Applying AI to manage the risks and costs of postmarketing requirements

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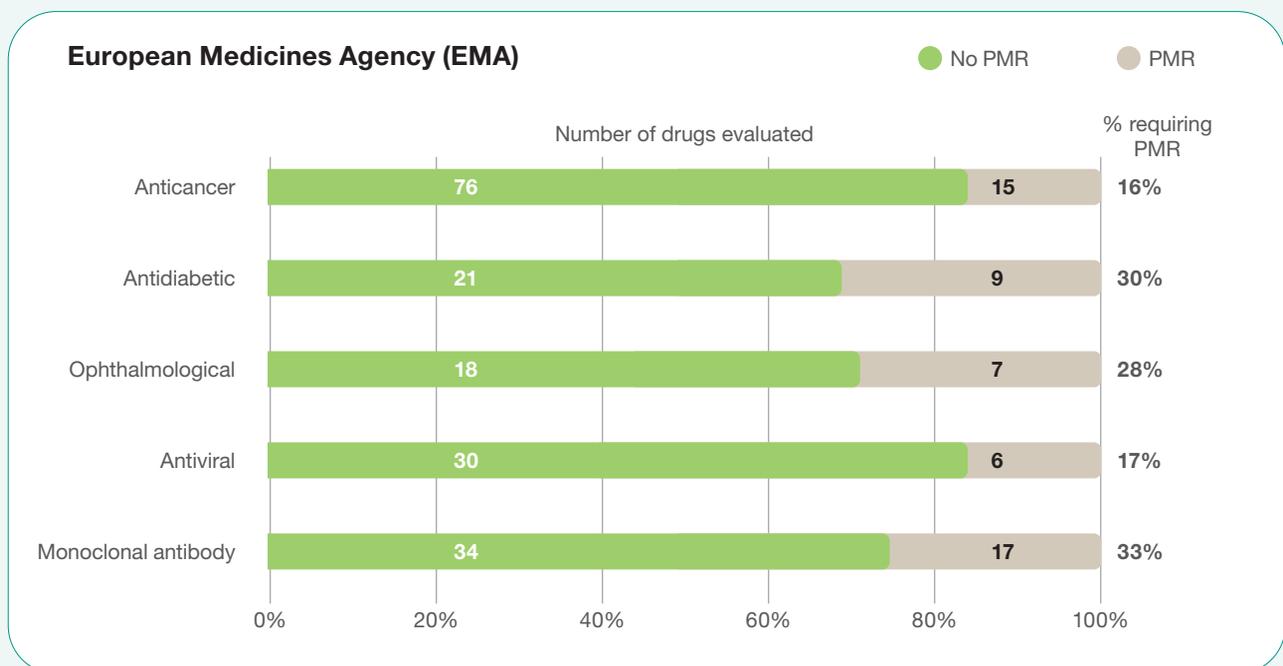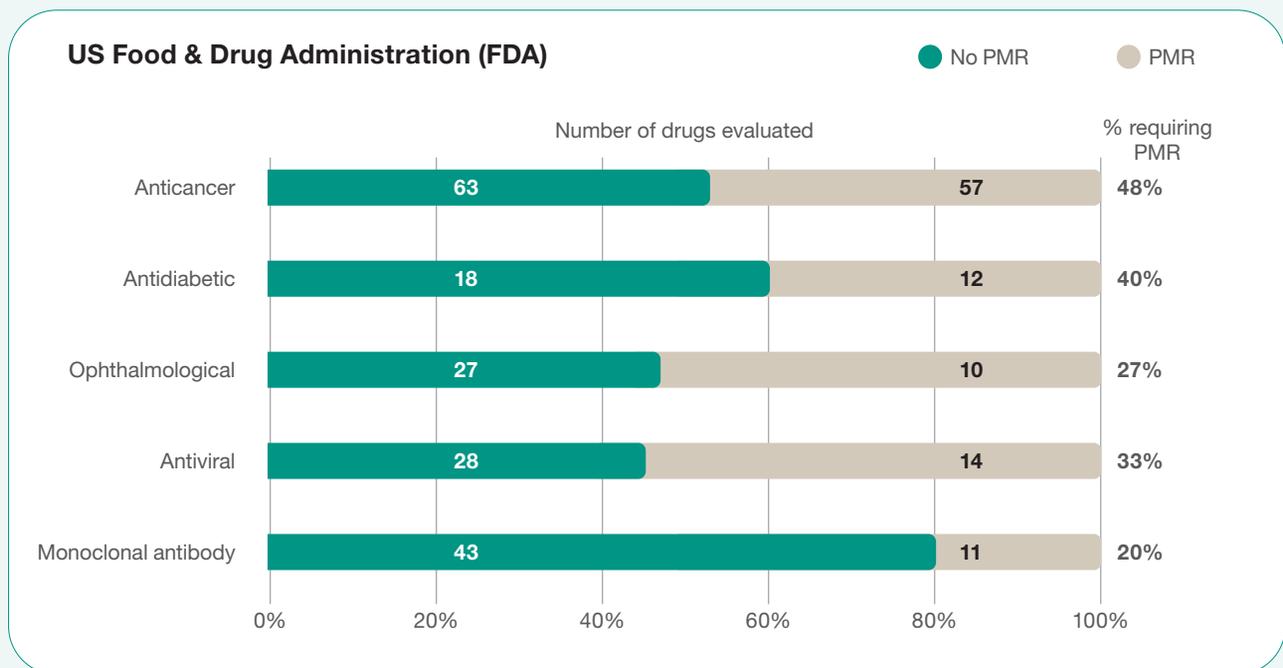
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Postmarketing requirements (PMRs)

