20 rule strategy (see "Strategic Planning – EBRS Scope"). For example, except for rare exceptions, it was decided not to scan exception paperwork into EBRS due to the error prone nature of manual document scanning and a desire for batch reviewers to review only master copies of GMP attachments (and not a scanned copy of the master). The overhead of handling exception batch paperwork was reduced to a minimum through quality process reengineering; i.e. by including reference to the exception paperwork in EBRS, the need for exception paperwork to travel with the batch record is reduced.
- Batch Review Location:** EBRS now facilitates users to review batches at any location throughout the plant. Furthermore, batches are no longer constrained to sequential review, and can be reviewed in parallel by various reviewers. Although this benefit is less easily quantifiable without numerous assumptions, this benefit has various resultant benefits in terms of cycle times, training, and health and safety risks.
- Batch Reporting:** The EBRS has centralised batch data into a secure repository, so previously time consuming reporting tasks are now automated within EBRS instantly. For example, Annual Product Review (APR<sup>3</sup>) report consolidation time was improved by 90% compared to manual reporting processes. See also the discussion on Operational Excellence at the end of this section.
- Production Data Entry:** Reduction in batch data entry time by production personnel was 51%. It typically takes longer to enter a piece of data electronically (e.g. a typed e-signature or process value) than manually (using a pen and paper). This is due to a number of factors including garbing constraints and keyboard skills, but the volume of entries eliminated by EBRS due to automatic calculation or data

<sup>3</sup> APR's (Annual Product Reviews) also known as PQR's (Product Quality Reviews) by EU Regulatory Authorities

## EBRS Roll Out at Takeda Ireland Limited

retrieval yields a significant net reduction in production entry effort.

It is noted that most benefits above demonstrated a trend towards further improvement, so benefits after the initial four months should be greater than those stated. However, the highest rate of improvement was seen in the initial months following go-live, and the rate of further improvement after this period is relatively low.

Quantifying system benefits was critical for investment justification. To develop a business case for MES/EBRS, the quantifiable benefits, converted to cash savings (through head count optimisation, materials savings, and other efficiencies), and the total cost of ownership of the EBRS (including initial capital cash flow and ongoing support costs) are used to determine the payback period and ROI at a given time point.

Figure 4 shows the typical payback curve for EBRS multi-plant projects, assuming that the roll-out is on a plant by plant basis so payback begins once the first plant goes live. For TIL, the payback period varied from plant to plant, ranging from 1 to 3.5 years, and the combined programme payback period was less than one year from final go-live.

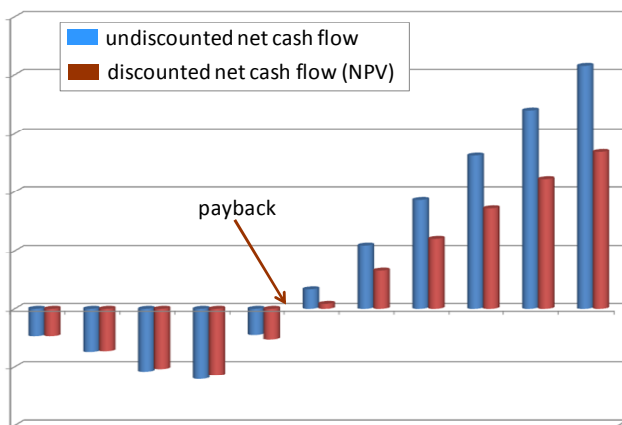


Figure 4: Typical EBRS Payback Curve

In conducting an ROI study for MES/EBRS, it is important that stake-holders understand the scope and limitations of ROI. As ROI is typically used for investment justification, only hard, quantifiable benefits are typically considered valid in the ROI model, as these benefits require less assumption, and are thus perceived to be more credible. Hence, stated ROI is typically conservative. Furthermore, quantified productivity savings can only be realised in practice if action is taken to utilise head count savings elsewhere in the overall operation. This can be difficult as typically no single role is made redundant from MES/EBRS. Instead, effort from multiple roles is reduced, so the approach to head count reduction must be carefully considered. Avoidance (or soft) benefits are less quantifiable as an up front project justification tool without making unprovable assumptions, as we cannot know what operational exception circumstances will occur in the future. However, avoidance benefits on their own provide a strong business case

for EBRS as they tend to address industry specific “big picture” and “big risk” challenges. Some examples of these EBRS benefits include; avoidance of batch disposal due to poor quality, improved process knowledge retention, increased customer and regulatory audit preparedness, improved confidence in regulatory compliance adherence, and most importantly, improved patient safety.

