Enablers and Barriers for Regulatory Approval of Schizophrenia Drugs in USA, Canada, UK, and EU

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Background

- Schizophrenia is a chronic mental illness that is characterized by psychotic symptoms including hallucinations and delusions
- Psychotic symptoms are usually categorized as positive symptoms (reflecting a distortion or abundance of normal functions) and negative symptoms (reflecting a loss or restrictions of normal functioning)
- The frequency, duration, and severity of symptoms of schizophrenia can lead to deterioration in social, cognitive, and occupational functioning
- Mainstay of schizophrenia treatment is antipsychotic agents (APAs) that target the dopaminergic system in the brain. There is an unmet need in this space because of factors such as side effect profile, poor treatment adherence, and treatment resistance with the existing APAs[1-3]
- Newer molecules are being developed for management of Schizophrenia, and large number of clinical trials are conducted for obtaining regulatory approvals
- Regulators, payers, prescribers, and patients look for strong evidence base for marketing approval, reimbursement approval, prescribing, and using these newer drugs, respectively. Thus it becomes necessary for sponsors to conduct well-designed clinical trials to strengthen the evidence surrounding efficacy, safety, and quality of life

Objective

- To compile the factors that favored (enablers) and hindered (barriers) the regulatory approvals for marketing and reimbursement for drugs used in the management of all forms of schizophrenia in:
  - USA
  - Canada
  - UK
  - Rest of the EU
- To compare the enablers and barriers in the above 4 regions to identify similarities/ differences in the regulatory frameworks in the Schizophrenia space

Methodology

Sources of Information

Region	Sources	
USA	1. USFDA	
Canada	1. CADTH Reimbursement Review Reports 2. Canada Drug and Health Product Register	3. Canada Medical Devices 4. Canada Drug Product Database
UK	1. MHRA 2. NICE 3. Electronic medicines compendium	4. All Wales Therapeutics and Toxicology Centre 5. Lancashire and South Cumbria Medicines Management Group 6. Oxford Health NHS Foundation Trust
Rest of EU	1. EMA	2. CHMP
General Sources	1. PubMed	2. ClinicalTrials.gov

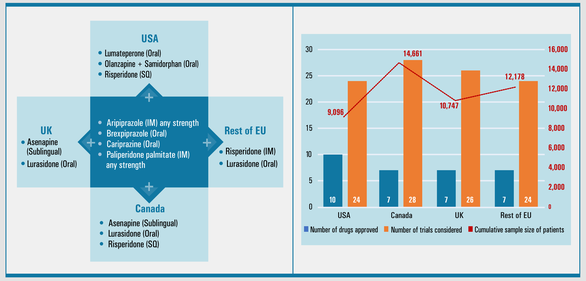
Data Collection

- We searched for marketing approvals and rejections, and reimbursement approvals and rejections of all drugs that are indicated for the management of all forms of schizophrenia over the past 12 years: Jan 2011 to Dec 2022
- From this list, we gathered all relevant regulatory documents, submissions, reports, news snippets, fact sheets, and other resources that provided additional insights towards what factors contributed to successful and unsuccessful regulatory decisions by the respective regulatory bodies
  - USA: USFDA
  - Canada: CADTH
  - UK: MHRA
  - Rest of EU: EMA
- We used a common template to extract all relevant data and summarize the same with supporting information

Results

Approved Drugs

	No	Generic Name	Brand Name	No of trials	Cumulative sample size
USA	1	Aripiprazole lauroxil (IM) (441 mg, 662 mg, 882 mg)	Aristada	5	838
	2	Aripiprazole lauroxil (IM) (675 mg)	Aristada Initio	3	320
	3	Aripiprazole monohydrate (IM) (300mg, 400 mg)	Abilify Maintena	1	403
	4	Brexpiprazole (Oral)	Rexulti	2	1310
	5	Cariprazine (Oral)	Vraylar	3	1795
	6	Lumateperone (Oral)	Caplyta	3	1307
	7	Olanzapine + Samidorphan (Oral)	Lybalvi	3	1262
	8	Paliperidone palmitate (IM) (273 mg, 410 mg, 546 mg, 819 mg)	Invega Trinza	1	305
	9	Paliperidone palmitate (IM) (1092 mg/ 3.5 mL; 1560 mg/ 5 mL)	Invega Hafyera	1	702
	10	Risperidone (SQ)	Perseris	2	854
			Total	**24**	**9096**
Canada	1	Aripiprazole (IM)	Abilify Maintena	2	1065
	2	Asenapine (Sublingual)	Saphris	8	3894
	3	Brexpiprazole (Oral)	Rexulti	3	2242
	4	Cariprazine (Oral)	Vraylar	4	2560
	5	Lurasidone (Oral)	Latuda	7	2611
	6	Paliperidone palmitate (IM)	Invega Trinza	3	1935
	7	Risperidone (SQ)	Perseris	1	354
			Total	**28**	**14,661**
UK	1	Aripiprazole (IM) (7.5 mg/ml solution)	Abilify	2	554
	2	Aripiprazole (IM) (400 mg powder/ solvent)	Abilify Maintena	4	1930
	3	Asenapine (Sublingual)	Sycrests	1	306
	4	Brexpiprazole (Oral)	Rxulti	5	1928
	5	Cariprazine (Oral)	Reagila	6	2569
	6	Lurasidone (Oral)	Latuda	7	2758
	7	Paliperidone palmitate (IM)	Byannli	1	702
			Total	**26**	**10,747**
Rest of EU	1	Aripiprazole (IM)	Abilify Maintena	2	1065
	2	Brexpiprazole (Oral)	Rxulti	5	2404
	3	Cariprazine (Oral)	Reagila	5	2966
	4	Lurasidone (Oral)	Latuda	6	2063
	5	Paliperidone palmitate (IM) (175 mg, 263 mg, 350 mg, 525 mg)	Trevicta	2	1935
	6	Paliperidone palmitate (IM) (700 mg, 1000 mg)	Byannli	1	702
	7	Risperidone (IM)	Okedi	3	1043
			Total	**24**	**12,178**