Postmarketing requirements (PMRs) for drug development are a common-place requirement. Their purpose is to gather information about a product's safety, efficacy, and/or optimal use. These may include additional studies or clinical trials to assess known risks, signals of risk, or identify a potential risk where data indicate one might exist.[1]

Given their individual decisioning, US and European regulator indicators for postmarketing requirements can differ.[2,3] Because drug commercialisation often includes both US and European markets, many drugs must follow the requirements and timelines issued from both, further complicating the process.

Postmarketing probabilities

The average probability of postmarketing requirements differs greatly by specialty, but two things are clear: No category is safe from them, and the statistics are significant across the board.

Figure 1: PMR probability in different therapeutic areas in the past 5 years[4]

US Food & Drug Administration (FDA)   ● No PMR   ● PMR

Number of drugs evaluated

Therapeutic area	No PMR	PMR	% requiring PMR
Anticancer	63	57	48%
Antidiabetic	18	12	40%
Ophthalmological	27	10	27%
Antiviral	28	14	33%
Monoclonal antibody	43	11	20%

0%   20%   40%   60%   80%   100%

European Medicines Agency (EMA)   ● No PMR   ● PMR

Number of drugs evaluated

Therapeutic area	No PMR	PMR	% requiring PMR
Anticancer	76	15	16%
Antidiabetic	21	9	30%
Ophthalmological	18	7	28%
Antiviral	30	6	17%
Monoclonal antibody	34	17	33%