A final consideration regarding benefit analysis is that MES/EBRS is a proven operational excellence enabler (in addition to ERP, MES is ranked no. 2 behind Business Intelligence and analytics as an operational excellence enabler)<sup>4</sup>. Apart from the system benefits discussed above, there were many secondary benefits that EBRS enabled to support lean manufacturing principles. The following is a non exhaustive list:

- Support for product inventory reduction, as batch review delays are eliminated. This is particularly realisable when EBRS is combined with a centralised Laboratory Information Management System (LIMS) integrated to laboratory equipment, to fast-track QC results and enable timely final batch approval. At TIL, this is achieved through Labware LIMS integrated to Waters Empower CDS (Chromatography Data System) for automated HPLC/GC data retrieval.
- Consistently timely batch review and consistently high RFT batches facilitate more consistent production and shipment planning, which helps to streamline manufacturing supply chain planning.
- Centralised batch data means that plant performance metrics are now more readily measurable. This includes a new ability to instantly trend batch cycle times (e.g. from materials receipt to production, start to end of production, end of production to batch approval, approval to shipment). This level of information availability provides a critical Business Intelligence capability, which is a central component towards operational excellence.

### Notable EBRS Challenges

In addition to hard and soft EBRS benefits, there are hard and soft EBRS project and operational challenges that must be managed carefully if they are not to disproportionately reduce the ROI. These relate to (1) project implementation strategy, (2) the level of process and quality automation versus the level of flexibility to deal with production batch exceptions, and (3) the risks involved in electronic master batch updates. These risks are explained below:

<sup>4</sup> Source: IDC Manufacturing Insights white paper “beating complexity, achieving operational excellence”, July 2010

- 1. Implementation Strategy:** As EBRS must be ROI focussed to make business sense, schedule, cost, and scope overruns can threaten projects before realisation. Hence, a business focussed, experienced based implementation strategy and detailed plan is a must. For example, the strategic question of roll out strategy is critical; do we develop EBRS for multiple plants in parallel and go live with a “big bang”, or do we address each plant sequentially (with some overlap)? The former approach can save on resources, but may provide a lower ROI due to increased costs and risks of large scale pre go-live change management as business processes change mid-project (for both customer and suppliers). The latter uses resources over a longer time period, but can give a fast payback as initial benefits are realised quicker and mid-project rework is manageable as business processes changes. The sequential approach also facilitates quick visibility of benefits, keeping management motivation high for successive phases. This premise is supported by the benefits achieved at TIL in the context of the decision to approach EBRS in bite sized chunks. Business change during the implementation lifetime is an important strategic consideration. In an ideal world, business process lockdown is desirable throughout EBRS development. The reality is that the project process must be agile and stress tested to deal with unexpected business process changes during the programme. This agility however does not preclude the imposing of a non critical process change lockdown during EBRS development with company Management support.

As EBRS for pharmaceutical manufacturing enables heavily manual processes, user involvement in design and prototype reviews is essential as is a thorough user training programme. As each EBRS workflow is specific to any life sciences customer in alignment with their own processes, system verification should not be underestimated. Supplier validation competency must be assessed for adequacy to stress test verification assumptions, and the pharmaceutical company must take ownership of the validated state of all configured EBRS workflows.

- 2. EBRS Design for Automation versus Flexibility:** EBRS for pharmaceutical manufacturing automates a manually interactive process, which typically (depending on the nature of production) requires a degree of flexibility. Hence, compromises are required to balance the level of process automation versus process flexibility, while ensuring that EBRS is designed to manage complexity. It does not make sense, again applying the 80-20 rule, to put 80% of project effort/cost into 20% of rare exception scenarios. Finding the right balance of automation versus flexibility is thus a major EBRS design consideration. For example, OEE (Overall Equipment Effectiveness) levels can be negatively affected if EBRS imposes excessive restrictions on equipment change-over processes, so a combination of carefully designed electronic workflows and documented procedures is typically the optimum

solution. In addition, engaging in an EBRS project necessitates the pharmaceutical company to take a hard look at production and quality processes as detailed current practices must be fully understood before the EBRS design stage. As a rule of thumb, an inefficient process may still be inefficient after EBRS if some degree of process leaning is not undertaken before or during EBRS design.