Enablers

	USA	Canada	UK	Rest of EU
Patient profile	• Diagnosis of schizophrenia, using DSM-IV-TR criteria • Sample size of pivotal studies: ranged from 300 to 732 patients • BMI between 18 to 35 • Patients had the diagnosis for at least 1 year	• Diagnosis of schizophrenia, using DSM-IV-TR criteria (confirmed by MINI) • Sample size: ranged from 149 to 1429 patients	• Diagnosis of schizophrenia, using DSM-IV-TR/ DSM-5 criteria • Sample size: ranged from 183 to 843 patients	• Diagnosis of schizophrenia, using DSM-IV-TR/ DSM-5 criteria
Study design	• Double blind, parallel group RCTs	• Double blind, parallel group RCTs • Study duration: ranged from 6 weeks to 92 weeks	• Double blind, parallel group RCTs	• Double blind, parallel group RCTs
Outcomes	**Clinical outcomes** • Key efficacy scales used: PANSS (positive and negative syndrome scale) and CGI-S (clinical global impression-severity) scale • Efficacy measurement: baseline vs week 4/ week 24/ week 52 in 3 different studies for both scales • Measuring relapse: Time to relapse, % relapsed • Supportive endpoints: PSP (personal and social performance) scale, cognitive function assessment, letter-number span assessments, and IAQ (investigator's assessment questionnaire) **Patient-reported outcomes** • Patient satisfaction through medication questionnaire-modified **Economic outcomes** • HCRU, drug cost	**Clinical outcomes** • Key efficacy sales used: PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) scale, CGI-I (clinical global impression-improvement) scale, BPRSd (Brief psychiatric rating scale derived), NSA-16 (negative symptom assessment-16 item) scale • Measuring relapse: Time to impending relapse, time to relapse, % of patients without relapse as primary/ secondary outcomes • Supportive endpoints: GAF (global assessment of functioning), PSP (personal and social performance) **Patient-reported outcomes** • HRQoL: using EQ-5D-5L, Q-LES-Q (quality of life enjoyment and satisfaction questionnaire), SF-12, S-QoL (Schizophrenia Quality of Life) scale • Patient satisfaction with medication: using MSQ (Medication Satisfaction Questionnaire) • Subjective well-being: using the SWN-S (Subjective Well-being under Neuroleptic treatment - Short Form) scale	**Clinical outcomes** • Key efficacy sales used: PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) scale, CGI-I (clinical global impression-improvement) scale, PANSS-FSNS (factor score for negative symptoms) • Measuring relapse: Time to impending relapse, time to relapse, relapse-free rate, as primary/ secondary outcomes • Supportive endpoints: GAF (global assessment of functioning), PSP (personal and social performance), SAND (short assessment of negative domains) • Favourable effect on metabolic parameters (lipids, glucose, Hba1c: Lurasidone) • Little effect on weight, no association with increase in prolactin levels (Cariprazine) **Patient-reported outcomes** • Quality of life: through QALYs	**Clinical outcomes** • Key efficacy sales used: PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) scale, PANSS-FSNS (factor score for negative symptoms) • Measuring relapse: Time to relapse, and relapse rate, as primary/secondary outcomes • Supportive endpoints: PSP (personal and social performance) • Favourable effect on metabolic parameters (lipids, glucose, Hba1c: Lurasidone) • No association with increase in prolactin levels (Aripiprazole)
Miscellaneous enablers	• Active comparator; placebo was also used in a 4 arm trial	No information	No information	• Route of administration: injectable formulations were noted to be effective compared to oral formulations (PP3M) • Longer dosing interval: prolonged release formulations were noted to have advantages relating to adherence; also useful to patients with limited healthcare access (PP3M, PP6M, risperidone, aripiprazole)