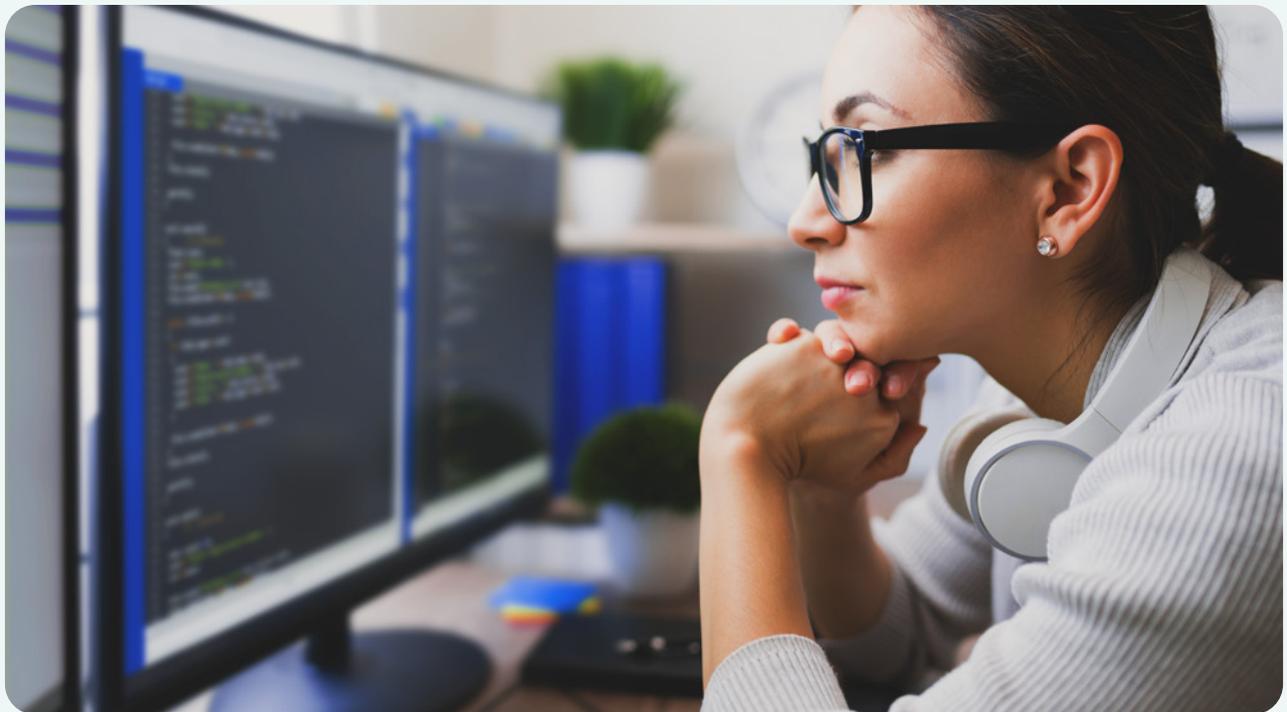0%   20%   40%   60%   80%   100%

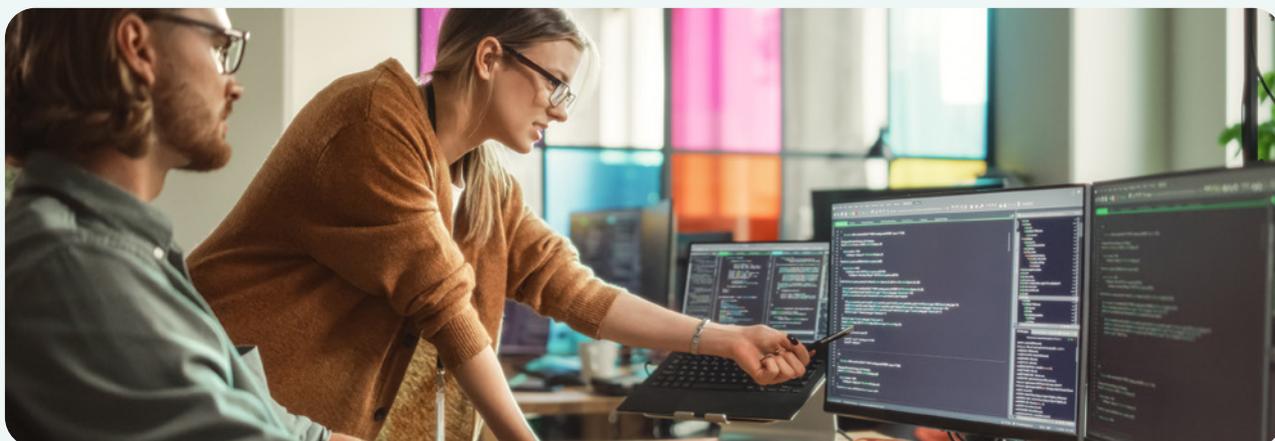## Unplanned postmarketing requirements can have a significant impact on development costs and timing

Drug development is an expensive process, with research and development average estimates ranging from less than $1 billion to over $2 billion.[5]

Budgets and sales projections are carefully planned to determine whether a project is or is not viable to pursue. Unneeded process can add substantial time and cost to getting needed treatments to patients or even derail them entirely.

Advancing drug trials and approvals efficiently is crucial to meeting patient and market needs. Likewise, understanding and efficiently handling postmarketing requirements are essential to continued availability and managing the cost to the sponsor, the payer, and the patient.