- 3. EBRS Operational Considerations:** This study does not focus on the operational, post “go-live” considerations of EBRS. However, as part of the project implementation, operational constraints, mainly in the areas of change management and business continuity, must be designed into the solution and corresponding procedures. In paper based master manufacturing instructions, the main factor to consider in making process changes is the process change itself. The paper instruction changes are relatively incidental due to the discrete nature of each entry on a paper form. Within EBRS however, both the business process change and the EBR electronic master change require significant consideration. This is because any element in an electronic batch workflow is part of an integrated, automated application, so a change in one area can have an impact in another. Hence, risk assessment is required for each change, and high risk changes may require significant verification effort. This risk assessment, and the EBR master update process, must be well proceduralised before go-live if this risk is to be managed. In addition, the EBRS must be designed to be supportable from an EBR master update perspective, sometimes at the expense of functionality or automation levels. For the same reason, the time taken to develop electronic instructions for routine New Product Introductions (NPI) must be considered as part of the operational reality of EBRS. Again, this is manageable once the necessary attention is given to NPI process awareness before go-live. Although electronic batch masters are generally more time and effort consuming to update than their paper equivalents, the net effect to the organisation is a positive ROI as explained above. It is important that any company that embraces EBRS becomes self sufficient in EBR Master Updates, and in routine system troubleshooting, as early as possible in the EBRS programme to ensure that EBR updates resulting from business changes do not become excessively cost intensive due to over reliance on external specialist EBR software configuration expertise. Consideration must also be given to business continuity; System infrastructure and ongoing business continuity safeguards must be robust enough to never fail catastrophically, but decisions about the retention of some level of “worst case scenario” paper based fallback must be made prior to go-live.

## Summary

This case study has highlighted some key considerations in successful EBRS programme roll outs and the nature of the business benefits attainable with reference to the Takeda Ireland EBRS introduction programme. The scope and limitations of these benefits are explained in terms of manufacturing operations, quality, and overall operational excellence. Key points raised are the need for solid programme planning and execution, while some notable challenges are put forward as a cautionary note. The programme was executed with planning and project management from Systematic I.S. Strategies Ltd., an internal project team of Takeda Subject Matter Experts, EBRS software and related services from Elan Software Systems (Siemens), and various other hardware and service suppliers.

## Glossary

EBRS	Electronic Batch Record System
EBR	Electronic Batch Record
TIL	Takeda Ireland Limited
MES	Manufacturing Execution System
LIMS	Laboratory Information Management System
GMP	Good Manufacturing Practice
GxP	General Good Practices for pharmaceuticals
SAN	Storage Area Network
RFT	Right First Time
QA	Quality Assurance
SCADA	Supervisory Control and Data Acquisition
DCS	Distributed Control System
MI	Manufacturing Instruction
GAMP	Good Automated Manufacturing Practice
ROI	Return On Investment
SME	Subject Matter Expert
FTE	Full Time Equivalent
URS	User Requirements Specification
IPT	In Process Testing
ROI	Return On Investment
RBFG	Rotating Bed Fluid Granulation
SOP	Standard Operating Procedure
FIFO	First In First Out
SKU	Stock Keeping Unit
APR	Annual Product Review
PQR	Product Quality Review
FDA	US Food and Drug Administration
ERP	Enterprise Resource Planning
CDS	Chromatography Data System
HPLC	High Performance Liquid Chromatography
GC	Gas Chromatography
OEE	Overall Equipment Effectiveness
NPI	New Product Introduction

## About the Author



Eddie Ryan has over 15 years industry experience of large scale quality and manufacturing information/execution systems. With a Masters Degree in Mechanical Engineering from University College Galway, Ireland, and an initial career with systems integrator companies, he has broad consulting and project management experience in Ireland, Europe, and the USA in the Life Sciences, Food & Beverage, Government, and Chemicals industries. He has held engineering, management, and executive director positions in the IT services sector. He is the founder and primary consultant of Systematic I.S. Strategies Ltd., an independent consulting company based in Dublin Ireland providing strategic planning, system selection, and project management services for information and execution systems in the regulated Life Sciences sector. He can be contacted through the "[contacts](#)" page at [www.sysiss.com](http://www.sysiss.com).



[info@sysiss.com](mailto:info@sysiss.com)  
[www.sysiss.com](http://www.sysiss.com)