Barriers

	USA	Canada	UK	Rest of EU
	Although we could not find any regulatory rejections by USFDA during the period of interest for schizophrenia, the USFDA raised some concerns during the course of regulatory review	**Although we could not find any regulatory rejections by CADTH during the period of interest for schizophrenia, the CADTH raised some concerns during the course of regulatory review**	**Although we could not find any regulatory rejections by NHS/ MHRA during the period of interest for schizophrenia, NHS/ MHRA raised some concerns during the course of regulatory review**	**CHMP/ EMA refused marketing approval for Iloperidone citing arrhythmogenic potential (QTc prolongation), modest efficacy, and delayed onset of action, leading to an overall negative risk-benefit balance**
Study design	• The study duration was asked to be increased from 4 weeks to 6 weeks (Lumateperone)	• Duration of trial (Risperidone): longer duration clinical trials were recommended to assess long-term efficacy of Risperidone ER • High proportion of trial drop outs (Asenapine, Lurasidone): could compromise randomization and bias the results • Withdrawal design, early termination (Aripiprazole) • Failure to demonstrate non-inferiority (Lurasidone) and superiority over placebo (Asenapine)	• Duration of trial (PP6M): longer duration clinical trials (< 12 months) were recommended to assess relapse prevention efficacy • High drop out rates (Lurasidone) • High treatment costs (Lurasidone) • Failure to demonstrate non-inferiority (Lurasidone vs risperidone) • Selection bias (Lurasidone): participants were enrolled from an initial 6-week study, and did not undergo re-randomization; regulator felt that this could have potentially introduced selection bias into the groups	No information

Outcomes	**Efficacy**
	• USFDA raised concern for including weight mitigating data in labelling of Olanzapine + Samidorphan, because of modest difference compared to olanzapine alone and difficult-to-interpret results
	Safety
	• Ocular toxicity (Cariprazine): pooled studies suggested higher incidence of ocular toxicity; under review to find if there is a risk of serious ocular toxicity
	• Weight gain (Brexrabiprazole, Risperidone): reported by 2 studies
	• SAEs leading to death: 13 deaths with brexrabiprazole; 4 deaths with aripiprazole
	• Medication error: Sound-alike brand names (Aristada and Aristada Initio) may cause lead to confusion
		Patient-reported outcomes
		• Lack of QoL outcomes (Aripiprazole) Economic outcomes
		• Higher drug costs (Cariprazine, Risperidone, vs other antipsychotics) in the absence of proportionate efficacy benefits
			Safety
			• Higher incidences of AEs were observed, as follows:
			  • Dystonia, somnolence (Lurasidone)
			  • Insomnia (aripiprazole)
			  • Weight gain (aripiprazole, brexrabiprazole, asenapine)
			  • Extra-pyramidal symptoms (lurasidone, aripiprazole, brexrabiprazole)
			  • Prolactin elevation and neuroleptic malignant syndrome (brexrabiprazole)
				Safety
				• QTc Prolongation: Iloperidone (marketing approval not granted), Paliperidone (caution)
				• Weight gain (Paliperidone, Cariprazine)
				• Extrapyramidal symptoms (Aripiprazole)

Miscellaneous barriers	No information	• Inappropriate/ limited comparators for reimbursement applications (Cariprazine vs other antipsychotics) • Lack of head-to-head comparisons between different antipsychotics (Lurasidone, Aripiprazole)	No information	• Prolonged onset of action: Iloperidone (marketing approval not granted)

Common Enablers and Barriers

Common Enablers

- Using PANSS and CGI-S as key efficacy scales
- Measuring relapse
- Measuring PROs using validated tools
- Using DSM-IV-TR/ DSM-5 criteria for the diagnosis of schizophrenia
- Study design: double blind, parallel group RCTs
- Sample size of pivotal studies: 300+

Common Barriers

- Safety concerns: common AEs considered by different regulators included weight gain, extrapyramidal symptoms, prolactin elevation, effects on sleep
- Clinical trial duration: long enough to establish efficacy

Conclusions

- Knowledge of enablers and barriers leading to regulatory decisions can help in smart clinical trial planning, which in turn can improve the chances of successful regulatory outcomes
- Planning clinical trials by including enablers and avoiding barriers will help in easier navigation through the regulatory process, thereby benefiting all stakeholders (sponsors, regulators, payers, prescribers, and patients)
- This can improve the methodology of ethical and scientific evidence generation, and can ultimately facilitate earlier market access of drugs for Schizophrenia

References

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