Engaging AI and machine learning to manage drug development risk and cost

AI has become a transformative tool in many areas of drug development, including:

- **Clinical trial site selection:** Human-enabled AI helps generate insights into how trial sites will perform across enrolment, speed, and quality markers more quickly and more effectively than could otherwise be done.[6]

- **Prediction of efficacy and toxicity of potential drug compounds:** AI techniques and machine learning overcome the limitations of labor-intensive and time-consuming experimentation by proposing new bioactive compounds based on identifying patterns and trends of trials not apparent to human researchers.[7]

- **Identification of drug-drug interactions:** AI has been used to identify specific interactions by comparing drug-drug structures to determine similarity and identify less risky replacements with similar pharmacologic profiles.[8,9]

AI and machine learning can offer specific potential for better management of postmarketing requirements, as well.

The capability offers two advantages over alternate methods:

1. More effectively leverages the massive amounts of data available related to various aspects of drug approval analysis [7,10]

2. More accurately makes decisions and adjusts to changes as the result of continually incorporating new and more current data [7]

The transition from a state of data overload to one of better-informed decision-making is a major benefit that AI and machine learning offer. Ultimately, this can provide an earlier and more accurate assessment of whether postmarketing requirements will be issued.

It can also leverage the commonalities and differences between FDA and EMA regulatory organization decision-making processes to improve efficiencies and accuracy of the assessments and necessary studies.

Cassandra: Accurately forecasting postmarketing requirements applying AI and machine learning

Cassandra is ICON's powerful AI system that harnesses real world data on drugs and data obtained from the FDA and EMA PMRs databases. This information is analysed by Cassandra to predict accurately whether the US FDA and/or EMA will or will not require postmarketing studies.

The benefits of Cassandra

Having the knowledge in advance offers several important advantages for drug development and commercialisation:

Total development cost can be better predicted, understood and potentially minimised earlier, which impacts budgeting including product pricing, profitability and return on investment

Total potential risk is better managed by understanding requirements for postmarketing studies in advance

Total development time can be minimized by beginning necessary work earlier instead of waiting for a decision that it will be required

Legal requirements are met without surprise additions, impacting cost, risk, and timing

Why Cassandra?

Greek mythology tells the story of Cassandra, a Trojan priestess whose beauty and intelligence attracted the attention of the god Apollo. To win her love, he gifted her the power to see the future. But after receiving the gift, she spurned him. Unable to revoke his gift, he cursed her so that her prophesies would not be believed.

Like the mythical Cassandra, the Cassandra AI application can forecast the future with incredible accuracy in relation to PMR requirements of the FDA or EMA.
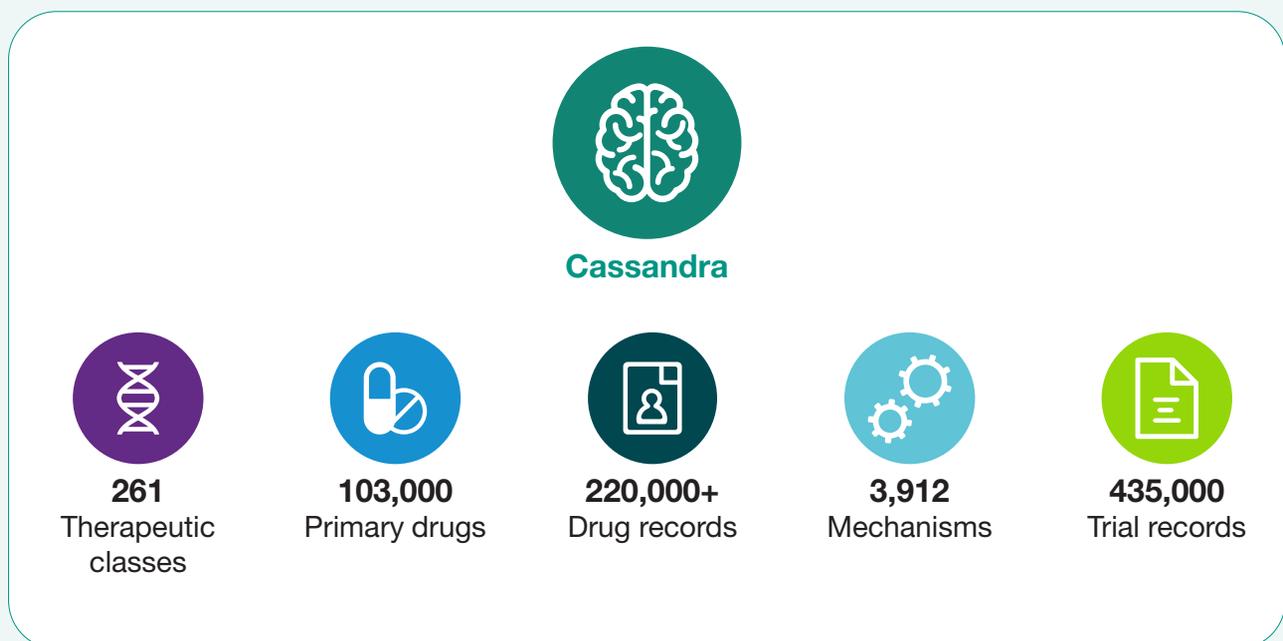
In the case of drug development, having this knowledge ahead of time brings the benefits of reducing risk, managing costs, minimizing time investment, and better ensuring that regulatory requirements are met.

How Cassandra works

To perform its sophisticated modeling and forecasting, Cassandra uses FDA, EMA, and Citeline data on drug applications and approvals/rejections dating back to 2003. As of March 2024, Cassandra contains more than 220,000 individual drug records and nearly 435,000 trial-related records, covering 261 therapeutic classes and 3,912 mechanisms of action for more than 103,000 primary drugs around the globe. A total of more than 3 million data points are incorporated into Cassandra evaluations.[1]

This provides an experience base far more expansive and accurate than any one company could ever hope to amass from its own individual experiences.

Information for existing and new entries are updated quarterly as new data is provided by the FDA and EMA commitment databases.

Cassandra

261 Therapeutic classes	**103,000** Primary drugs	**220,000+** Drug records	**3,912** Mechanisms	**435,000** Trial records

Cassandra provides maximum value when implemented early in the drug approval process. This offers sponsors the ability to budget the development cost and timing more accurately, and to make better-informed decisions regarding continued development and resource deployment.

Cassandra offers unmatched accuracy

The quantity and quality of input data is crucial, but any system is only as good as the results it produces. Cassandra's performance is outstanding, making it an essential tool for drug development.

Cassandra's accuracy: **99%** FDA PMRs   **97%** EMA PMRs

The source of Cassandra's accuracy

The accuracy Cassandra offers is a function of the data quantity and quality provided, and of the processes used to manage and process that data.
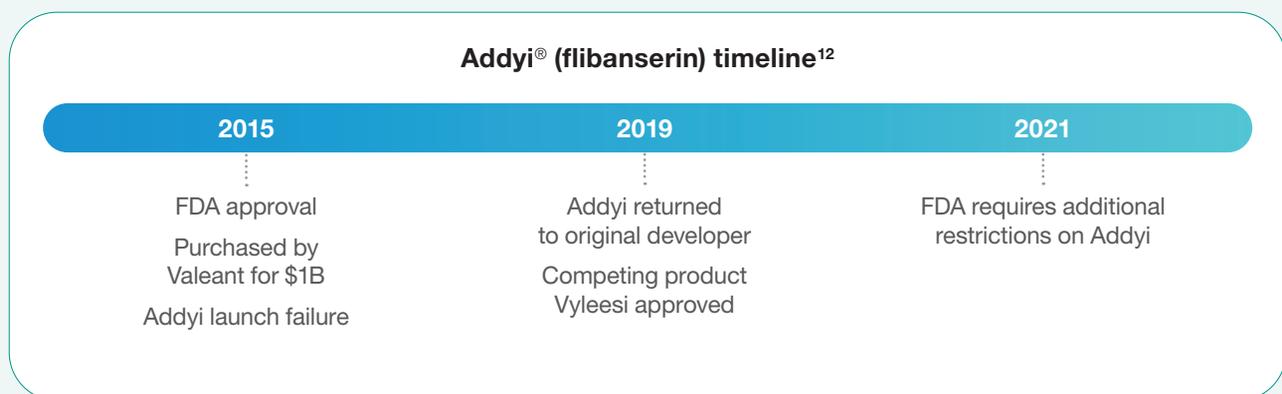
Proprietary algorithms analyze the data provided, comparing and contrasting it to the existing bank of information and FDA/EMA decisioning to deliver an evaluation on the likelihood that the drug will require postmarketing requirements and the nature of information that may be required. To do this, Cassandra takes into account the same and similar molecules and mechanisms and previous regulatory actions.

Cassandra, with its integrated AI and machine learning capabilities, is a supplement to and not a replacement for human insights and involvement. Results are always validated by highly skilled professionals, including ICON's experts in real-world solutions, scientific affairs, therapeutics, and drug development services. Experienced professionals provide additional insights using Cassandra data as a foundation for processing the millions of data points. Human analytics remain an important element in Cassandra's accuracy and ultimate success.

The case for the need – an example of commercialisation failure

Failure to forecast and understand postmarketing requirements can severely impact even a highly anticipated drug. Unexpected postmarketing requirements can add significant challenges to drug development, including additional short- and long-term costs, time delays, and increased risk including approval rejections or restrictions.

Sprout Pharmaceutical's Addyi® (flibanserin) serves as one example. The female libido drug received FDA approval in 2015 after being twice rejected, and was quickly purchased by Valeant for $1 billion.[11] The launch failed and, following a lawsuit, drug rights were returned to the former shareholders.[12] On relaunch, the FDA restricted marketing and modified a black box warning over risks of alcohol use.[13] In 2021, the drug was flagged again, this time for possible risks of drug hypersensitivity. In 2019, AMAG Pharmaceuticals received approval for a competing product, Vyleesi® (bremelanotide). Addyi failed to get the traction it needed and never achieved its commercialisation potential as a breakthrough treatment.[12]

Addyi® (flibanserin) timeline[12]

2015	2019	2021
FDA approval	Addyi returned to original developer	FDA requires additional restrictions on Addyi
Purchased by Valeant for $1B	Competing product Vyleesi approved	
Addyi launch failure		

Lost timing advantage. Additional restrictions on and after launch. Missed sales projections. Subsequent competitive entry into the market. Each is part of the cautionary tale of what can happen when a company doesn't fully manage the risk associated with drug development, including an understanding of potential postmarketing requirements.

A complete solution – leveraging the full capabilities of ICON

Cassandra offers a highly accurate assessment on the need for postmarketing requirements. Cassandra analysis may be used specifically to identify situations where sponsors work to capture enough additional long-term safety data on patients treated during the early phases of the development cycle to convince the authorities that a post-authorisation safety study is not needed. That offers significant risk management advantages.

ICON offers the integrated capabilities to address the anticipated regulatory requirements to manage risk, including increased spending and expanded time frames.

Accept   Avoid   Transfer   Reduce

Clinical trial design and management

From initial trial design to full implementation, ICON brings the ability to implement a clinical trial from start to finish. This includes global site selection, decentralised trial implementations, and providing integrated systems for coordinating the activities and communications necessary for all parties to drive successful clinical trial management.

Clinical trial tokenisation, a way to de-identify personally identifiable information (PII), can also increase efficiency in meeting postmarketing requirements. Consenting patient identifying details are replaced with ICON's Synoma encrypted token, which allows the connection of the patient token to real world data for analysis. Real world data from other systems can then be referenced for a wider, longer-term picture on relevant health topics. Sponsors can identify trends to help them address postmarketing requirements. This process adheres to good clinical practices and Health Insurance Portability and Accountability Act (HIPAA) guidelines.

ICON's Symphony Health experts, data, and technology provides the data needed from third-party sources. This includes information on over 85% of dispensed drugs sourced from more than 300 million patients and third-party data across the entire healthcare realm.

ICON's comprehensive market access services span the product commercialisation journey. Empowered by healthcare intelligence, we offer integrated global experience, expertise, insights, and technology to drive success. We offer healthcare provider, patient, payer, and industry research to drive the strategies that target each group. From those strategies, we partner with sponsors to construct the sales, marketing, and reimbursement elements vital to successful commercialisation.

Integration of the ICON service offerings provides tangible benefits over selecting separate mismatched solutions or using only internal resources:

- **Faster knowledge of postmarketing requirement expectations** including the specific nature of what likely will be needed

- **More accurate budgeting of total costs and time requirements** for better informed "go/no go" decisions

- **Reduced and managed risk to approvals** by more accurately forecasting regulatory requirements and paths to optimize speed while minimizing cost

- **Time saving**s over building conduits to connect separate systems and groups, and elimination of management overlap

- **Cost savings** by eliminating duplicate resources and project management activities

- **Better internal resource management** by getting the specialized support as needed to free up internal capabilities for other work

Conclusion

Cassandra is a needed and valuable resource for drug commercialisation. By integrating AI and machine learning with human expertise, Cassandra offers an accurate understanding of postmarket requirements early in the development cycle.

For more information on Cassandra and how it might benefit your drug development, please visit ICONplc.com/contact.

Winner, Silver Stevie 2023

Business Technology (Artificial Intelligence/ Machine Learning Solutions) recognises Cassandra as an AI solution exhibiting intelligent behaviour in complex situations to solve problems.

References

1. US FDA. Postmarket requirements and commitments: Introduction. Accessed April 1, 2024. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments

2. Salib V. Regulating and authorizing medicines: a comparison of the FDA and EMA. Accessed April 1, 2024. https://pharmanewsintel.com/features/regulating-and-authorizing-medicines-a-comparison-of-the-fda-and-ema

3. Kreatsoulas J. The EMEA and the FDA: a comparison. Accessed April 1, 2024. https://crstoday.com/articles/2011-oct/the-emea-and-the-fda-a-comparison

4. ICON plc data on file. Cassandra 2.0 Stats

5. Congressional Budget Office, US Congress. Research and development in the pharmaceutical industry. Accessed April 1, 2024. https://www.cbo.gov/publication/57126

6. ICONplc. Advancements in artificial intelligence for site selection. Accessed April 1, 2024. https://icon.widen.net/s/vrwcbpw7gs/advancements-in-ai-for-site-selection_onesearch

7. Xu Y, Liu X, Cao X, et al. Artificial intelligence: a powerful paradigm. *Innovation (Camb)*. 2021;2(4):100179. doi: 10.1016/j.xinn.2021.100179.

8. Davenport L. AI tool reveals MS drug interactions, offers safer options. http://Medscape.com. Accessed April 1, 2024. https://www.medscape.com viewarticle/997331?form=fpf#vp_2

9. Jang HY, Song J, Kim JH, et al. Machine learning-based quantitative prediction of drug exposure in drug-drug interactions using drug label information. *NPJ Digit Med.* 2022;5(1):88. doi: 10.1038/s41746-022-00639-0.

10. Pfizer. Artificial intelligence: on a mission to make clinical drug development faster and smarter. Accessed April 5, 2024. https://www.pfizer.com/news/articles/artificial_intelligence_on_a_mission_to_make_clinical_drug_development_faster_and_smarter

11. Carroll J. Controversial Valeant Pharma swoops in with a $1B Addyi buyout. Accessed April 1, 2024. https://www.fiercebiotech.com/financials/controversial-valeant-pharma-swoops-a-1b-addyi-buyout https://www.fiercebiotech.com/financials/controversial-valeant-pharma-swoops-a-1b-addyi-buyout

12. Sagonowski E. Sprout's female libido drug Addyi back in FDA's crosshairs years after controversial approval. Accessed April 1, 2024. https://www.fiercepharma.com/pharma/sprout-s-female-libido-drug-addyi-back-fda-s-regulatory-spotlight-years-after-controversial

13. Barber J. FDA loosens alcohol restrictions on Sprout's sexual desire disorder drug Addyi. Accessed April 1, 2024. https://firstwordpharma.com/story/4772739

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About ICON

ICON is the world's leading clinical research organisation, powered by healthcare intelligence. From molecule to medicine, we advance clinical research providing outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. We develop new innovations, drive emerging therapies forward and improve patient lives. With headquarters in Dublin, Ireland, ICON operates from 99 locations in 46 countries and has approximately 41,150 employees as of 1 March 2023.